FORMATION AND PROPERTIES OF OPTICALLY ACTIVE SCHIFF BASES

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HUANG Su-Eng, B.Sc.

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SUMMARY

The rates of condensation of L-tyrosine ethyl ester with substituted benzaldehydes have been studied polarimetrically. Electron donating substituents in the aldehyde ring in general retard the rate of condensation to a marked extent. In comparison, electron attracting substituents cause very little activation. The log. of rate constants (k) when plotted against Hammett's σ constants did not give a linear relationship. The major cause of this behaviour has been attributed to deactivation of the carbonyl function, by the presence of para-resonance interaction. The high reactivities for o-substituents in comparison with the corresponding p-substituents are anomalous. This phenomenon has been explained in terms of 'ortho' effects.

A representative number of the product of condensation were isolated from the reaction mixtures. These were found to racemize very readily in the presence of heat, base, and cupric ion. The ease of racemization has been attributed to the presence of the ester function in the amino ester. The schiff bases possessed very high specific rotations in the sodium D line and led to investigation of their optical rotatory dispersion.

As the N-arylidene derivatives of L-tyrosine

ethyl ester are optically unstable, the N-arylidene derivatives of (+)-amphetamine and (-)-α-phenylethylamine were studied, the chromophores being the -C=N- and the benzene absorption bands. All the schiff bases exhibit anomalous dispersion curves. From the results, the benzene absorption band can be assumed to be optically active. The -C=N- appear to be optically active only when an ortho-substituent is present in the aldehyde ring. The rotatory dispersion curves of N-arylidene derivatives of (-)-α-phenylethylamine were compared with those of (-)-α-p-methylphenylethylamine, (+)α-p-methoxyphenylethylamine and (+)-α-p-bromophenylethylamine.

(-)-α-Phenylethylamine and (+)-amphetamine have the same absolute configuration. Although the former has a negative dispersion curve and the latter a positive one, the rotatory dispersion curves of their 1,4-benzoquinone derivatives are both positive. Therefore by the formation of benzoquinone derivatives other amines or related compounds can be configurationally related to the two known amines by studying their rotatory dispersion curves. The benzoquinone derivative has the further advantage in that the cotton effect curve is observed in the visible region, and can be used in the determination of absolute configuration.

STATEMENT

To the best of my knowledge and belief, this thesis contains no material previously submitted for a degree in any University either by myself or any other person, except where due reference is made.

S. E. HUANG

1961

CHAPTER I

Introduction

The interaction between carbonyl and amino groups has been a subject of interest ever since Sorensen[1] showed that formaldehyde will react with amino acids in such a manner that their carboxyl groups could be accurately titrated. Most important of all is the reaction between α-amino and α-keto acids in biological systems which can result in either transamination, decarboxylation, deamination, and racemization. In model systems all these transformations have been postulated by Snell[2] and his co-workers,[3] to occur through an intermediate schiff base which is stabilized by the formation of a complex with metals such as copper, aluminium, and iron, and in the presence of pyridoxal and its derivatives.

It is an interesting fact that all naturally occurring amino acids exist in the optically active L-form.[4] This property has been widely used in studying the reaction between amino acids and carbonyl compounds.

The effect of the carbonyl function on the rotation of the amino group has been widely demonstrated. Loiseleur and Crovisier[5] showed that amino acids may undergo mutarotation at pH 7 in the presence of formaldehyde. Frieden, Dunn and Coryell[6] observed an increase in the rotatory power of the amino acid in formaldehyde but did not report any mutarotation. Gulland and Mead[7] found such an effect with D-phenylalanine sodium salt and 2,3-, 2,5-, 3,4-dimethoxybenzaldehyde in 50% aqueous ethanol. However, none of the above workers reported the isolation of the mutarotated product. The effect of the carbonyl function on amino groups has been further demonstrated by Bergel and Lewis[8] in studies of simple dissolution of α-amino esters in aliphatic ketones. The product invariably possessed high specific rotation of opposite sign to the parent amino ester. Again they were not able to isolate the product but considered the high rotation to be due to the formation of an amino-carbinol by interaction of the amino group of the ester and the carbonyl group of the ketone.

$$(CH_3)_2CO + H_2N.CHR.CO_2C_2H_5 \rightleftharpoons (CH_3)_2C(OH).NH\,CHR\,CO_2C_2H_5$$

Since in several cases they recovered most of their starting material (when it was crystalline) merely by precipitation with petroleum ether, it seems that any bond formed would be of low energy.

The most systematic physical measurement of the interaction between carbonyl and amino groups have been

carried out by Hargreaves[9] and his co-workers.[10] They carried out the interaction under various conditions of pH, temperature, and solvents such as dioxane and acetone, and found that generally, the effect is one of exaltation of the rotatory power of the amino compound. More recently Bergel and his co-workers,[11] were successful in isolation of a solid from a saturated solution of L-tyrosine ethyl ester in cyclopentanone. The product, N-cyclopentylidene L-tyrosine ethyl ester ($[\alpha]_D^{21}$ - 102°) was obtained as a solid and proved by infrared evidence to possess an azomethine linkage. Nevertheless, it would appear that generally, azomethines from aliphatic carbonyl and amino compounds are more difficult to isolate. The formation of azomethines from amino esters and aromatic aldehydes has been described by Velluz and his co-workers,[12] and Pfeiffer, Offermann, and Werner.[13] The former group of workers were mainly interested in the synthesis of peptide systems, and the latter were concerned with inner complexes formed from salicyldehyde and the amino ester. It would appear then that the interaction of aromatic aldehydes and amino compounds would lend itself to the isolation of optically active stable products which could be isolated in a pure form,

and characterized. This has therefore led to the study in this work of the reaction between L-tyrosine ethyl ester and substituted benzaldehydes. The use of aromatic aldehydes has the advantage in that ring substitution patterns can be studied systematically. Furthermore, aromatic aldehydes are closer models of pyridoxal and its derivatives which are known to play an important role in the transformation of α-amino acids.

A representative number of the schiff bases from L-tyrosine ethyl ester and substituted benzaldehydes have been isolated. These optically active schiff bases were observed to racemize quite readily in the presence of heat. It is of interest in relation to the above to investigate the rate of racemization of these schiff bases with a view to gain more insight to the behaviour of compounds of this type. In addition, the schiff bases were found to possess very high specific rotations in the sodium D line, and it appeared that the study of their optical rotatory power in the ultraviolet would prove an interesting one.

The application of optical rotatory dispersion in solving organic problems (mainly stereochemical) has

become invaluable in the last decade. Previous to that it was confined to physicochemical rather than organic chemical aspects. Since 1952, with the introduction of the Rudolf photoelectric spectropolarimeter unit the laborious task of measuring optical rotatory dispersion curves was reduced from three weeks to a few days. It must be stressed that the application of optical rotatory dispersion in organic chemistry at the moment is mainly of a qualitative nature. The majority of modern work has been carried out on ketosteroids by Djerassi *et al.*[14] The ketosteroids presented a fruitful field of investigation because amongst other properties they have stereochemical simplicity and 'frozen' conformations. The optical rotatory dispersion of schiff bases have not been reported in the literature. Since the N-arylidene derivatives of L-tyrosine ethyl ester are prone to racemization, the N-arylidene derivatives of α-phenylethylamine and α-benzylethylamine (amphetamine) were investigated instead. These schiff bases posses the -C=N- and benzene chromophores similar to that of the N-arylidene derivatives of L-tyrosine ethyl ester. It was hoped to observe if the benzene absorption is optically

active or not. From the results obtained, it appeared to be so. Only in a few cases has the optical rotatory dispersion of aromatic compounds been studied.[15] These include the work by Kuhn and Biller[15a] on phenylcarbinol, and certain derivatives of mandelic and atrolactic acids. They found that the benzene absorption band at 260 mμ in the ultraviolet was optically inactive in phenylcarbinol, while it was optically active in derivatives of mandelic and atrolactic acids.

CHAPTER II

Part I

Gulland and Mead[7] observed polarimetrically the interaction of 2,3-, 2,5-, 3,4-dimethoxybenzaldehyde with sodium D-phenylalaninate in 50% aqueous solution. An increase in the rotation of the amino compound was observed to accompany condensation. They attributed the higher rotation obtained to the formation of a compound with an azomethine linkage. Bergel and Lewis[8] observed that when α-amino esters and N-alkylated or N-acylated amino esters were dissolved in aliphatic ketones, mutarotation occurred as well. The rotation of the condensed product had a sign opposite to that of the amino esters. Similarly in this case, the condensation of L-tyrosine ethyl ester with substituted benzaldehydes has been studied polarimetrically. When the amino ester and a benzaldehyde were mixed in equimolecular proportions in ethanolic solutions, the initial rotational values were found to change gradually until a steady level is reached over a period of time. Fig. 2.1 shows graphically the change in rotation observed in the condensation of L-tyrosine ethyl ester with a few benzaldehydes.

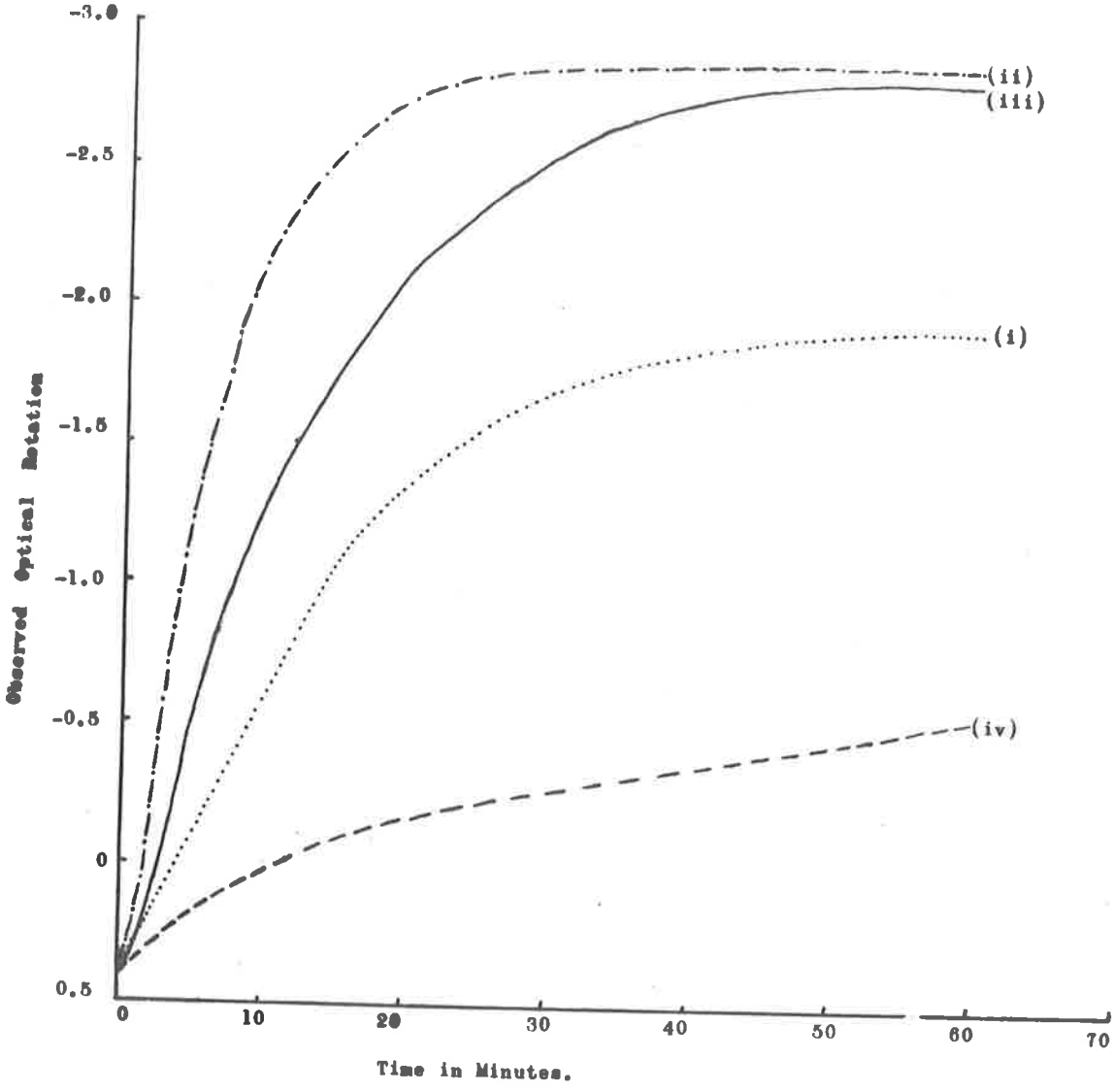


Fig.2.1. Rate of change in the Optical Rotations of tyrosine ethyl ester with (i) benzaldehyde (ii) salicyldehyde (iii) p - nitrobenzaldehyde (iv) p - dimethylaminobenzaldehyde, at 35° in 95% aqueous ethanol buffered to an apparent pH of 8.4 .

Preliminary studies in ethanolic solutions have shown the condensation reaction to be catalysed by the presence of acid. When a very small quantity of benzoic acid (0.001 g) was added to the condensation reaction between benzaldehyde and the amino ester, the rate was found to increase by three-fold. The use of buffered solutions for the rate studies has therefore been made necessary. This would help to eliminate the effect of the presence of acid caused by the ease of oxidation of the aldehydes. To ensure their absence, the aldehydes have been purified by recrystallization, or nitrogen distillation under reduced pressure just before use. A suitable buffer was prepared by an admixture of citric acid (0.3 M) and triethanolamine (0.3 M) in 95% aqueous ethanol.

Rate studies at 25° of the amino ester and benzaldehyde at various pH resulted in a curve of decreasing rate from the neutral to the alkaline region (Fig. 2.2). Rate constant values below pH 6.5 were not obtained as no change in optical rotation was observed, and the rotation measured was that of the amino ester. It was found that an apparent pH of about 8 would be most suitable for rate studies as the rate of the reaction is not too fast for accurate measurement.

From final rotational readings it was found

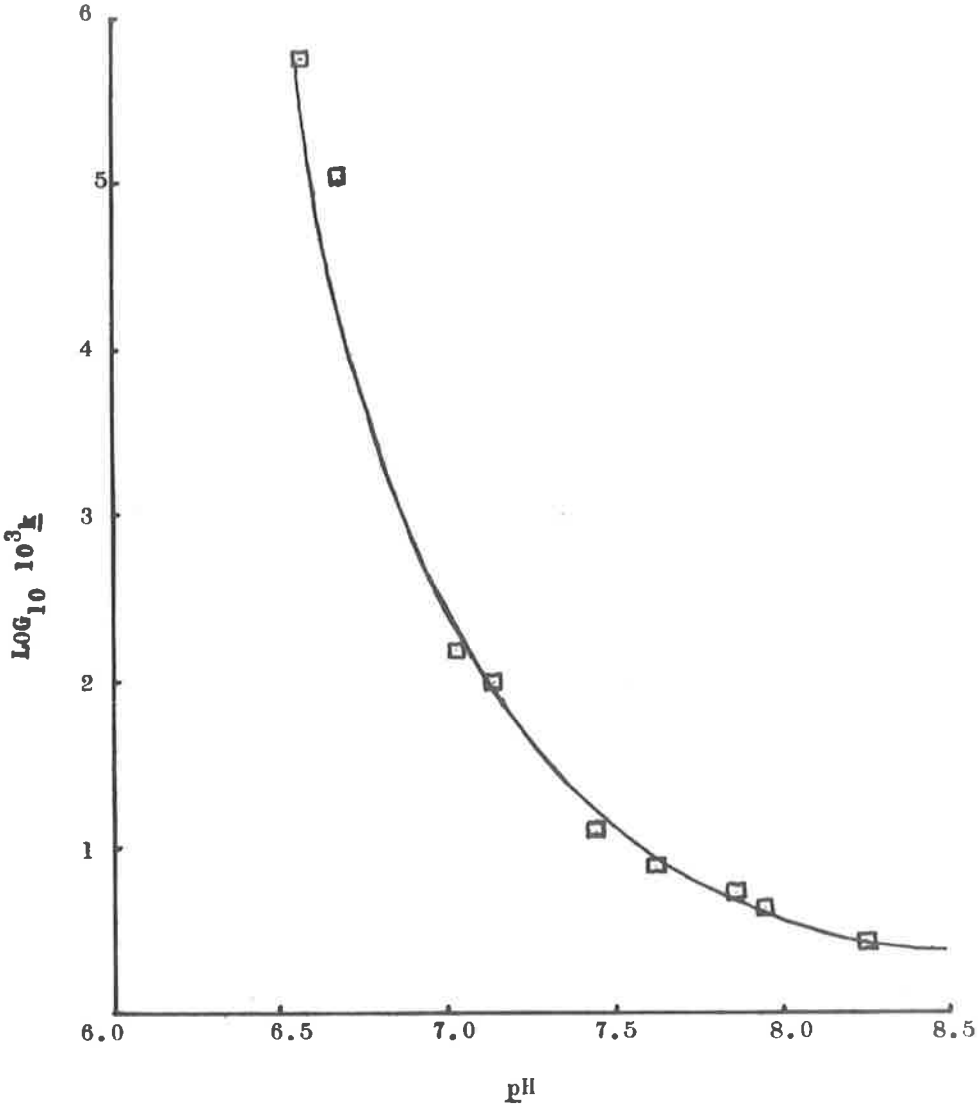


Fig.2.2. Rate of change with pH in the condensation of tyrosine ethyl ester with benzaldehyde at 25° and in 95% aqueous buffered ethanol.

that the formation of the product, which is a schiff's base, in every instance is an equilibrium reaction. It could be forced to virtual completion by using a moderate excess (4-10 fold) of aldehyde. Readings obtained from the change of rotation with time indicated the reaction to be consistent with a second order process opposed by one of first order:

$$-NH_2 + O{=}CH- \underset{}{\overset{k}{\rightleftharpoons}} -N{=}CH- + H_2O$$

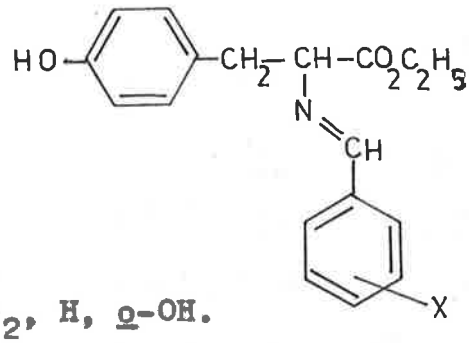
The forward rate constants (k) at 25°, 35° and 45° with their Arrhenius activation energies (E) are recorded in Table 2.1. The mean value for the series is 8.6 kcal. $mole^{-1}$, and deviations are as large as 1.5 kcal. $mole^{-1}$. From results obtained for the rate constants of m and p-substituents, it would appear generally that electron attracting substituents in the aldehyde increase the rate of reaction while electron donating substituents decrease the rate. The rate constants obtained for o-substituents are extremely large compared with the m and p-substituents, and will be discussed separately. The discussion will be confined to rate constant values obtained at 35°.

Table 2.1

Rate Constants (k), and Arrhenius Activation Energies (E)
for the Reaction of L-tyrosine ethyl ester with substituted Benzaldehydes

No.	Substituent	10^3 k (l. mole^{-1} min.$^{-1}$)			E kcal. mole^{-1}
		25°	35°	45°	
1	p-NMe_2	0.08 ± 0.002	0.18 ± 0.005	0.23 ± 0.02	9.7
2	p-OH	0.37 ± 0.017	0.65 ± 0.005	0.99 ± 0.076	8.2
3	p-OCH_3	0.59 ± 0.01	0.94 ± 0.033	1.44 ± 0.045	8.1
4	p-CH_3	2.10 ± 0.04	2.71 ± 0.07	4.67 ± 0.46	7.2
5	None	2.25 ± 0.03	3.86 ± 0.05	6.93 ± 0.30	10.1
6	m-OH	2.72 ± 0.10	4.32 ± 0.19	6.92 ± 0.40	7.8
7	m-OCH_3	2.68 ± 0.20	4.04 ± 0.14	5.90 ± 0.10	7.1
8	p-Cl	2.78 ± 0.05	4.03 ± 0.14	6.18 ± 0.22	7.3
9	m-NO_2	2.51 ± 0.14	4.69 ± 0.18	6.53 ± 0.32	8.8
10	p-NO_2	3.04 ± 0.017	5.07 ± 0.15	7.84 ± 0.74	8.6
11	o-OH	10.55 ± 0.45	18.4 ± 0.83	29.7 ± 1.40	9.4
12	o-OCH_3	7.34 ± 0.36	10.8 ± 0.48	15.6 ± 1.40	7.1
13	o-Cl	3.37 ± 0.05	6.59 ± 0.37	10.45 ± 0.5	10.3
14	o-NO_2	1.37 ± 0.11	2.44 ± 0.23	4.67 ± 0.31	11.0

The high rotatory power obtained in the condensation of the amino ester with substituted benzaldehydes have been attributed to the formation of schiff bases. A representative number of schiff bases of the general formula I. were isolated from reaction mixtures of the ester and various benzaldehydes in aqueous ethanolic solutions. Details of characterization are



X = p-NO_2, p-NMe_2, H, o-OH.

I

provided in Table 2.2. The presence of an azomethine linkage has been shown by infrared studies (Fig. 2.3). The optical rotations of the schiff bases were found to correspond quite well with the α_∞ readings obtained in rate studies.

Table 2.2

N-arylidene Derivatives of L-tyrosine Ethyl Ester

Substituent	m.p.	$[\alpha]_D^{25}$	Yield %		Calculated %			Found %		
					C	H	N	C	H	N
H	78-79	-274	65	White needles	72.7	6.4	4.7	72.8	6.5	4.8
o-OH	138	-311	85	Bright yellow needles	69.0	6.1	4.5	69.4	6.2	4.3
p-NO_2	96-97	-292	70	Pale yellow needles	63.2	5.3	8.2	62.8	5.2	7.9
p-NMe_2 [a]	89-90	-397	75	Cream needles	68.7	7.2	8.0	68.6	7.0	8.0

a. $(C_{20}H_{24}O_3N_2)_2\ H_2O$.

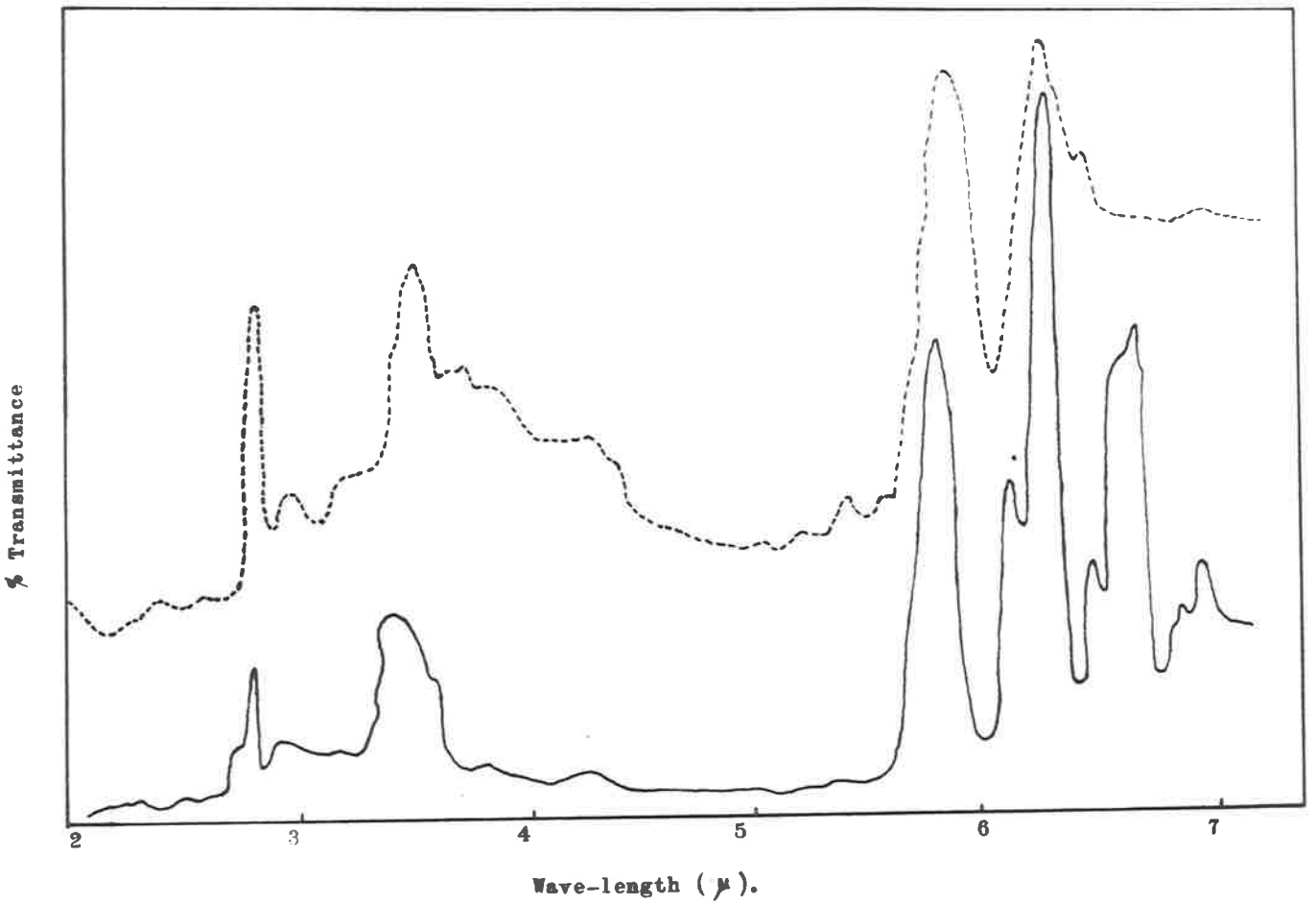


Fig.2.3a. N-salicylidene-L-tyrosine ethyl ester (- - - - - - - -), and
N-p-dimethylaminobenzylidene-L-tyrisine ethyl ester (————).

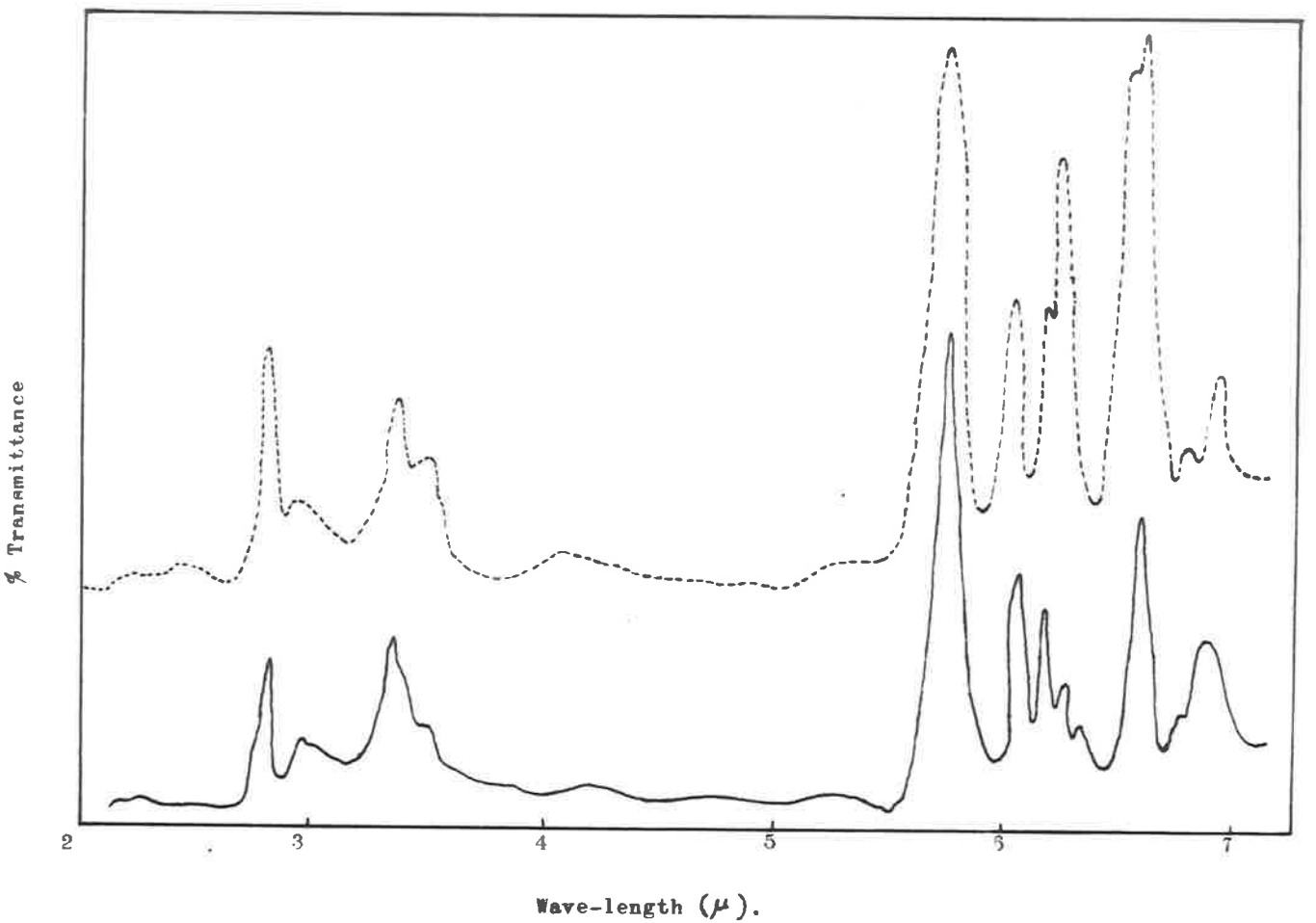


Fig.2.3b N-benzylidene-L-tyrosine ethyl ester (————), and
N-p-nitrobenzylidene-L-tyrosine ethyl ester (- - - - - -).

Discussion

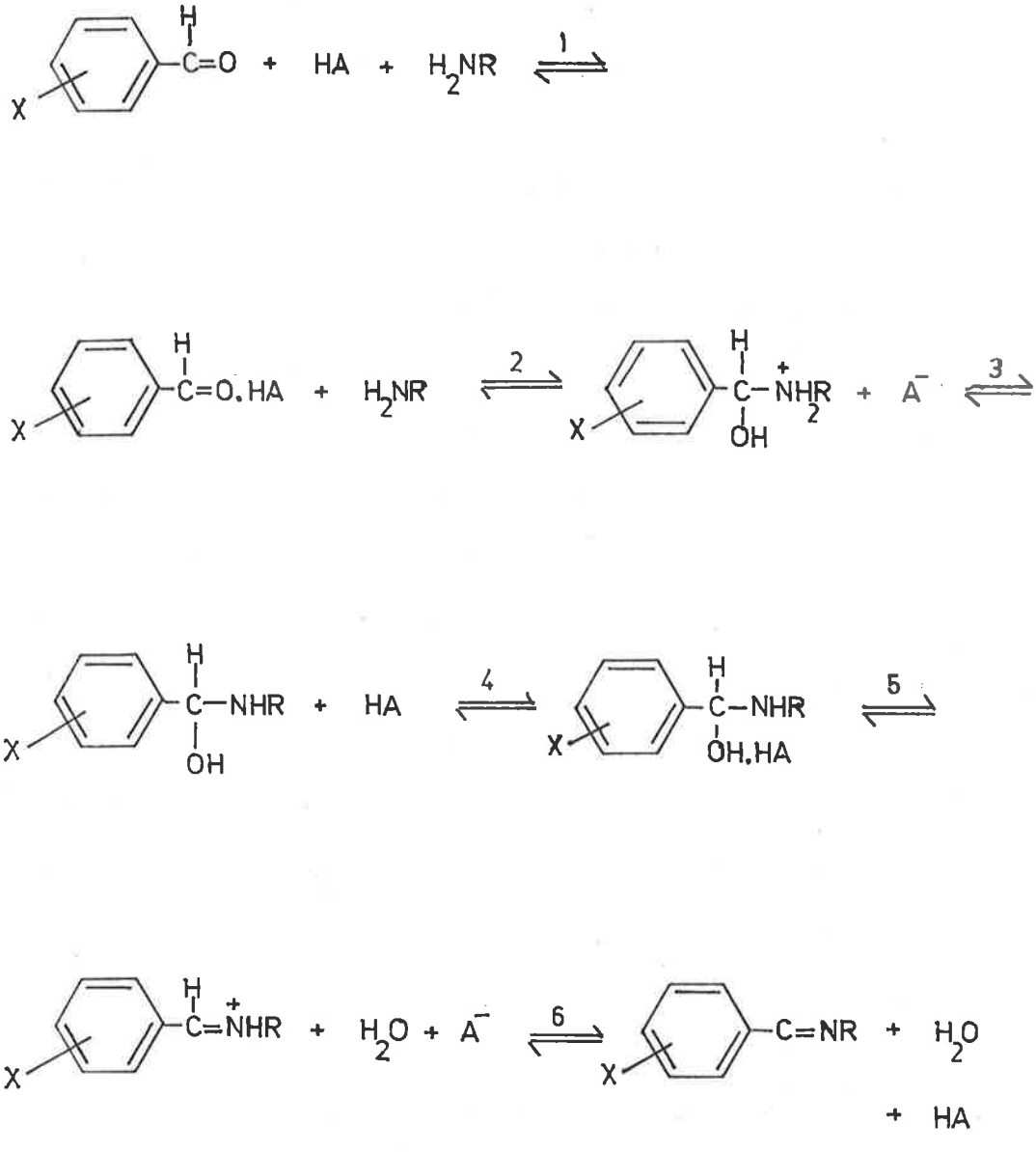
Earlier work carried out on semicarbazone formation and similar reactions has shown that the reaction is an acid catalysed one exhibiting striking maxima in pH-rate profiles.[16-19] These pH-rate maxima have been attributed to the opposing effects of general acid catalysis and the decrease in the concentration of the attacking free nitrogen base due to the conversion to the conjugate acid at low pH. These properties seem to indicate that the condensation of L-tyrosine ethyl ester with substituted benzaldehydes is probably subject to general acid catalysis as well. Although a pH-rate maxima profile has not been obtained similar to the above studies, nevertheless, there seems to be a suggestion of a maximum by the curve shown in Fig. 2.2. No observed change in the optical rotation in the acid region suggests that probably all the amino ester is in the form of its conjugate acid RNH_3^+, thereby reducing greatly the concentration of the free nitrogen base for aldehyde attack. It is perhaps not very surprising when one considers the

fact that L-tyrosine ethyl ester is fairly basic and would readily add on a proton in acid pH.

Increase in temperature invariably increases the rate of a chemical reaction to a marked extent, and for homogeneous processes, the rate is approximately doubled.[20] This has been demonstrated in this series where the rate constants increased by a factor of 1.5 - 2 for every rise of 10^{o} in temperature (Table 2.1.). Little significance can really be placed on the apparent differences between the derived activation energies (E_a) for the different substituents in the aldehyde as the deviation is as large as 1.5 kcal. $mole^{-1}$. Although substituents in the aldehyde ring appear to exert a certain amount of influence in the reaction, no correlation could be obtained from a plot of E_a against the log of the rate constant at 35^{o}, similar to that obtained in rate studies of the hydrolysis of esters,[21] and esterification of acids.[22]

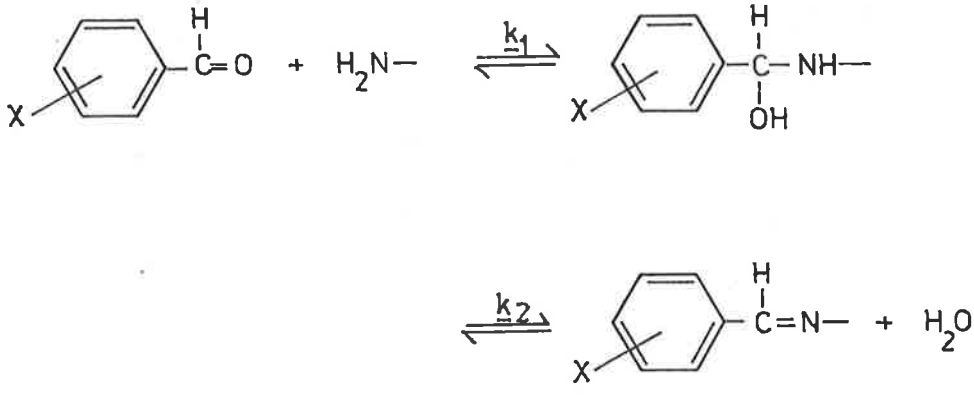
The established general mechanisms of semicarbazone formation and similar reactions[16-19] can be

represented in detail in II.[18]



II

From the evidence obtained above, it may be inferred that the condensation between a benzaldehyde and tyrosine ethyl ester would most likely proceed through a carbinolamine intermediate (IIa). The rate of formation of the schiff base may depend on either the initial co-ordination of the amino ester nitrogen atom with the carbonyl carbon atom of the aldehyde (k_1), or the removal of the hydroxyl group from the intermediate carbinolamine (k_2).

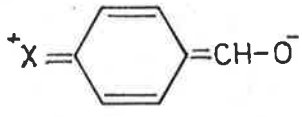


IIa

On these assumptions, one may expect electron attracting substituents in the aldehyde ring to accelerate step k_1, and retard step k_2, while electron donating substituents have the opposite order of effects, i.e. p-nitro groups in the aldehyde would increase step k_1, and

p-dimethylamino substituents would retard step k_1, but increase step k_2. The rate constant (k) values for the whole reaction obtained from the condensation reaction at 35° recorded in Table 2.1 for m and p-substituted benzaldehydes appear to be generally in qualitative agreement with k_1 being the rate determining step.

However, it appears that the effect brought about by electron attracting substituents in increasing the rate of reaction is very small compared with the retardation caused by electron donating groups when log k values are plotted against standard substituent constants (σ), the curve shown by a solid line in Fig. 2.4 is obtained. For consistancy the σ values derived by McDaniel and Brown,[23] from ionization constants of substituted benzoic acids have been adopted. It is plausible that the basic cause of this non-linearity is the existance of para-resonance interaction of the type illustrated in III, leading to a



X = p-NMe_2, p-CH_3, p-OCH_3, etc.

III

marked deactivation of the carbonyl group by strongly electron donating substituents.

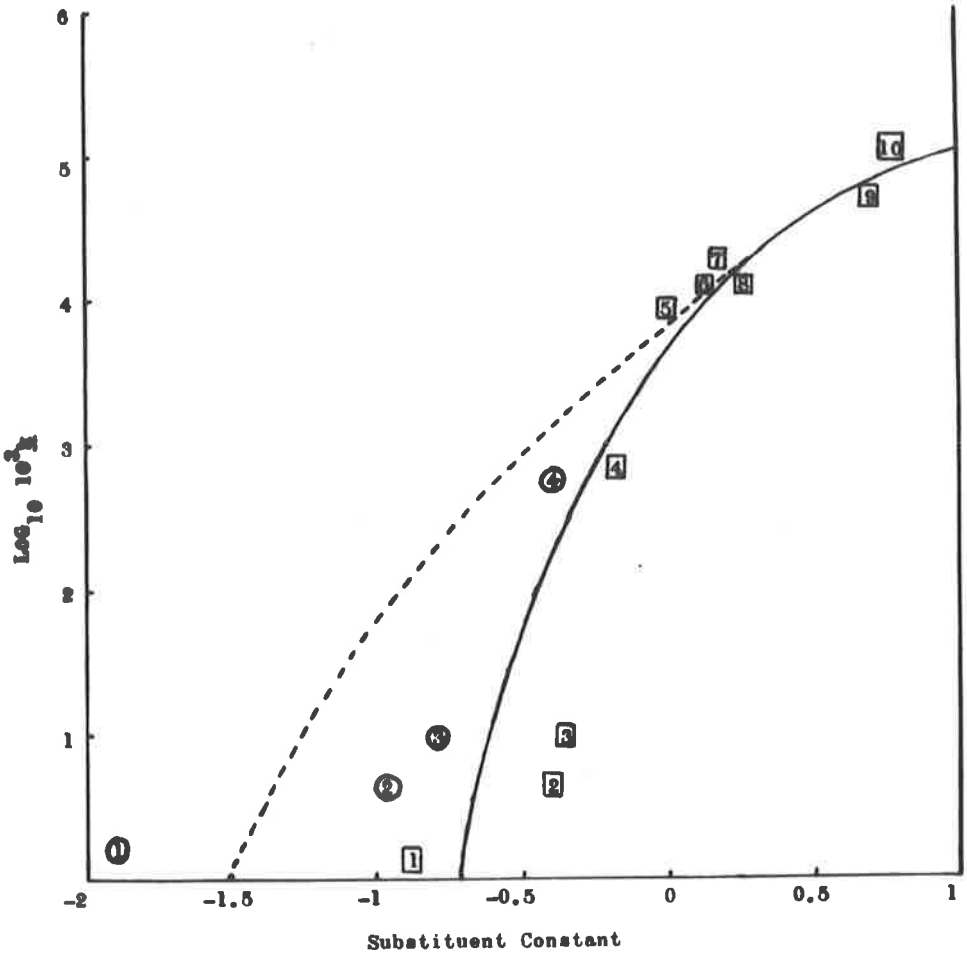
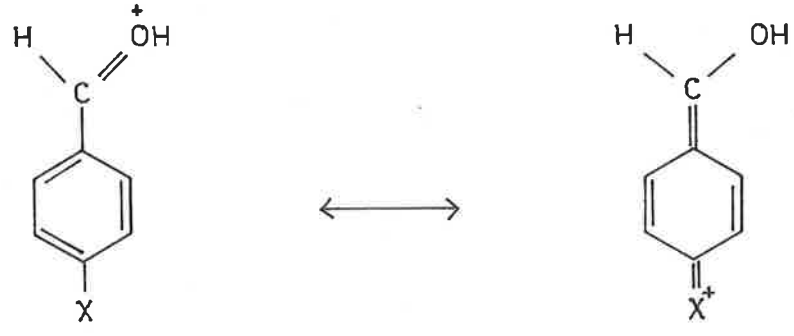


Fig.2.4. Relation between Substituent Constants and Logarithms of Rate Constants (35°) for Reactions of Substituted Benzaldehyde with Tyrosine Ethyl Ester: σ constants[23] (————), σ^+ constants[25,27] (-------)
The key to the number is given in Table 2.1.

The effect of electron donating substituents on the basicities of substituted benzaldehydes have been observed by Stewart and Yates[24] spectrophotometrically in sulphuric acid media. When they plotted the values of $-pk_{BH^+}$ of the substituted benzaldehydes against Hammett's σ constants, the correlation obtained was rather poor. However, they were able to draw a straight line through those substituents which are not able to supply electrons to the negatively charged conjugate acid by direct resonance with the group, i.e. all the meta substituents, and the p-nitro substituent. These substituents are expected to obey Hammett's equation. Values of electron donating substituents viz., p-methyl and p-methoxy were observed by them to fall below the line and this has been explained by the presence of contributing forms like IIIa.



IIIa

These electron donating substituents give higher basicities than their σ values predict owing to increased stabilization of the conjugate acid. It was observed that when the $-pk_{BH^+}$ values were replotted against σ^+ constants,[25] a good linear correlation now exists for both meta and para forms. These σ^+ values have been derived by Brown and Okamoto[25] in studies of the solvolysis of meta and para substituted phenyldimethyl carbinyl chloride. The new σ^+ constants were applied by them to several other reactions which had previously shown great deviations when plotted against Hammett's σ values. These now give good agreements. It is noteworthy that the curvature of a similar curve to that of Fig. 2.4 (solid line) obtained in the plot of carbonyl stretching frequencies of substituted benzaldehydes against σ constants,[26] has also been reduced by the use of these new σ^+ constants of Brown and Okamoto.

When the log k values for the present series of reactions are replotted using σ^+ constants, the curvature is reduced to a certain extent as shown in Fig. 2.4 (broken line). The σ values of 1.79 for p-NMe_2, and 0.96 for p-OH derived by Deno and Evans[27] were used in this correlation. It is quite obvious that the curvature is not entirely eliminated. This indicated that highly exalted values similar to those deduced from the intensities of infrared

$-C\equiv N$ absorption of substituted benzonitriles by Brown,[28] might be necessary to eliminate the curvature entirely. It is not surprising that the ordinary substituent constants are inadequate in cases such as these. Wepster and his co-workers[29] have demonstrated without doubt that a substitient may require a multiplicity of exalted σ values as a result of varying degrees of para-resonance interactions with functional groups. In other words, a substituent which enters into para-resonance interaction with the reaction centre, may expect a multiplicity, a sliding scale of exalted values in addition to the normal constant σ constant. So it is feasible that in this particular case with electron attracting substituents, the activation caused by the above interaction calls for an exalted σ value which is more than the normal σ constant, and similarly, with electron donating substituents, a σ constant value different to the normal is required.

The failure to obtain linear rho-sigma relationship has also been observed by several groups of workers. Of closely related interests are the formation of schiff bases from substituted benzaldehydes and butylamine carried out by Santerre, Hansrote and Crowell,[30] and the formation of semicarbazone from aromatic aldehydes by Noyce, Bottini and

Smith.[31] In both cases completely inverted log k *vs.* σ relationships have been observed almost similar to that in Fig. 2.4 (solid line). Except in their case the reactivities of the aldehydes with strongly electron attracting groups have been less than benzaldehyde *i.e.* the rate constant value for *p*-nitro is less than the value for benzaldehyde. A possible mechanistic interpretation was put forward by these workers that the first step of condensation (k_1), and the second step of dehydration (k_2) are probably comparable in rate (see IIa). This implies that electron attracting substituents might retard the second step of dehydration sufficiently to render it effectively rate determining. Of significant importance in this respect is the spectrophotometric studies of Jencks,[32] Jencks and Anderson,[33] in the mechanism of semicarbazone and oxime formation. They made use of the fact that the ultraviolet absorption spectrum of the aldehyde is very similar to that of the semicarbazone and oxime. (The only difference is a slightly higher absorbance in the products). If the second step of dehydration is rate determining *i.e.* slow, then an accumulation of the carbinolamine intermediate would result. This would bring about a marked decrease in the absorption spectrum as the carbinolamine is non-absorbing at the wave-length studied. These workers

have been able to detect the presence of the intermediate carbinolamine and thus obtained rate constants for the individual steps of addition and dehydration. The rate constants for each step were plotted against Hammett's σ constants and gave very good correlation. They further demonstrated that at acid pH of 1.75 and alkaline pH of 10 or above, electron attracting substituents increase the rate constant i.e. k_1 is rate determining, and at neutral pH, the rate is dependent on the addition product (which is dependent on step k_1), and on k_2, the dehydration step (see IIa). The opposing effects cancel each other and they obtained only very slight variation with substituent effects. Apparently the pH of the medium plays an important part in determining which step of the reaction is rate controlling.

The schiff bases isolated in this series have been observed to possess the same ultraviolet absorption as the corresponding aldehydes, i.e. N-salicylidene-L-tyrosine ethyl ester, has exactly the same absorption spectrum as salicyldehyde. The condensation has been carried out at an apparent pH of 8.3. Ultraviolet studies at this pH of a mixture of L-tyrosine ethyl ester (4×10^{-5} M) and the aldehyde (4×10^{-5} M) did not indicate the presence of a non-absorbing addition compound. The interpretation of negative results here is difficult because of the high dilution used.

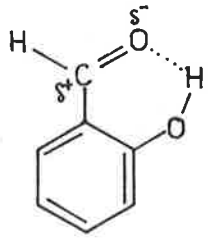
It would appear that perhaps to a certain extent the rate of reaction is dependent on the dehydration step. If one considers the position to be between that of a neutral, and alkaline condition of Jencks' semicarbazone formation, then the rate would be dependent on the equilibrium concentration of the carbinolamine, the addition and the dehydration steps. This would mean that electron attracting substituents would exert a less effect on the rate of the reaction than they normally would, and electron donating substituents a greater effect than normal. However, it is more feasible that the major contribution to the non-linearity of the log k vs. σ constant in this case is the presence of para-resonance interaction.

The rate constants of ortho-substituted benzaldehydes with L-tyrosine ethyl ester when compared to the corresponding p and m-substituted compounds are anomalous, i.e. they exhibit unusually high reactivities (Table 2.1). Hydroxy and methoxy substituents in the ortho position of the aldehyde activate the carbonyl function greatly, while chloro and nitro groups cause slight activation and deactivation. From the electronic properties of nitro groups, the o-nitro substituent could be expected to exert a certain amount of activation. Apparently in this case, ortho effects play an important role, and it is likely that

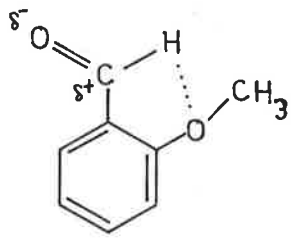
the effect is sufficiently powerful here to mask the ordinary inductive and mesomeric effects. The unusually high reactivities of o-hydroxybenzaldehyde and o-methoxybenzaldehyde have been observed by Vavon and Montheard[34] in their condensation reaction studies. They have shown that the formation of phenylhydrazones, semicarbazones, oximes and schiff bases to be much faster with these two aldehydes when compared to the corresponding p-substituted ones. This behaviour however, was not observed by these workers to occur with the corresponding ketones. They attributed this marked accelerating influence of the o-hydroxy, and o-methoxy groups in the aldehydes to the formation of chelate rings. In the case of salicyldehyde, the formation of the chelate ring would take place between the hydrogen of the hydroxyl and the oxygen of the carbonyl group of the aldehyde (IV). With o-methoxybenzaldehyde the chelation would have to occur between the hydrogen of the aldehyde and the oxygen of the methoxyl group (IVa). For these o-substituted aldehydes to cause such high reactivities, their effect must be one where the carbonyl carbon is somehow made more positive so as to facilitate the attack by the lone pair of electrons of the nitrogen in the amino ester.

The existence of an intramolecular hydrogen bond in o-hydroxybenzaldehyde (IV) is well established and supported

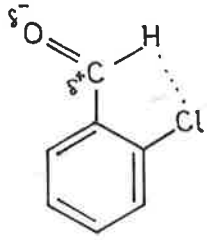
by infrared evidence.[35] This may account for an increase



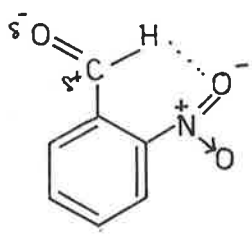
IV



IVa



IVb



IVc

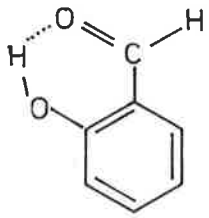
in the partial positive charge on the carbonyl carbon atom, making it more favourable for attack by a nucleophilic group, which in this case is provided by the lone pair of electrons from the amino nitrogen of the ester. Similarly, the presence of hydrogen bonding in o-chlorobenzaldehyde (IVb), o-methoxybenzaldehyde (IVa) and o-nitrobenzaldehyde (IVc) have also been established by infrared evidence.[36] However, in the last two compounds, the carbonyl hydrogen must be bonded to the o-group (IVa, IVc). In o-chlorobenzaldehyde (IVb) the bond is formed between the hydrogen of the carbonyl and the chlorine atom.

One must not overlook the fact that direct field effects could contribute in modifying the reactivity of the

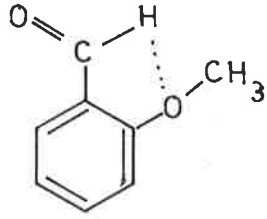
carbonyl function. Direct field effects by chloro and alkyl groups have been known to increase the acidity of an acid.[37] Although more evidence is necessary, it may be tentatively suggested that electron attraction by o-methoxy and o-chloro substituents operating through a direct field mechanism in some way intensifies the positive charge at the reaction centre. With o-nitrobenzaldehyde one would have expected the rate of reaction to be much faster if effects of chelation and direct field effects come into play. However, steric hindrance here could well cause a certain amount of loss of reactivity as the nitro group being large would make the approach of the amino ester to the carbonyl carbon atom more difficult. At the same time the nitro group could be thrown out of plane with the benzene ring, reducing the mesomeric effect. In addition, deactivation of the aldehyde function by the o-nitro group can also be attributed to the partial neutralization of the positive charge at the reaction centre, by the presence of a nearby oxygen atom (IVc). It would appear that to explain the reactivities of o-substituted benzaldehydes, hydrogen bonding, ortho effects, and steric hindrance must all be taken into consideration.

These o-substituted benzaldehydes are interesting with regard to the nature of the ortho group. They are similar to pyridoxal (V) and its analogues. The observation obtained above may have some bearing on the reaction of

pyridoxal and ∝-amino compounds. Interest in this field has been shown by the preparation of pyridoxal analogues by several workers.[38,39] Of these 4-nitrosalicyldehyde was found to be of importance because its electron distribution

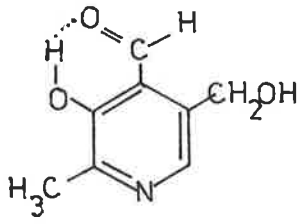


VI

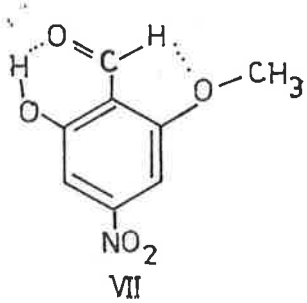


VIa

is very closely related to that of pyridoxal, and have been shown to behave in the same manner as pyridoxal towards certain amino acids. The essential substituents appear to be the hydroxyl group in the <u>ortho</u> position for hydrogen bonding with the metal, an electron attracting group which could be a p-nitro substituent. The carbonyl groups in salicyldehyde (VI) and o-methoxybenzaldehyde (VIa) lie respectively <u>s-cis</u> and <u>s-trans</u> to the <u>o</u>-substituent. It



V



VII

is therefore possible that the <u>o</u>-methoxy group, because of its high reactivity could contribute in forming a compound of the type 6-methoxy-4-nitro-salicyldehyde (VII) which could prove to be an interesting pyridoxal analogue.

Part II

In the studies of the rates of condensation of L-tyrosine ethyl ester with substituted benzaldehydes (Part I), the schiff base N-salicylidene-L-tyrosine ethyl ester was observed to be prone to racemization. The melting point of the schiff base was found to increase with repeated recrystallization in absolute ethanol. At the same time a gradual loss of optical activity occurred (Table 2.3). The optically active and inactive schiff bases both have the same empirical formulae and crystalline forms. It may be noted here that the only case reported in the literature very similar to this is that of N-salicylidene-tyrosine methyl ester which melted at 147°, but on further very slow heating solidified, and sharply melt again at a higher temperature of 165°.[40] However, these workers did not explain it in terms of optical activity.

Under the mild conditions of recrystallization it is surprising that the schiff base should lose its optical activity so readily, and it would be interesting to investigate the cause of the instability. This was hoped to be achieved by comparing it with very similar schiff bases which have slightly different groups around the asymmetric centre, and also by comparing it with other N-arylidene-

Table 2.3

Table showing the Effect of Recrystallization on the Optical Activity of N-salicylidene-L-tyrosine ethyl ester

No. of recrystallization	m.p.	$[\alpha]_D^{25^\circ}$ *
None	138°	-311°
1st	139 - 142°	-200.6°
2nd	141 - 143°	-163.6°
3rd	142 - 144°	- 64.0°
4th	145 - 149°	- 6.4°
5th	153 - 154°	± 0.0°

* Observed in ethanol.

L-tyrosine ethyl ester.

The racemization studies of the optically active schiff bases were followed polarimetrically in ethanol at 45° in the presence of pyridine, triethanolamine, sodium ethoxide, and cupric ions. The effect of the various bases on N-salicylidene-L-tyrosine ethyl ester (Fig. 2.5) was found to follow the order of

NaOEt > triethanolamine > pyridine > no base.

In every case, the greater the concentration of base or metal used, the faster is the loss of optical activity.

The configurational stability of N-salicylidene-L-tyrosine ethyl ester (VII), when compared with that of N-salicylidene-α-phenylglycine ethyl ester (VIIa), and N-salicylidene-α-phenylethylamine (VIIb) in the presence of the bases have shown the schiff base from tyrosine ethyl ester (VII) to be more stable than that from α-phenylglycine ethyl ester (VIIa), but less stable than the α-phenylethylamine derivative (VIIb). The time for half racemization is given in Table 2.4. It must be pointed out that N-salicylidene-α-phenylethylamine did not show any sign of racemization even after being fused for 100 hours.

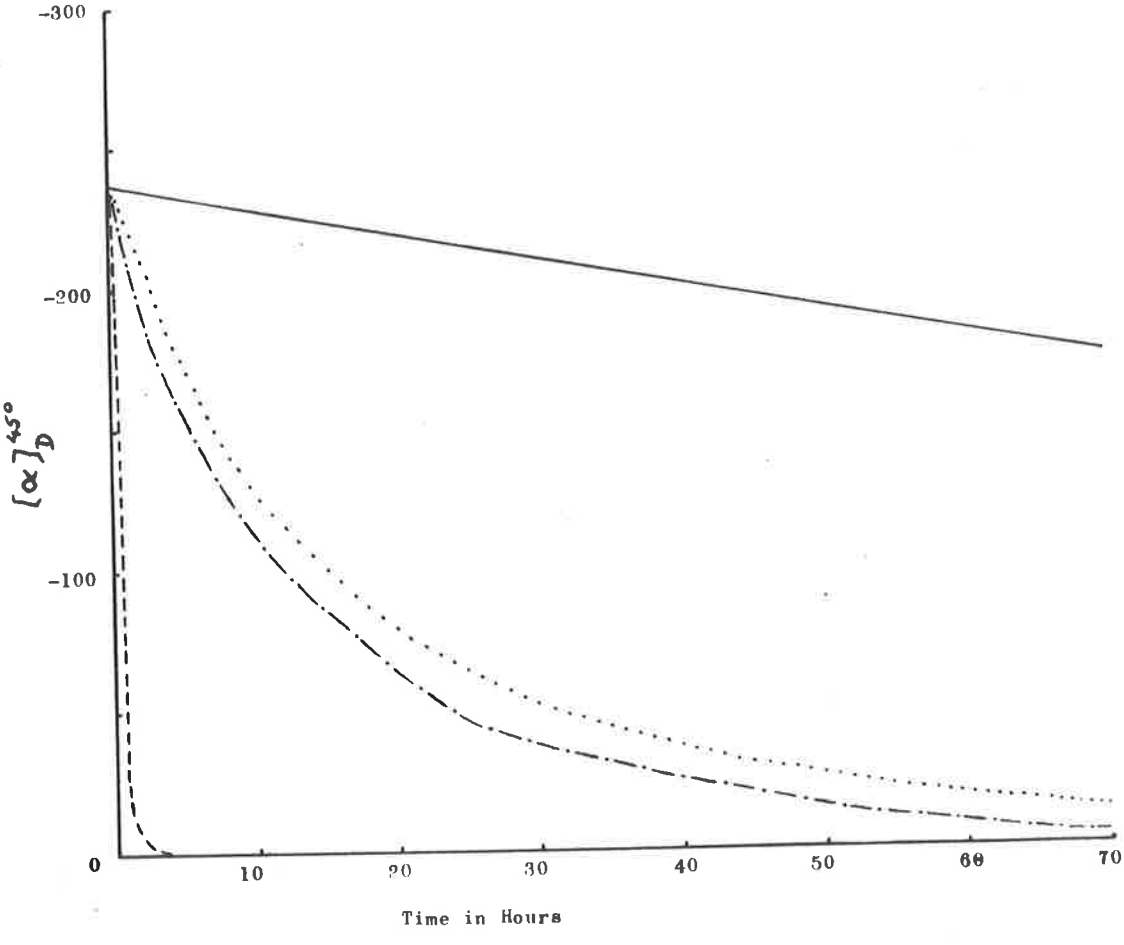
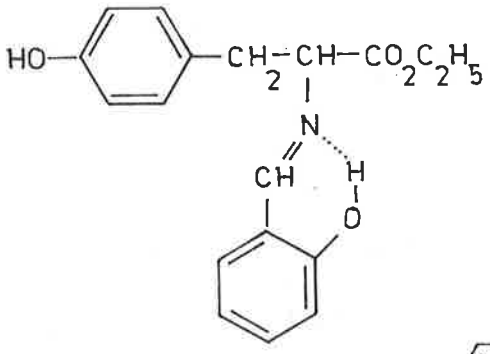
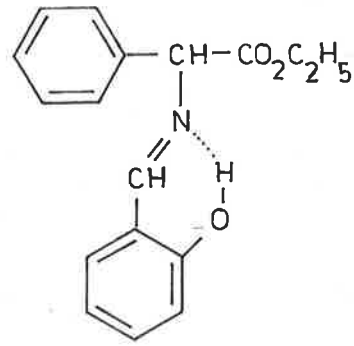


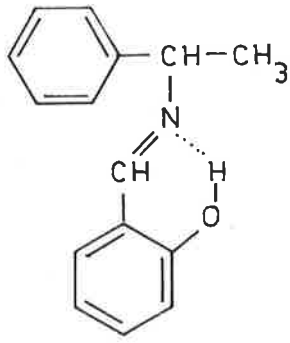
Fig.2.5 Rate of racemization of N-salicylidene tyrosine ethyl ester in the presence of sodium ethoxide (– – – – –), triethanolamine (—·— – –), pyridene (· · · · · · ·), and standard (————).



VII



VIIa



VIIb

The stability of N-salicylidene-tyrosine ethyl ester was also compared with other N-arylidene derivatives of tyrosine ethyl ester, viz. N-benzylidene-, N-p-dimethyl-aminobenzylidene, and N-p-nitrobenzylidene. Table 2.4 shows the time for half racemization of these schiff bases in the presence of base and copper. It appears that the N-salicylidene schiff base racemizes faster in every case, except in the case when no base was used, the p-dimethyl-aminobenzylidene derivative racemized more readily.

Table 2.4

Racemization of N-arylidene derivatives of tyrosine ethyl ester, N-salicylidene-α-phenylglycine ethyl ester, and N-salicylidene-α-phenylethylamine

N-arylidene L-tyrosine Ethyl Ester	Time for half racemization in Hours				
	None	Cu^{++}	NaO Et	Pyridine	Triethanolamine
o-OH	120	4	0.24	13	9
p-NO_2	216	9	6	120	91
p-NMe_2	75	7	32	60	39
H	336	63	36	288	264
N-salicylidene-α-phenylglycinate	6	-	0.05	5	5
N-salicylidene-α-phenylethylamine*	∞	∞	∞	∞	∞

* The schiff base did not racemize at all under the experimental conditions.

It was found that the optically inactive schiff bases obtained thermally by fusion could be isolated and characterized readily. Details are shown in Table 2.5. The optically inactive and active forms possessed very similar properties and the same empirical formula. However, attempts to isolate the optically inactive schiff base from other racemization reactions, i.e. in the presence of base and cupric ion, were not successful, except in the case of the N-salicylidene derivatives. All these optically inactive N-salicylidene schiff bases were recovered in quantitative yields and showed the same properties as that obtained thermally. The copper complex of N-salicylidene ethyl tyrosine ester was found by analysis to be made up of two molecules of the schiff base, to one of copper. The presence of a copper complex in the other cases have been indicated by the green colour of the solution which apparently is quite a typical colour for copper complexes of this type.[13]

Hydrolysis of the optically inactive N-arylidene tyrosine ethyl ester with ethanolic hydrogen chloride in every case yielded the optically inactive amino ester or acid, and the corresponding aldehyde. The aldehydes were recovered in qualitative yields and identified as their 2:4-dinitrophenylhydrazone or semicarbazone. The amino

Table 2.5

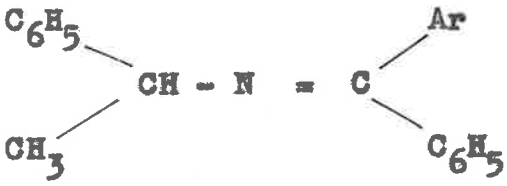
Optically Inactive N-arylidene Derivatives of Tyrosine Ethyl Ester and ∝-phenylglycine Ethyl Ester

N-arylidene tyrosine Ethyl Ester	m.p.	Racemisation time by fusion	Yield %		Calculated %			Found %		
					C	H	N	C	H	N
H	105 - 106°	75 mins.	90	White needles	72.7	6.4	4.7	72.8	6.5	4.6
o-OH	153 - 155°	7 mins.	98	Bright yellow needles	69.0	6.1	4.5	69.2	6.1	4.5
p-NO_2	85 - 86°	10 mins.	90	Pale yellow needles	63.1	5.3	8.2	62.8	5.3	7.9
p-NMe_2	114 - 115°	9 mins.	95	Straw needles	70.6	7.1	8.2	70.3	6.9	8.2
N-salicylidene-∝-phenylglycinate	80 - 81°	60 mins. over steam bath	100	Bright yellow needles	72.1	6.1	4.9	71.9	6.0	5.0

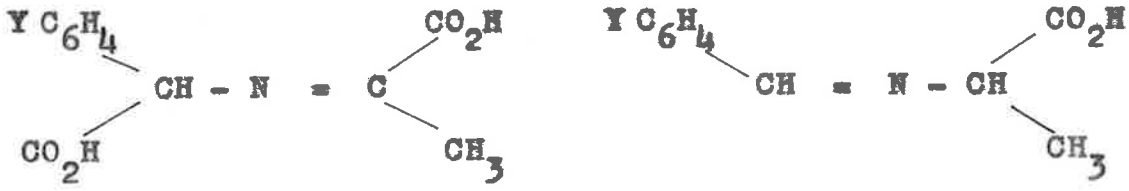
ester or acid were tested for a free amino group by using ninhydrin, and further proved by making a benzoyl derivative. From the results it appears that no tautomerism had occurred in racemization otherwise hydrolysis of the optically inactive product would have yielded a keto ester (p-hydroxyphenylpyruvic ester), and an aromatic amine (a benzylamine with a substituent in the aromatic ring).

Discussion

The loss of optical activitiy with compounds containing an azomethine linkage is well known.[41,42] In every case it is the lability of the hydrogen atom attached to the asymmetric carbon atom that is the cause of the loss of optical activity. The systems that have been studied are of the type VIIIa,[41b] where the rate of racemization is equivalent to its isomeride change, and VIIIb,[42] where the rate is dependent on the formation of carbon dioxide. Baddar and his co-workers[43] in their studies of the effect



VIIIa.



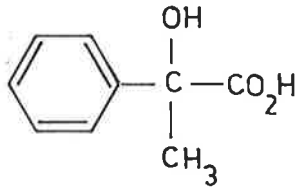
VIIIb.

of substituents on the mobility of azomethine carboxylic acid

attribute the prototropy to decarboxylation of the acid group, as no tautomerism was observed to occur with the corresponding ester. In general, all these workers observed an increase in the racemization of the schiff base with electron attracting substituents and phenyl groups. However they were mainly interested in the prototropy of the azomethine linkage. The loss of optical activity occurring by enolization is well established.[44,45,46] The enolization of optically active ketones and amides have been shown by McKenzie and his co-workers[44,45] to result in racemization VIIIc. Enolization destroys the asymmetry of the molecule,

VIIIc

and hence when the enol reverts to the keto form the probability of obtaining the d-form is equal to the probability of obtaining the l-form. This results in a racemic modification. Enolization has been shown[44] to occur only when a hydrogen atom is attached to the asymmetric carbon, e.g. atrolactic acid (IX) is very stable, and this is attributed to the fact that no hydrogen atom is present in the asymmetric centre, and hence enolization is not possible.

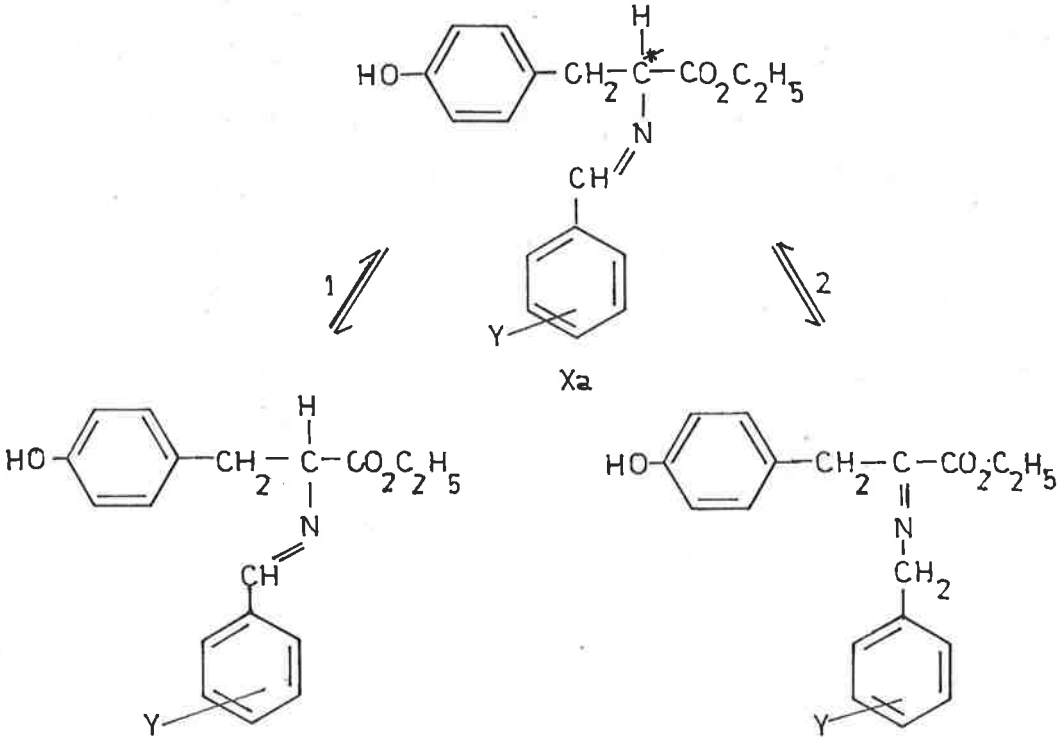


IX

It would appear in this case that the loss of optical activity of the N-arylidene derivative of L-tyrosine ethyl ester can be attributed to the lability of the hydrogen atom attached to the asymmetric centre. α-Hydrogen adjacent to a carbonyl function of an ester group is known to be activated, and in this case would probably explain the ease of racemization of these schiff bases. Racemization brought about by the presence of copper is probably slightly different from that brought about by the presence of base, and will be discussed separately.

The mobility of the asymmetric hydrogen atom could result in either of two products, both being optically inactive. One is the removal of the labile hydrogen atom, and its recombination to the same carbon atom, but the resulting product is optically inactive (Xb). The other is the migration of the labile hydrogen in a 1:3 shift to give the tautomer (Xc). The resulting molecule no longer

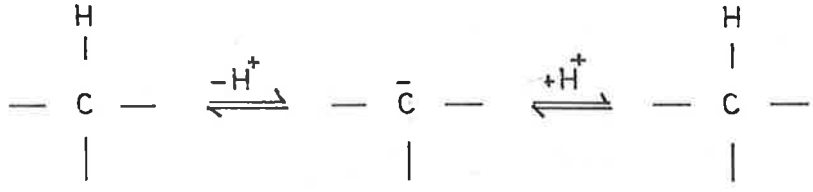
possesses an asymmetric carbon and the product obtained is therefore optically inactive.



It is quite apparent from the hydrolysis products of racemized schiff bases that pathway one (Xb) is more likely than pathway two (Xc). However, one must not overlook the fact that hydrolysis of the schiff bases at the position of the azomethine linkage (-C=N-) would also result in a loss of optical activity as the optical rotation of the amino ester is very small ($[\alpha]_D$ + 18°) compared to

that of the schiff base ($[\alpha]_D$ > -250). In any case, the isolation of racemized products in good yields seems to indicate that hydrolysis of the -C=N- is quite unlikely (Table 2.5).

The loss of optical activity of the schiff base (XIa) is probably brought about first by the expulsion of the α-hydrogen as a proton, and the formation of the rest of the molecule into a carbanion (XI). The activation of the asymmetric hydrogen is most likely caused by the attraction of electrons by the carbonyl function of the ester group. On reassociation of the carbanion with the proton, either isomer could be possible (XIa or XIb). This therefore results in a loss of optical activity. Isotopic studies



tetrahedral planar planar

XIa XI XIb

in deuterium oxide have shown that the rate of racemization is equivalent to the rate of exchange of the asymmetric hydrogen for deuterium.[41c,47] The formation of carbanions in the presence of base such as hydroxyl and acetate ions, and pyridine is well known.[48] Apparently the carbanion is obtained by attack of the base on the acidic hydrogen.

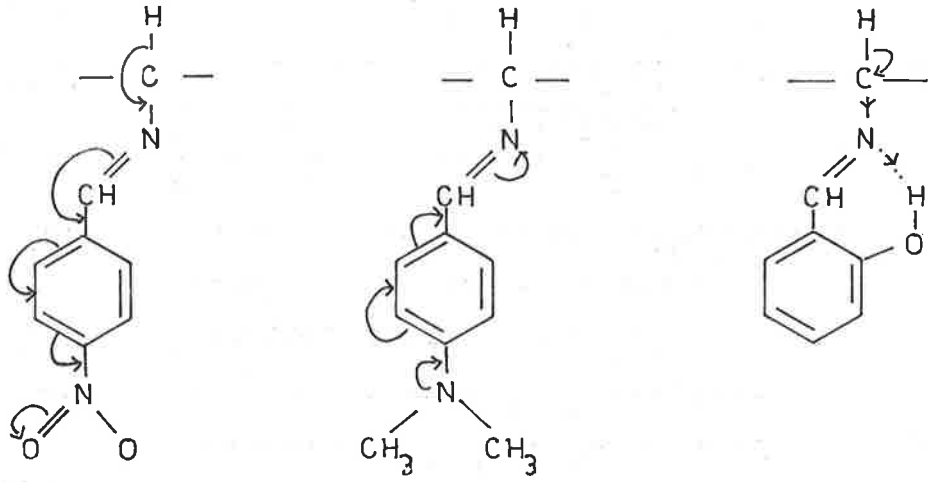
Formation of a sodio derivative in the presence of sodium ethoxide has been demonstrated by Kenyon and Young.[49] They demonstrated that disubstituted acetic acid and esters formed a sodio derivative $\left[(RR^1\bar{C}HCO_2Et)\ \overset{+}{N}a\right]$ in the presence of sodium ethoxide. This results in a release of the proton in the α-carbon bringing about a loss of asymmetry.

The configurational stability of N-salicylidene-L-tyrosine ethyl ester (VII) was compared with that of N-salicylidene-α-phenylglycine ethyl ester (VIIa), and N-salicylidene-α-phenylethylamine (VIIb), with respect to the effect different groups have on the asymmetric centre. From the results (Table 2.4) it is quite apparent that the presence of the ester function is essential for promoting racemization. The necessity of the ester group in racemization has also been observed by Japanese workers.[50] They found that p-nitrobenzylidene methionine did not show any tendency to racemize while the corresponding ester racemized readily. N-Salicylidene-α-phenylglycine ethyl ester (VIIa), being less stable than N-salicylidene tyrosine ethyl ester (VII), seems to indicate that the extra activating influence comes from the phenyl radical. In the case of the former, the phenyl group is conjugated to the asymmetric centre, but in the case of the latter, conjugation of the aromatic ring to the centre of optical

activity is prevented by the presence of the methylene group. Phenyl groups are electrophilic, and when they are directly attached to an asymmetric centre, they activate it by assisting in the expulsion of the α-hydrogen.[42b,44b,51] However, the overall effect of the activation of the asymmetric hydrogen is probably governed by the presence or absence of the ester group. This is demonstrated by the optical stability of N-salicylidene-α-phenylethylamine (VIIb). This schiff base can be expected to undergo a certain amount of racemization because of the influence of the phenyl group. However it is extremely stable and this has been attributed to the absence of the ester function, and the presence in its place of an electronegative methyl group.

Considering the N-arylidene derivatives of L-tyrosine ethyl ester, substituents in the aldehyde moiety appear to have an effect on the stability of the schiff base (Table 2.4). The effect of the substituent on the asymmetric centre can be transmitted through the azomethine linkage (XII). The ease of racemization of the N-salicylidene derivative can be further attributed to hydrogen bonding (XIIc). The formation of a bond between the azomethine nitrogen and the phenolic hydrogen will result in an attraction of the lone pair of electrons of the

nitrogen to the new ring. This would tend to draw electrons



XIIa XIIb XIIc

from the asymmetric carbon toward the nitrogen and in this way the ionization of the proton is made easier. Similarly nitro groups could facilitate the removal of the proton by its electron attracting properties (XIIa). Not only mesomeric but inductive effects occur as well. Thus the effect caused by o-hydroxy substituent is greater than that caused by nitro groups as the former is closer to the reactive centre. The behaviour of the p-dimethylamino schiff base appears to be anomalous. One would have expected by electronic effects that the racemization of this schiff base would be slow in comparison to the p-nitro and salicylidene derivatives. Its electron donating effect would tend to retard the ionization of the proton. However

results have shown that the p-dimethylaminobenzylidene anil racemizes more readily than the other N-arylidene derivatives when heat alone was used; when the base pyridine was used it racemized more readily than the p-nitrobenzylidene derivative (Table 2.4). The rate of racemization when no base is used, and in the presence of pyridine are very slow ones compared to the racemization reactions in the presence of sodium ethoxide and triethanolamine. If one considers the mechanism of racemization in this case, where the ionization of the proton constitute one step and the addition of the proton another. Electron donating substituents would increase the charge of the carbanion (XI) and thereby make it more reactive towards any proton attack, but electron attracting substituents would decrease the charge on the carbon, neutralizing it and therefore make it more stable. Perhaps in the very slow racemization reactions, the second step could become rate-controlling. This would mean that electron donating substituents would increase the second step while electron attracting substituents retard it. This could afford an explanation to the behaviour of the p-dimethylaminobenzylidene anil. However, one must remember that the major cause of racemization here is the activity of the asymmetric hydrogen being adjacent to an ester group, and that the effect caused

by other substituents in the schiff base is only secondary.

The ease of isolation of the N-salicylidene-L-tyrosine ethyl ester is mainly due to the presence of hydrogen bonding. Infrared data of the schiff base have indicated that the bond is a very strong one (Fig. 2.3a, Part I). McIntire[52] in his study of schiff bases from amino acids and aromatic aldehydes recorded the isolation of those schiff bases which were formed from aldehydes with an o-hydroxy substituent. He attributes the ease of isolation to the stability of the schiff base caused by hydrogen bonding of the phenolic hydrogen and the nitrogen of the azomethine linkage. Other workers[53] also reported the isolation of schiff bases from amino acids and aromatic aldehydes, only when the aldehyde possessed an o-hydroxy substituent.

The study of inner complexes involving copper, an amino compound and salicyldehyde is wide and varied.[2,3,13,53,54] The resulting copper complex formed normally possess two molecules of the amino component and salicyldehyde, to one of the copper.[13,53,54] Optically active complexes as well as optically inactive ones have been isolated. The copper has four donar sites and the four groups co-ordinated to it are all in one plane. Copper complexes with six donar sites are quite common.[55]

They usually have a tetragonal bipyramidal structure where the two extra groups are made up by water molecules. The water molecules are situated one above and one below the plane.

Racemization of an amino ester brought about by the formation of a complex has been observed by Pfeiffer and his co-workers.[13] Of closely related interest is the formation of a complex from copper, optically active ∝-phenylalanine ethyl ester and salicyldehyde. The product obtained was optically inactive and hydrolysis yielded the dl-∝-phenylalanine ethyl ester and salicyldehyde. They attribute the loss of optical activity to the lability of the hydrogen attached to the asymmetric centre. It would appear that in this case, the loss of optical activity of the N-arylidene derivatives of L-tyrosine ethyl ester can be caused by the formation of a copper complex. Although only the copper complex from the N-salicylidene schiff base was isolated, the presence of it in the others have been indicated by the familiar green colour of the solution.[13,54] In addition it is also shown by the faster rate of racemization of these schiff bases in the presence of copper as compared to when no copper was used (Fig. 2.6). The only indication that an optically active copper complex have been formed is the higher rotation observed for zero-time

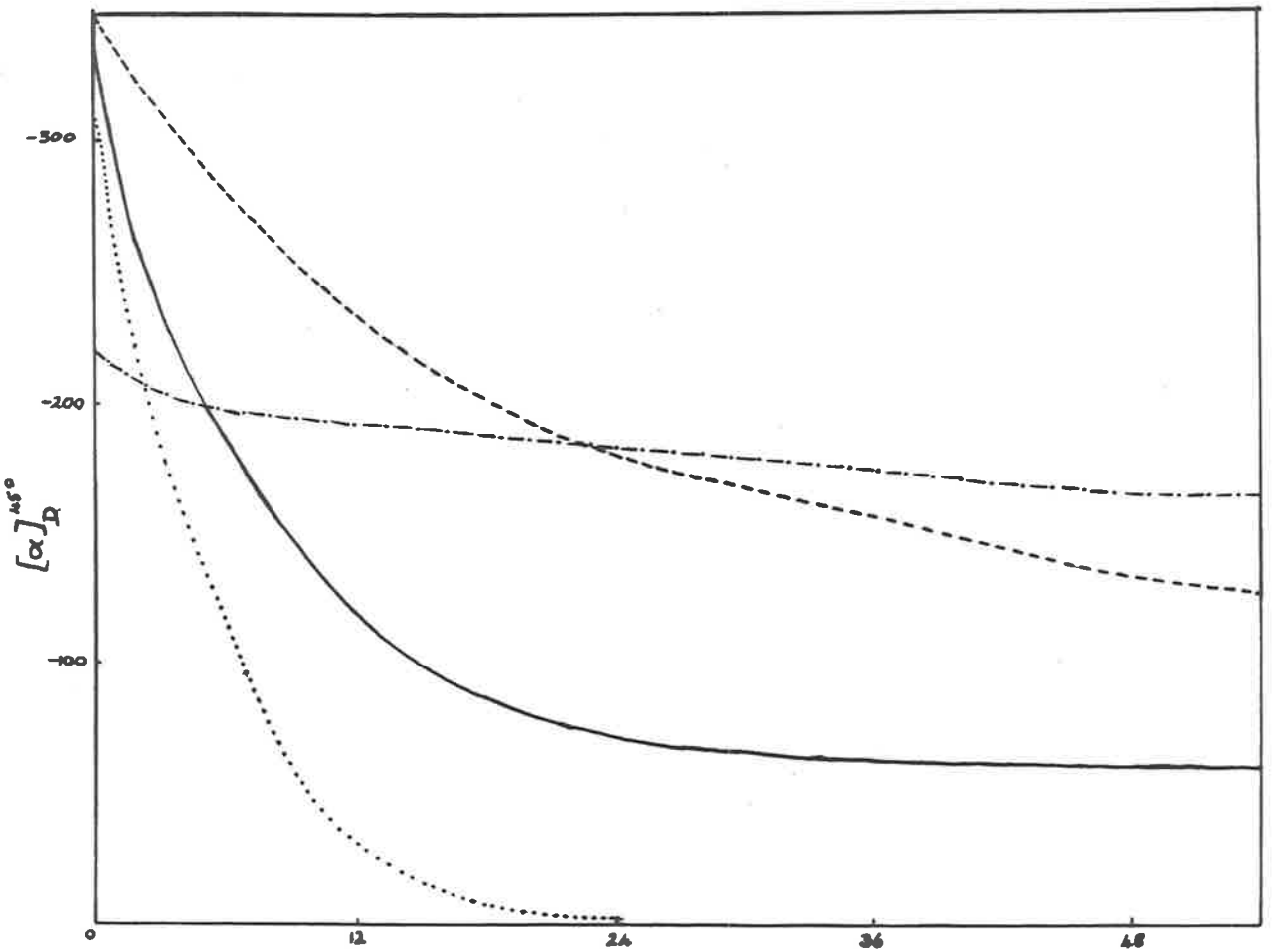


Fig.2.6a. N-salicylidene-tyrosine ethyl ester with Cu. (·····), without Cu. (-·-·-·-), N-p-dimethylaminobenzylidene-L-tyrosine ethyl ester with Cu. (———), without Cu. (- - - - -).

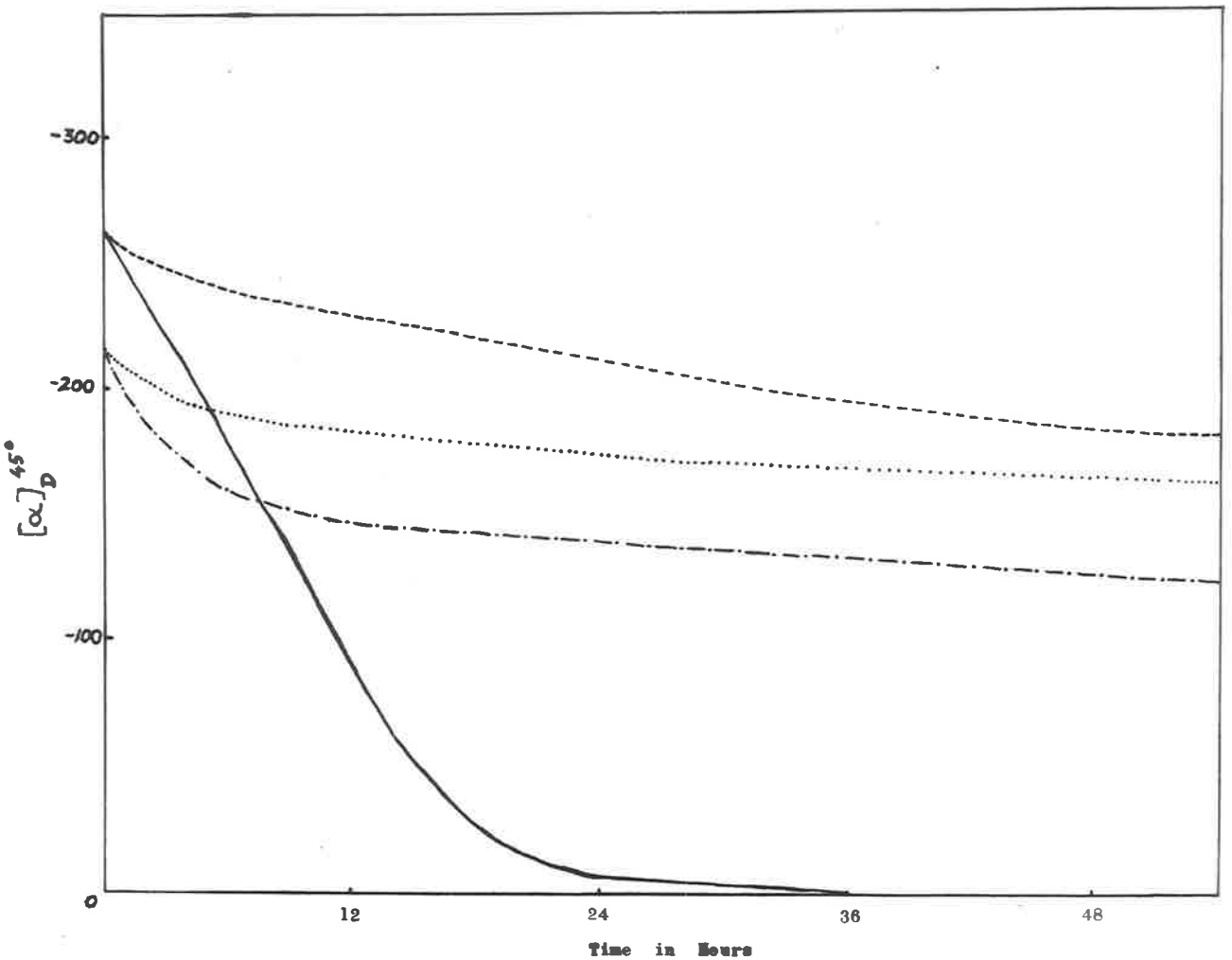
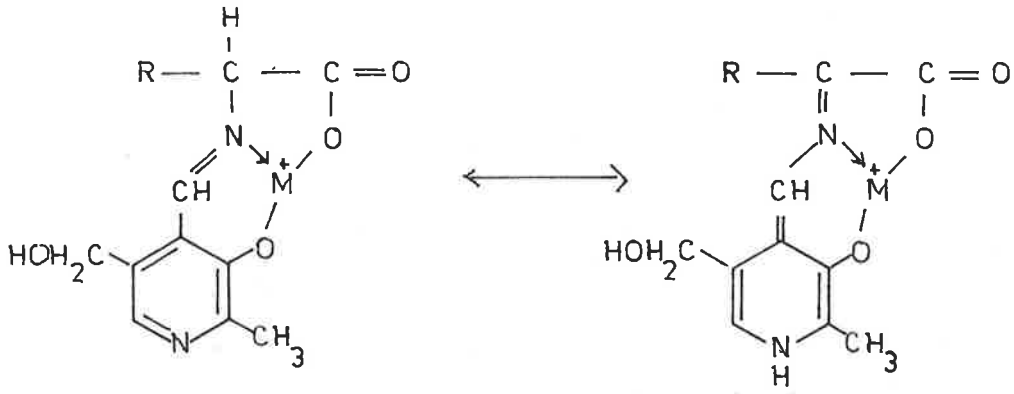


Fig.2.6b. N-p-nitrobenzylidene-tyrosine ethyl ester with Cu. (————), without Cu. (- - - - - -); N-benzylidene-L-tyrosine ethyl ester with Cu. (-·-·-·-), without Cu. (·····).

rotation when the N-salicylidene schiff base was racemized in the presence of copper. The rotation obtained is higher than the one obtained when no copper was used (Fig. 2.6a). It is quite apparent from the graph that the optically active complex was most unstable and rapidly lost its optical activity.

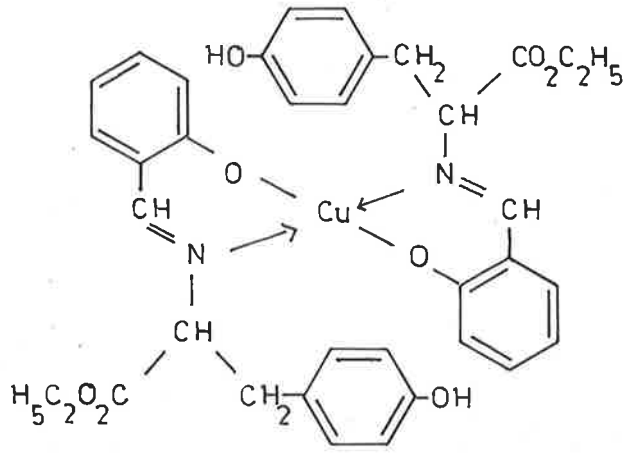
Snell and his co-workers[2,3] postulated the formation of an intermediate like (XIII) in transformation reactions of α-amino acids and pyridoxal and its derivatives. The formation of the schiff base provide a



XIII M = metal. XIIIa

conjugated system of double bonds from the electron attracting group (i.e. the pyridine nitrogen) to the site of reaction (XIIIa). The metal being electropositive would tend to draw electrons towards it, making the formation of the carbanion easier. The carbanion formed is then stabilized by hydrogen bonding. From that, several reactions can occur

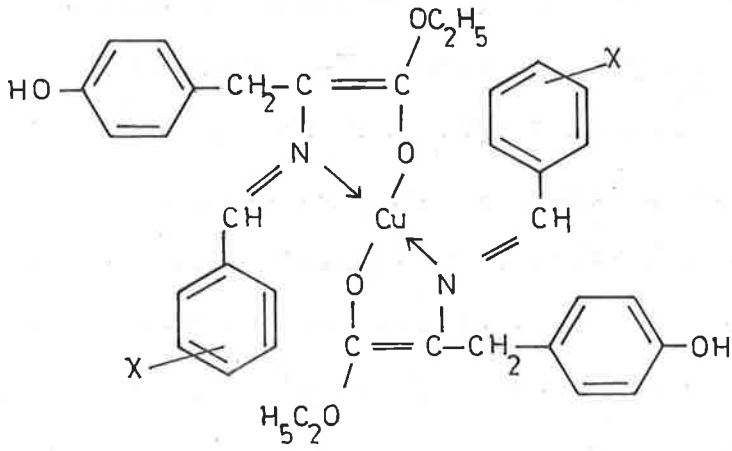
resulting in either transamination, decarboxylation, or racemization. In N-salicylidene-L-tyrosine ethyl ester the complex formed would more likely have the structure XIV similar to that postulated by Pfeiffer,[13] Witkop and Beiler.[53]



XIV

With the other N-arylidene schiff bases, the absence of a phenolic group in the aldehyde clearly shows that a copper complex of the type XIV is not possible. It is feasible to consider that these schiff bases form complexes with copper in their enol forms. The intermediate would have structure XV. Enolization will cause a loss of optical activity to the asymmetric carbon. This could afford an explanation to the ease of racemization of these anils. The possibility of enolization is further indicated by the optical stability of N-salicylidene α-phenylethylamine (VIIb) in the presence of cupric ions (Table 2.4). The latter schiff base cannot form an enol,

and therefore retains its optical activity.



XV

Investigation to the behaviour of N-arylidene derivatives of L-tyrosine ethyl ester in the presence of copper has shown that no transamination has taken place. However, the observation that racemization has occurred is quite clear. o- and p-Nitrobenzaldehyde have been shown by Witkop and Beiler[53] to form amino acid schiff bases which do not exhibit any transaminating property. Similarly Snell and Ikawa[3] also observed the non-mobility of the azomethine linkage in schiff bases obtained from amino acids and salicyldehyde, and 4-nitrobenzaldehyde. It would appear that the electron distribution of these aromatic aldehydes studied here is not sufficient for it to behave in the same manner as pyridoxal, and as a result no transamination could be observed.

EXPERIMENTAL

Part I

Materials.

(a) L-Tyrosine ethyl ester was prepared by esterification of the amino acid L-tyrosine in anhydrous ethanolic hydrogen chloride.[56] The hydrochloride isolated was basified with sodium carbonate solution (10%) and extracted with ethyl acetate. The oily ester obtained after evaporation of the ethyl acetate was swamped with ether, and the solid obtained was further recrystallized from benzene. A final recrystallization from benzene gave white crystals m.p. 104-105°, $[\alpha]_D^{20}$ + 18° (c 2.09 in ethanol).

(b) Benzaldehyde and substituted benzaldehydes were obtained commercially (B.D.H.). Because of the ease of most of the aldehydes to undergo oxidation on standing, they were all purified just before use. The liquids were purified by reduced pressure distillation in an atmosphere of nitrogen, and the solids fractionally recrystallized from ethanol, pentane, or pentane-benzene mixtures.

(c) Ethanol was fractionally distilled in a long column over potassium hydroxide pellets.

Buffer solutions.

The buffer was prepared by an admixture of citric acid (0.3 M), and triethanolamine (0.3 M) in 95% aqueous ethanol. Both citric acid and triethanolamine were obtained commercially (B.D.H.). In pH-rate studies they were mixed in varying proportions to give the required pH (4 - 8.5). In rate studies, citric acid and triethanolamine were mixed in proportions of 1:9 respectively giving an apparent pH of 8.4. All pH measurements were carried out in a Cambridge bench-type pH meter, standardized against 0.05 M aqueous sodium borate solution.

Determination of rate constants.

L-tyrosine ethyl ester (5×10^{-4} mole) was dissolved in a thermostated solution of the aldehyde (5×10^{-4} mole) in slightly less than 10 ml. of the buffered 95% aqueous ethanol. The volume was quickly adjusted to 10 ml. and the mixture introduced into a polarimeter tube (1 dm.), which was jacketed for temperature control by water circulated from an external thermostat. Temperatures in the tube were maintained generally to within $\pm 0.3^{\circ}$. Optical rotations were measured in a Hilger polarimeter fitted with a sodium vapour lamp. The change in rotation was recorded at appropriate intervals of time until the reaction had proceeded to apparent completion. In every case

the rotations were plotted against time and curves similar to Fig. 2.1 were obtained.

Zero-time rotations (α_o) were checked by extrapolation of time-dependent (α_t) readings, and found to correspond to the rotation of the amino ester. When equivalent concentrations of the ester and aldehyde were employed, the final rotations (α_e) were found to be an equilibrium mixture of schiff base, and amino ester. Repeating the above, using the same concentration of amino ester, but successively increased concentrations of aldehydes (4-10 fold), led to a higher final rotation which provided the limiting value (α_∞) with respect to the aldehyde concentration. In the cases of benzaldehyde, salicyldehyde, p-nitrobenzaldehyde and p-dimethylamino-benzaldehyde, α_∞ readings corresponded with the measured optical rotations of the schiff bases isolated (Table 2.2). With the remaining aldehydes, the α_∞ readings were assumed to represent the rotations of the respective schiff bases only. In each experiment, α_o, α_t, α_e, and α_∞ values were applied to the rate equation for a second order reaction opposed by one of the first order[57] i.e.,

$$k = \frac{1}{t} \frac{x_e}{a^2 - x_e^2} \ln \frac{x_e(a^2 - x x_e)}{a^2(x_e - x)}$$

or using the symbols for rotations,

$$k = \frac{1}{t} \frac{\alpha_e}{\alpha_\infty^2 - \alpha_e^2} \ln \frac{\alpha_e(\alpha_\infty^2 - \alpha_t \alpha_e)}{\alpha_\infty^2(\alpha_e - \alpha_t)}$$

Isolation of optically active schiff bases.

In each case, L-tyrosine ethyl ester (0.63 g) and an equivalent amount of aldehyde were separately dissolved in warm (40-45°) aqueous ethanol (3 ml.), and mixed. After standing the mixture in an ice-bath, the schiff bases separated out were recrystallized from the minimum amount of aqueous ethanol. (For N-benzylidene-L-tyrosine ethyl ester, 50% aqueous ethanol was used, N-p-dimethylamino- 40%, N-p-nitrobenzylidene- 40%, and N-salicylidene- 90%). Care has been taken to avoid excess warming, which could result in partial racemization. The schiff bases were obtained in pure crystalline forms and results of characterization are shown in Table 2.2. The optical rotations were all measured in ethanol.

Infrared measurements.

These were determined in a Grubb Parsons S4 double beam spectrometer with calcium flouride prisms and 0.4 mm. cells in chloroform solutions.

Part II

Materials.

(a) L-tyrosine ethyl ester, benzaldehyde, and substituted benzaldehydes were prepared as for Part I.

(b) (-)-α-phenylethylamine: The optically inactive amine (b.p. 185-190°) was prepared by Leukart's synthesise for amines,[58] using acetophenone (1 mole) and ammonium formate (4 moles). It was resolved with D-(+)- tartaric acid in methanol.[59] The optically active amine was obtained as a pure colourless liquid b.p. 105°/43 mm., $[\alpha]_D^{20}$ - 38° (pure liquid) (lit.[59] b.p. 73°/12 mm., $[\alpha]_D^{22}$ - 38.3°).

(c) (-)-α-phenylglycine ethyl ester: (-)-α-phenylglycine (5 g) was refluxed (2 hours) in 2N ethanolic hydrogen chloride (100 ml.) as for the preparation of tyrosine ethyl ester. The ester was isolated as the hydrochloride, m.p. 201° (lit.[60] ester hydrochloride m.p. 202°), and this was used in the preparation of the schiff base.

(d) Bases: A.R. pyridine, and triethanolamine were obtained commercially (B.D.H.). Sodium ethoxide (0.1 M) was prepared by dissolving sodium (0.155 g) in ethanol (50 ml.).

Preparation of optically active schiff bases.

The schiff bases from L-tyrosine ethyl ester were

prepared as for Part I. Details of characterizations are shown in Table 2.2.

N-salicylidene (-)-α-phenylethylamine: The amine (0.05 mole) and the aldehyde (0.05 mole) were each dissolved in warm (40-50°) aqueous ethanol (90%, 3 ml.) and mixed. On standing the mixture in an ice-bath, needles (bright yellow) were obtained in 85% yield, m.p. 74-75°, $[\alpha]_D^{20}$ + 224° (c 1.2 in ethanol), $[\alpha]_D$ + 200° (c 1.0 in benzene) (lit.[61] m.p. 76°, $[\alpha]_D$ + 187 in benzene).

N-salicylidene-α-phenylglycine ethyl ester: The schiff base was prepared in the same way as the above from the ester hydrochloride (0.05 mole), and salicyldehyde (0.05 mole). Needles (bright yellow) were obtained in 80% yield, m.p. 94-95°, $[\alpha]_D^{20}$ + 87° (c 2.8 in ethanol).

Anal. Cald. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94.
Found: C, 72.35; H, 6.15; N, 5.01.

Racemization studies at 45°.

Racemization studies at 45° were followed polarimetrically. The schiff base (0.001 mole) was dissolved in 10 ml. of thermostated ethanol and introduced into a polarimeter tube (1 dm.), which was jacketed for temperature control by water circulated from an external thermostat. The temperature in the tube was generally kept within ± 0.3°. Optical rotations were measured with a Hilger

polarimeter fitted with a sodium vapour lamp. The rotations were measured at appropriate intervals of time and the racemization reaction followed until the rotation was virtually zero.

For base-catalysed racemization studies, the appropriate base pyridine (0.16 ml.), triethanolamine (0.15 g) and sodium ethoxide (0.1 ml.) were each added to less than 10 ml. of the schiff base (0.001 mole) in ethanol, and the volume quickly adjusted to 10 ml. It was then introduced into a jacketed polarimeter tube (1 dm.), and rotations recorded at intervals of time.

When copper was used in the racemization study, cupric acetate monohydrate (0.003 g) in ethanol (3 ml.) was added to a solution of schiff base (0.001 mole) in approximately 5 ml. ethanol. The volume was quickly adjusted to 10 ml. and the change in rotation observed in a jacketed polarimeter tube (1 dm.).

In the case where the rotations altered very rapidly, zero time rotation was obtained by extrapolation of time-dependent readings and shown to be that of the original schiff base.

Isolation of thermally racemized schiff bases.

The optically active N-arylidene derivatives of tyrosine ethyl ester (0.05 mole) was introduced into an

ignition tube, and placed in an oil-bath which was kept slightly above (5-10°) the melting point of the schiff base. At intervals of time, a small amount of it was taken out and the rotation observed in ethanol. When the observed rotation was zero, the schiff base was cooled and recrystallized from aqueous ethanol.

Optically inactive N-salicylidene-∝-phenylglycine ethyl ester was prepared by refluxing (1 hr.) the schiff base (0.05 mole) in ethanol (10 ml.). The schiff base obtained on cooling was pure, and needed no recrystallization. Details of characterization of the optically inactive schiff bases are given in Table 2.5.

The N-salicylidene-∝-phenylethylamine did not lose its optical activity even after 100 hours of fusing.

Hydrolysis of optically active and optically inactive N-salicylidene tyrosine ethyl ester.

The schiff base (0.5 g) was refluxed (0.5 hr.) with 2N ethanolic hydrogen chloride (10 ml.). The alcohol was evaporated under reduced pressure. The residue obtained was mixed with water (1 ml.), and extracted several times with benzene. The benzene fractions after washing with water was dried with anhydrous sodium sulphate, and evaporated. In both cases, a yellow liquid (0.2 g) was obtained and characterized as salicyldehyde by formation of 2:4 dinitrophenylhydrazone m.p. 250-252° (decomp.) (lit.

m.p. 252°). The aqueous fraction on standing afforded the hydrochloride m.p. 162-164° (lit.[56] m.p. 166°). The hydrochloride was dissolved in the minimum amount of water, and basified with sodium bicarbonate (10%). From the aqueous mixture, a white solid was obtained which gave a positive test with ninhydrin. When the schiff base hydrolysed was optically active, the white solid had m.p. 103-105°, $[\alpha]_D^{20}$ + 16° (c 0.9 in ethanol) (mixed m.p. with L-tyrosine ethyl ester was not depressed). When the schiff base hydrolysed was optically inactive, the white solid had m.p. 109-110°, $[\alpha]_D^{20}$ 0 (in ethanol) (m.p. of admixture with DL tyrosine ethyl ester was not depressed).

Hydrolysis of copper racemized schiff bases of tyrosine ethyl ester.

The schiff base (0.002-0.005 mole) in ethanol (5 ml.) was added to a solution of cupric acetate (0.09 g) in hot ethanol (5 ml.). When the observed rotation of a diluted sample showed zero rotation, (dilution of the mixture was necessary because of the intense green colour), the mixture was refluxed (5-10 mins.) with 2N ethanolic hydrogen chloride (2-5 ml.). The red gum obtained after reduced pressure evaporation of the ethanol, was dissolved in water (1 ml.), and extracted repeatedly with benzene. After washing the benzene layer with water, it was dried with

anhydrous sodium sulphate and evaporated. The residue obtained in each case was characterized by their 2:4-dinitrophenylhydrazone or semicarbazone. In the case of the p-nitrobenzylidene and p-dimethylaminobenzylidene schiff bases, the residue obtained was a solid, which had correct melting points of the corresponding aldehydes. Admixture with authentic samples of the aldehydes did not depress the melting point.

The copper in the aqueous fraction was removed as cuprous sulphide by bubbling a stream of hydrogen sulphide gas into it. The excess hydrogen sulphide gas was boiled off, and the cooled solution basified with sodium bicarbonate (10%). From the mixture, a white solid was obtained m.p. 295° (decomp.). It gave a positive test with ninhydrin and a benzoyl derivative m.p. 192-194° (lit. m.p. 192°). Details of hydrolysis products are provided in Table 2.6.

Isolation of Cu complex of N-salicylidene ethyl-L-tyrosine ester.

The schiff base (0.3 g) in ethanol (1 ml.) was added to a solution of cupric acetate monohydrate (0.09 g) in ethanol (2 ml.). The solution was left to stand at room temperature, and dark green needles m.p. 180-185° (decomp.) was obtained. It is insoluble in most organic solvents, but slightly soluble in ethanol.

Anal. Cald. for $(C_{18}H_{18}NO_4)_2Cu$: C, 62.82; H, 5.27; N, 4.07.

Found: C, 62.93; H, 5.16; N, 4.35.

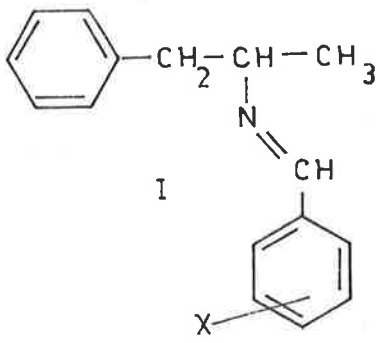
Table 2.6

Substituent with weight of schiff base used	Benzene fraction		Aqueous fraction	
	Yield of Aldehyde	m.p. Derivative	Yield of amino acid	Benzoyl Derivative
o-OH (0.6 g)	- 0.2 g	249-251° (2:4 DNP)	0.25 g	192-194°
p-NMe_2 (0.5 g)	0.2 g (m.p. 72-73°)	222° (semicarbazone)	0.15 g	192-194°
H (0.6 g)	- 0.2 g	235° (2:4 DNP)	0.2 g	192-194°
p-NO_2 (0.5 g)	0.2 g (m.p. 102-104°)	210° (semicarbazone)	0.15 g	192-194°

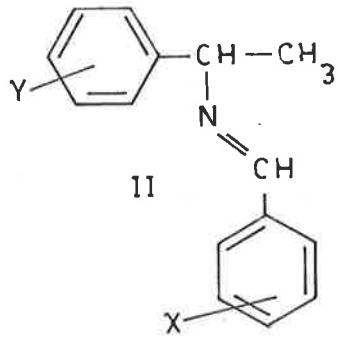
CHAPTER III

Part I

The N-arylidene derivatives of L-tyrosine ethyl ester were found to be prone to racemization. This has led to the investigation of N-arylidene derivatives of (+)-amphetamine (∝ -benzylethylamine) (I), and (-)- ∝-phenyl-ethylamine (II, Y = H). Anils of this type have been found to be stable (Chapter II, Part II). The schiff bases from



I



II

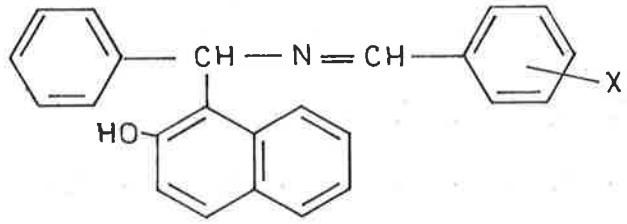
X = p-NO_2, p-OCH_3, H, o-OH, o-OCH_3, p-NMe_2, etc.

Y = p-CH_3, p-OCH_3, H, and p-Br.

∝ -phenylethylamine were further compared with N-arylidene derivatives from (-)- ∝-p-methylphenylethylamine, (II, Y = p-CH_3) (+)- ∝-p-methoxyphenylethylamine, (II, Y = p-OCH_3) and (+)- ∝-p-bromophenylethylamine (II, Y = p-Br).

The literature contains relatively little

information about optically active schiff bases of this type. Betti[62] described a series of such compounds derived from (+)-(2-hydroxy, 1-naphthyl) phenyl amino methane (III), and substituted benzaldehydes. All the



X = p-NMe_2, p-OCH_3, o-OH, H, etc.

III

anils had a positive rotation except in the case where the aldehyde had a substituent in the ortho-position, i.e. when X is o-NO_2 or o-OH, the rotation is negative. He inferred that the magnitude of the rotation of the schiff base is dependent on the 'electronegative' or 'electropositive' character of the substituent in the aldehyde. The rotations of the anils were related to the dissociation constants of the corresponding acids. The schiff base with electron donating substituent in the aldehyde moiety were found to have dextro-rotation larger than the schiff base with no substituent in the aldehyde. However, the corresponding acid with electron donating substituent has a dissociation constant smaller than benzoic acid.

Similarly, schiff bases with electron attracting substituents in the aldehyde moiety are less dextro-rotatory (or even laevo-rotatory) than the anil with no substituent; but the dissociation constant of the corresponding acid is larger than benzoic acid. In other words, when the electron donating substituent is p-NMe_2, the rotation of the schiff base is large and positive, but the dissociation constant of the corresponding acid is small, and when the substituent is o-nitro, the rotation of the schiff base is negative, but the acid has a large dissociation constant.

According to Lowry and his co-workers,[63] amines can be divided into two types. The majority of amines show circular dichroism in the near ultraviolet bands of the nitrogen lone pair. Large changes in the rotatory power are observed on neutralization, caused by the saturation of these lone pair of electrons. The second type of amines are those where the absorption band at 230 mμ are inactive, and little change takes place on neutralization. According to them, the amine (+)-(2-hydroxy, 1-naphthyl) phenylamino methane (III)[62] ($[\alpha]_D$ + 58.8°) fall into the second group as the formation of the hydrochloride ($[\alpha]_D$ + 52°) had little effect on the rotation of the amine.

Of closely related interest is the work carried out by Russian workers. Potapov and Terent'ev[61,64]

described N-arylidene derivatives of (+)-amphetamine (I), and (+)-α-phenylethylamine. The rotatory power of the anils were observed at the sodium D line in benzene, methanol, dichloroethane and acetone. The N-arylidene derivatives of (+)-α-phenylethylamine all possessed negative rotations when the substituent in the aldehyde moiety is in the para position, and when the substituent in the o-position is o-hydroxy. All the o-substituted N-arylidene derivatives had the same rotation as the amine i.e. positive. However, with (+)-amphetamine the anils (I) all had the same sign of rotation as the amine. Since neutralization, by formation of a hydrochloride ($[\alpha]_D$ + 8.3) had a great effect on the rotation of (+)-α-phenylethylamine ($[\alpha]_D$ + 36°), these workers have included it under the category of the first type of amines (see Lowry). (+)-Amphetamine ($[\alpha]_D$ + 38°) is not greatly affected by formation of a hydrochloride ($[\alpha]_D$ + 24.8), and therefore it is included in the same group of amines as (+)-(2 hydroxy, 1-naphthyl)phenylamino methane (III), i.e. the second type of amines. However, they concluded that the data accumulated was not sufficient to permit any far-reaching conclusions in the case of the observed peculiarities.

The German school under Nerdel[65] were also interested in the effect substituent have on the optical

rotatory power of the amine. They described a few schiff bases from (-)-α-phenylethylamine and substituted benzaldehydes, viz. the benzylidene-, m-nitrobenzylidene-, p-methoxybenzylidene-, and p-chlorobenzylidene- derivatives. The rotations were observed at four wavelengths; the sodium D line, the 546 mμ mercury emission line, and the Fraunhofer lines at 656 mμ and 486 mμ in various solvents. They found the rotations of the anils all to be positive and slightly dependent on the solvent effects.

The optical rotatory power of a compound depends on the chemical nature of the groups linked to the asymmetric centre and to the chemical nature of substituents on these groups. It also depends on the molecular electrical moments of these groups. The investigation of the optical rotatory dispersion of these schiff bases into the ultraviolet region might yield more information with regard to the relationship between substituent effects and the rotatory power. At the same time other properties like the optical activity of the chromophores, -C=N- and the aromatic ring can be observed.

The N-arylidene derivatives of (+)-amphetamine, (-)-α-phenylethylamine, and substituted α-phenylethylamines were readily obtained from equimolecular quantities of aldehyde and amine in ethanol. Details of characterization

are shown in the experimental section. (Except for one case, the schiff bases were all isolated in a pure form). The purity of the schiff base was indicated by the complete absence of the -NH- and -C=O stretching frequencies in the infrared absorption spectra. At the same time the presence of the -C=N- stretching frequency at 1635-1640 cm^{-1} were obtained. The ultraviolet absorption spectra of each anil was carried out before the optical rotatory dispersion was measured. Optical rotatory dispersion curves of the schiff bases are shown in Fig. 3.2 - 3.6.

The effect of the substituent X-C_6H_4-CH=N- on the rotation of the schiff bases observed here appear to follow very closely to that observed by Potapov and Terent'ev,[61,64] and by Nerdel *et al.*[65] In the sodium D line the schiff bases have much larger rotations than the corresponding amine. The N-arylidene derivatives of (+)-amphetamine all possessed a positive sign of rotation, while the N-arylidene derivatives of(-)-α-phenylethylamine behaved in the same manner as those observed by Nerdel and co-workers[65] *i.e.* when X is in the *para* position and is *o*-OH (II where Y = H), the sign of rotation is positive, but when X is in the *ortho* position, the sign of rotation is negative. The N-arylidene derivatives of the other substituted α-phenylethylamines (II) follow the behaviour

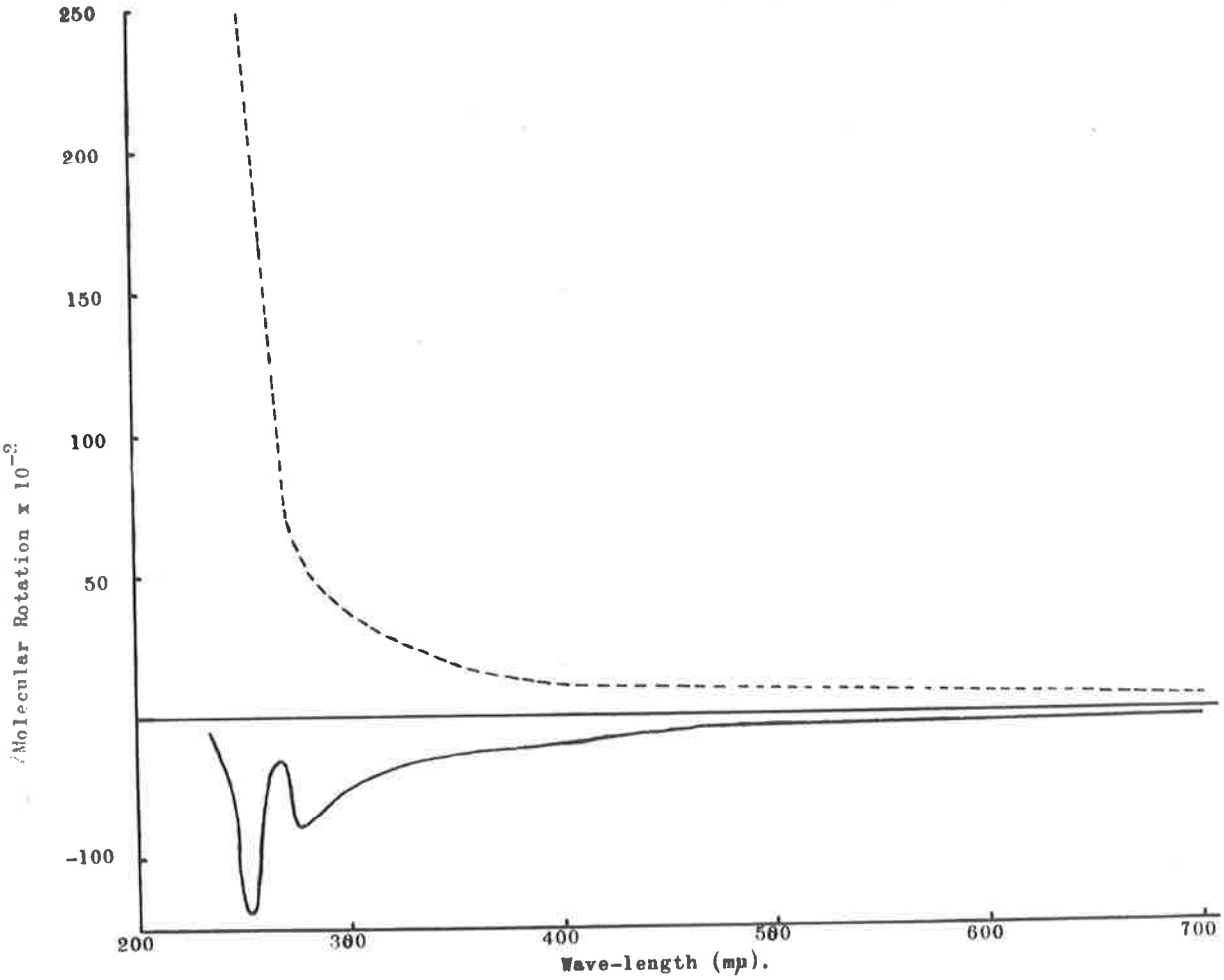


Fig.3.1a. Rotatory dispersion curves of (-)-α-phenylethylamine (————), and amphetamine (- - - - - - -).

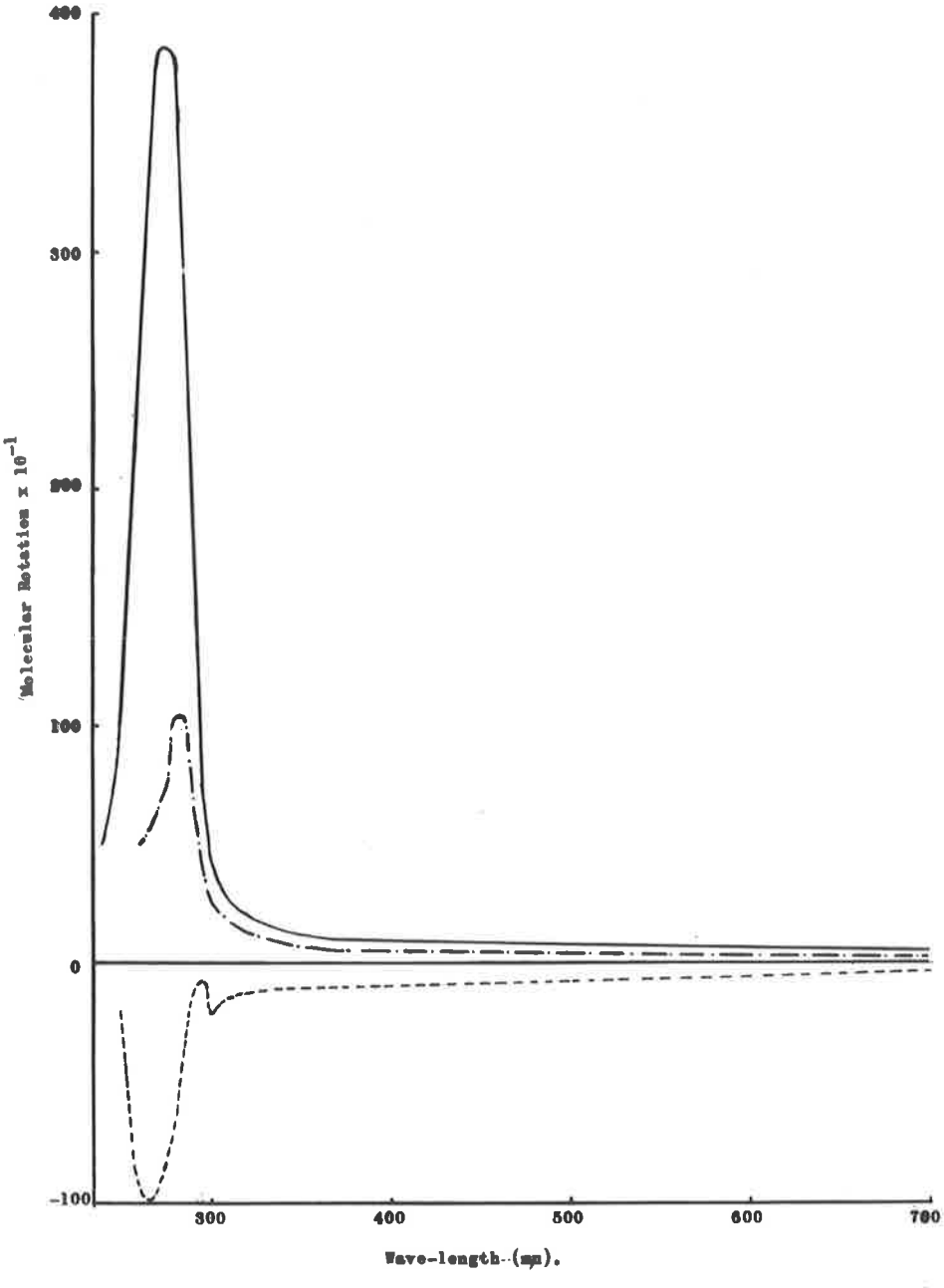


Fig.3.1b. Rotatory dispersion curves of ≪-p- methylphenylethylamine (————), (+) -≪-p- bromophenylethylamine (—·—·—·—), and (-) -≪-p- methoxyphenylethylamine (– – – – –).

of schiff bases from (-)-α-phenylethylamine.

When X is in the *para* position (I and II), the magnitude of the rotation of the schiff base is larger than the rotation observed when X is in the *ortho* position. The larger rotation is observed throughout the rotatory dispersion curve (Fig. 3.2 - 3.6), no matter what the electronic contribution of the substituent X is. Generally, the larger the substituent X is the larger is its contribution to the magnitude of the rotation. In other words, *p*-nitro and *p*-dimethylamino substituents would have a large effect on the magnitude of the rotation while the *p*-methyl and *o*-methoxy substituents have smaller effects. In this respect, the results are very similar to the observation of the Russian[61.64] and German[65] workers, but quite dissimilar to that of Betti.[62]

All the schiff bases exhibit anomalous curves. However, schiff bases with an *ortho*-substituent in the aldehyde ring are the most interesting ones as they generally exhibit a multiple cotton effect curve (*e.g.* Fig. 3.2a), while the majority of the schiff bases with a substituent in the *para* position possess only a peak or a trough (*e.g.* Fig. 3.2e). The exact molecular rotations of a few selected wave-lengths (peaks, and troughs) of the schiff bases with their ultraviolet absorption maxima are provided in the experimental section.

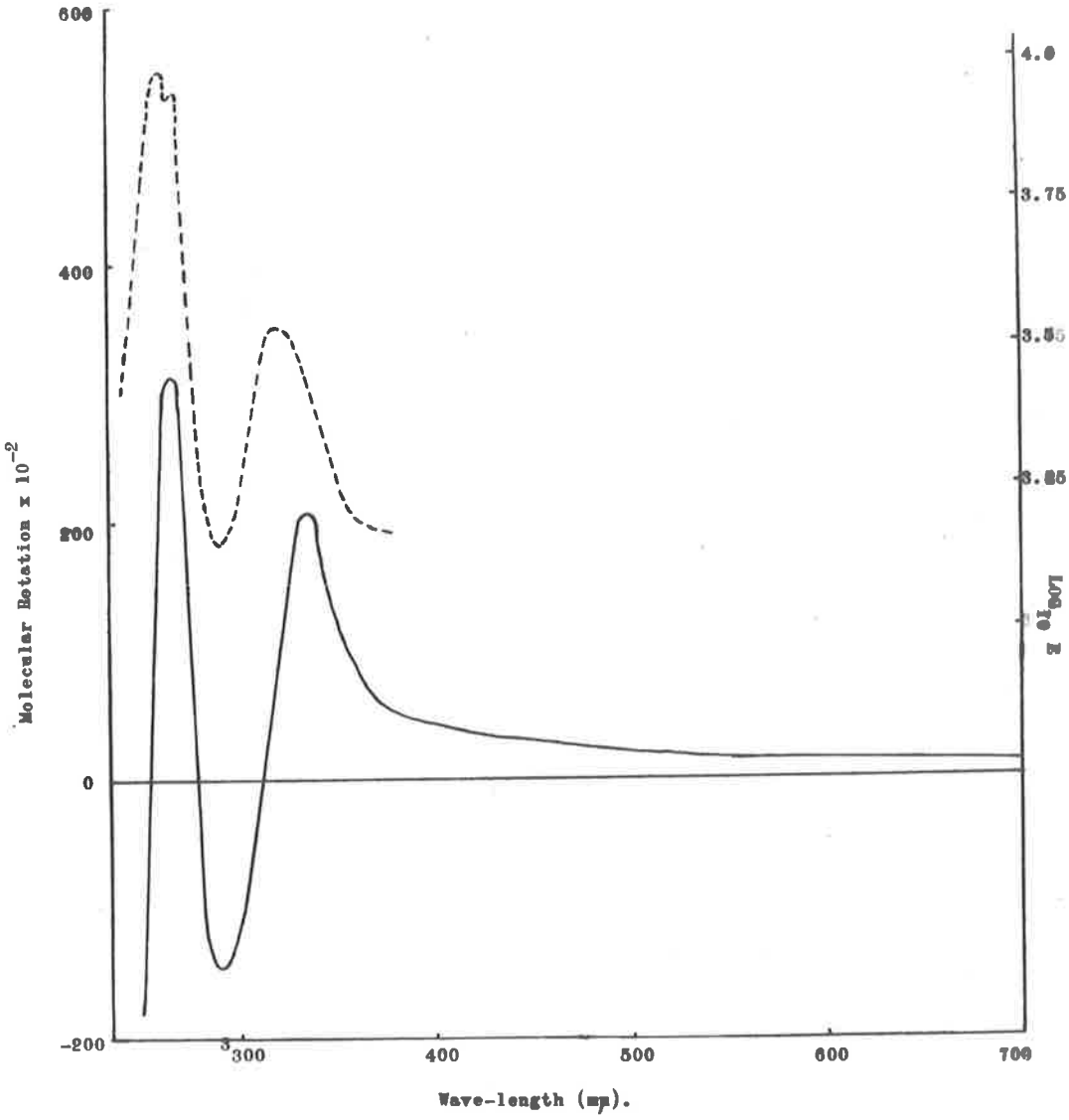


Fig.3.2a. N-salicylidene-α-phenylethylamine, Rotatory dispersion curve (———), ultra-violet spectrum (- - - - -).

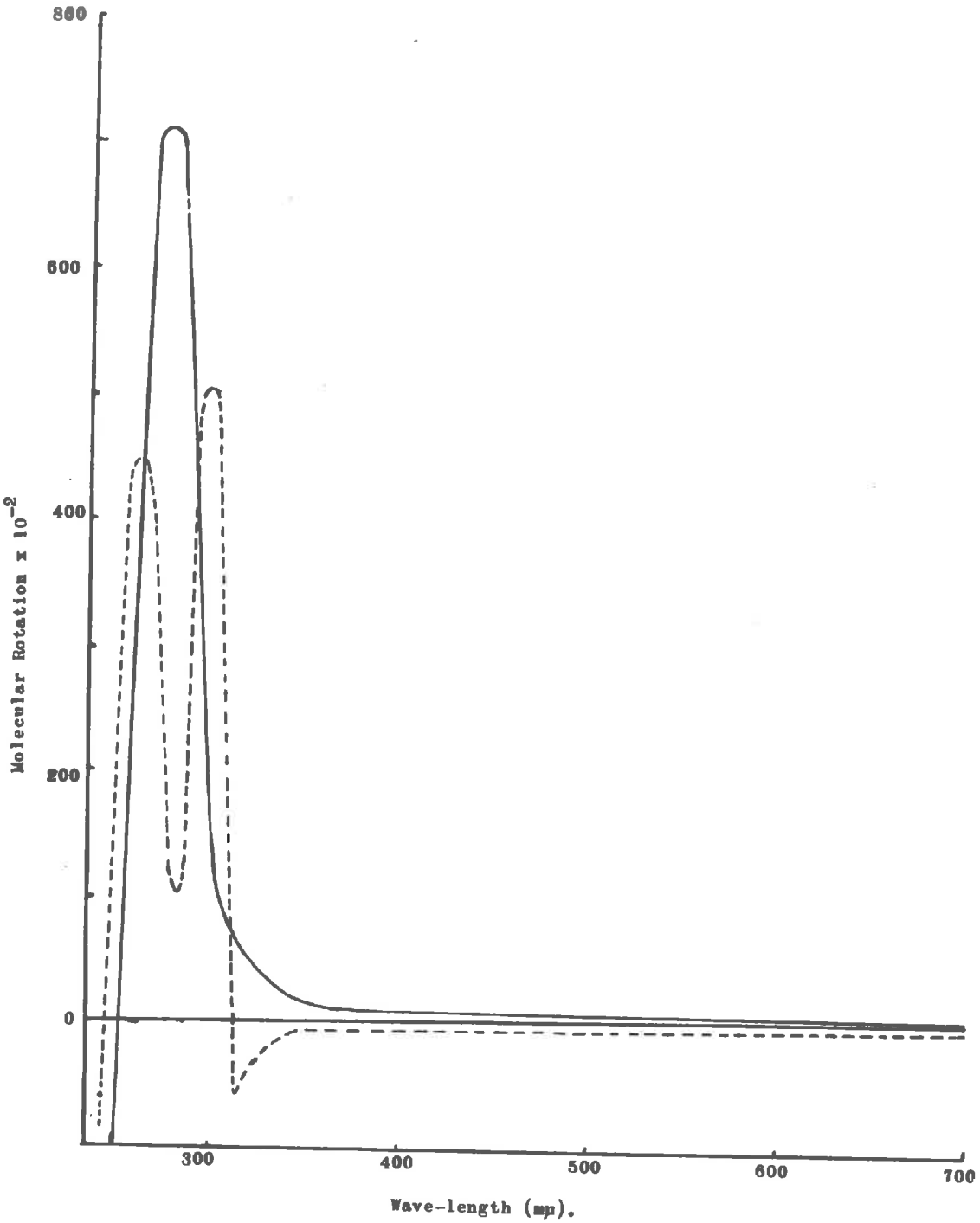
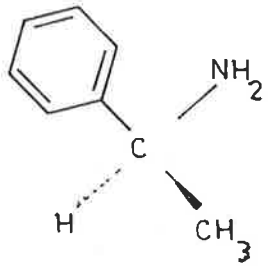


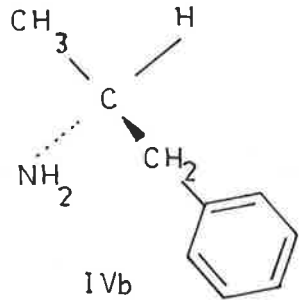
Fig.3.2b. Rotatory dispersion curves of N-o- methoxybenzylidene -α-phenylethylamine (--------), and N-p- methoxybenzylidene -α-phenylethylamine (————).

General Discussion

(-)-α-Phenylethylamine (IVa) and (+)-amphetamine (IVb) both have the same absolute configuration.[66] It is S according to the Cahn, Ingold and Prelog system of nomenclature and L according to the Fischer projection system. The optical rotatory dispersion of these two amines (Fig. 3.1a), however, are quite different. (-)-α-phenylethylamine (IVa) exhibits a cotton effect curve while the curve for (+)-amphetamine (IVb) is plain. During the



IVa



IVb

course of this work, there appeared in the literature a report by Lyle[67] on the same two amines. The result she obtained is very similar to this, and she attributed the cotton effect in (-)-α-phenylethylamine (IVa) to the benzene ring being attached to the asymmetric centre. (+)-Amphetamine (IVb) did not exhibit a cotton effect presumably because the benzene ring is separated from the

asymmetric centre by a methylene group. This means that the benzene absorption band is optically active only when it is attached directly to an asymmetric centre. However, it is a pertinent question whether this is true for all compounds or only in this instance. The optical rotatory dispersion curves for all the other para-substituted ∝-phenylethylamines are anomalous (Fig. 3.1b). Nevertheless, the schiff bases of these two amines (IVa and IVb) appear to be more related (Fig. 3.2 - 3.3).

From a close scrutiny of the rotatory dispersion curves of the schiff bases and their corresponding ultraviolet absorption spectra a certain correlation can be observed in particular with derivatives where the substituent in the aldehyde ring is in the ortho-position. The wave-length of the mean value of peak and trough of the cotton effect curve, corresponds to the wave-length of maximal absorption in the ultraviolet, e.g. in N-salicylidene-∝-phenylethylamine (Fig. 3.2a), the wave-length of maximal absorption in the ultraviolet at 320 mμ coincides very well with the wave-length of the mean value of peak and trough (318 mμ). This seems to indicate that the absorption at 320 mμ is therefore an optically active absorption band. Relationship between ultraviolet absorption and anomalous rotatory dispersion has already been discussed by Djerassi and his co-workers.[68] It was pointed out that

the rotatory dispersion method will generally be of value when the dispersion curve shows 'maxima' and 'minima' and these in turn will be produced only by optically active chromophores which absorb in a suitable range. If the absorption is due to only one electronic transition the mean value of peak and trough should coincide with the wave-length of zero rotation. Since in this series the majority of the schiff bases have a mean wave-length of peak and trough that do not coincide very well with the zero rotation, it could be inferred that the rotatory dispersion is due to more than one elctronic transition.

From the rotatory dispersion curves of the schiff bases it would appear that the benzene absorption band is optically active (Fig. 3.2 - 3.6). In several cases the complete cotton effect curve was not obtained especially in schiff bases where the substituent in the aldehyde ring is in the <u>para</u> position. This is mainly due to the difficulty in measuring rotations below 240 mμ. Nevertheless, it is very likely that if rotations below 240 mμ can be measured, the benzene ring in the schiff bases will be conclusively shown to be optically active.

N-Salicylidene-∝-phenylethylamine (V) has a sign of rotation (positive) opposite to that of the other o-substituted schiff bases of ∝-phenylethylamine

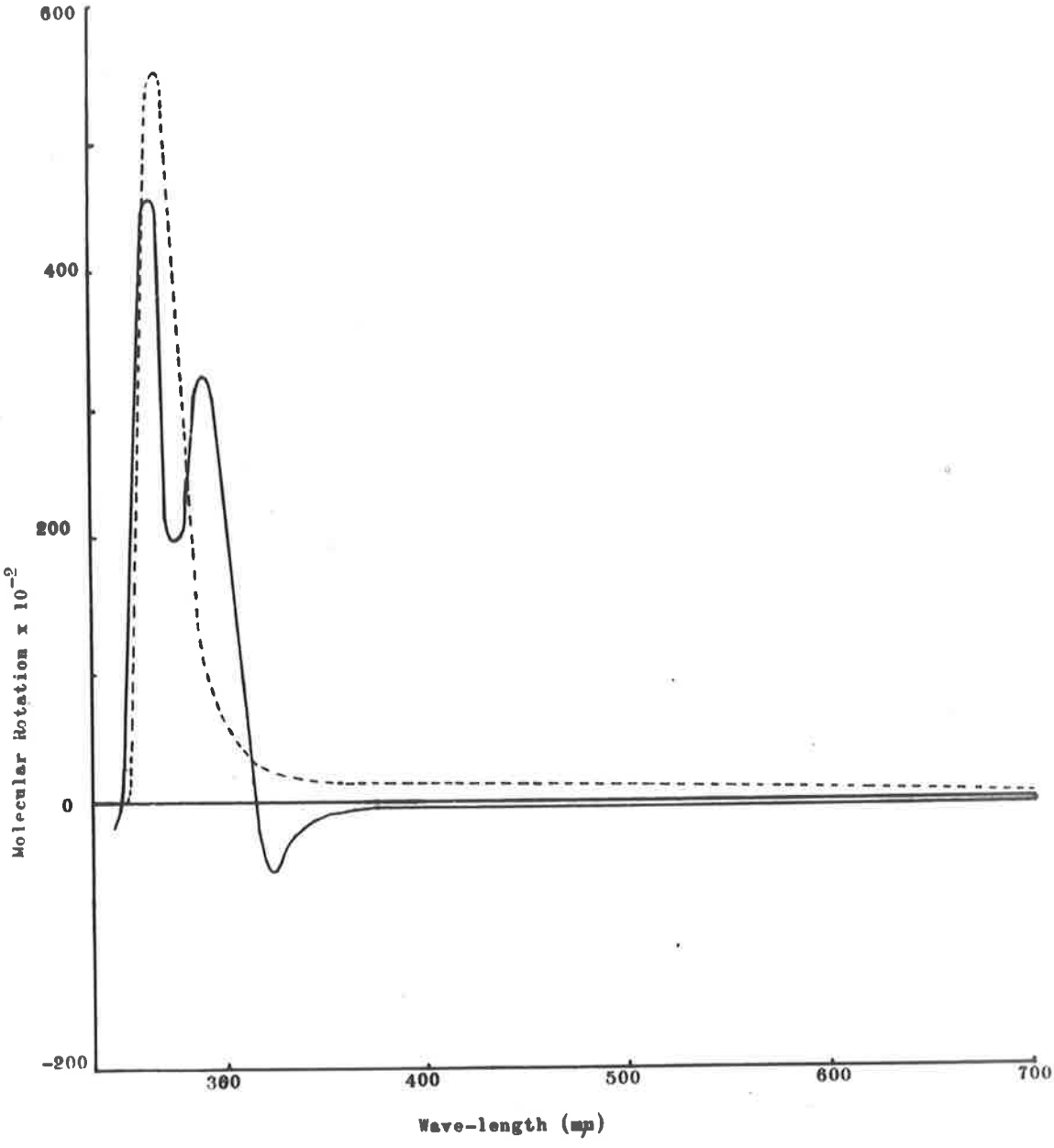


Fig.3.2c. Rotatory dispersion curves of N-o-ethoxybenzylidene-α-phenylethylamine (————), and N-p-methylbenzylidene-α-phenylethylamine (- - - - - -).

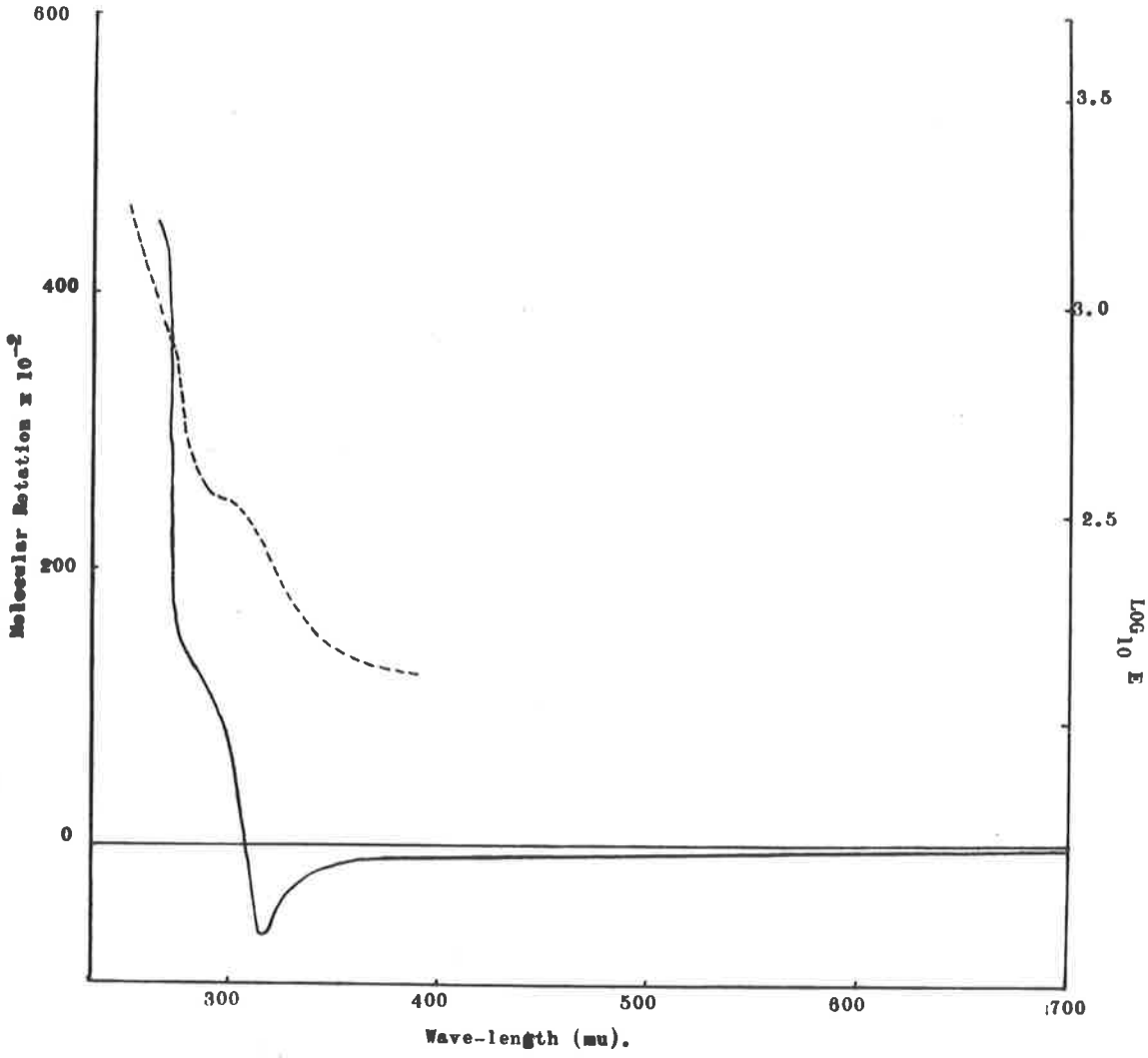


Fig.3.2d. N-o-nitrobenzylidene-α-phenylethylamine. Rotatory dispersion curve (————); ultra-violet spectrum (- - - - -)

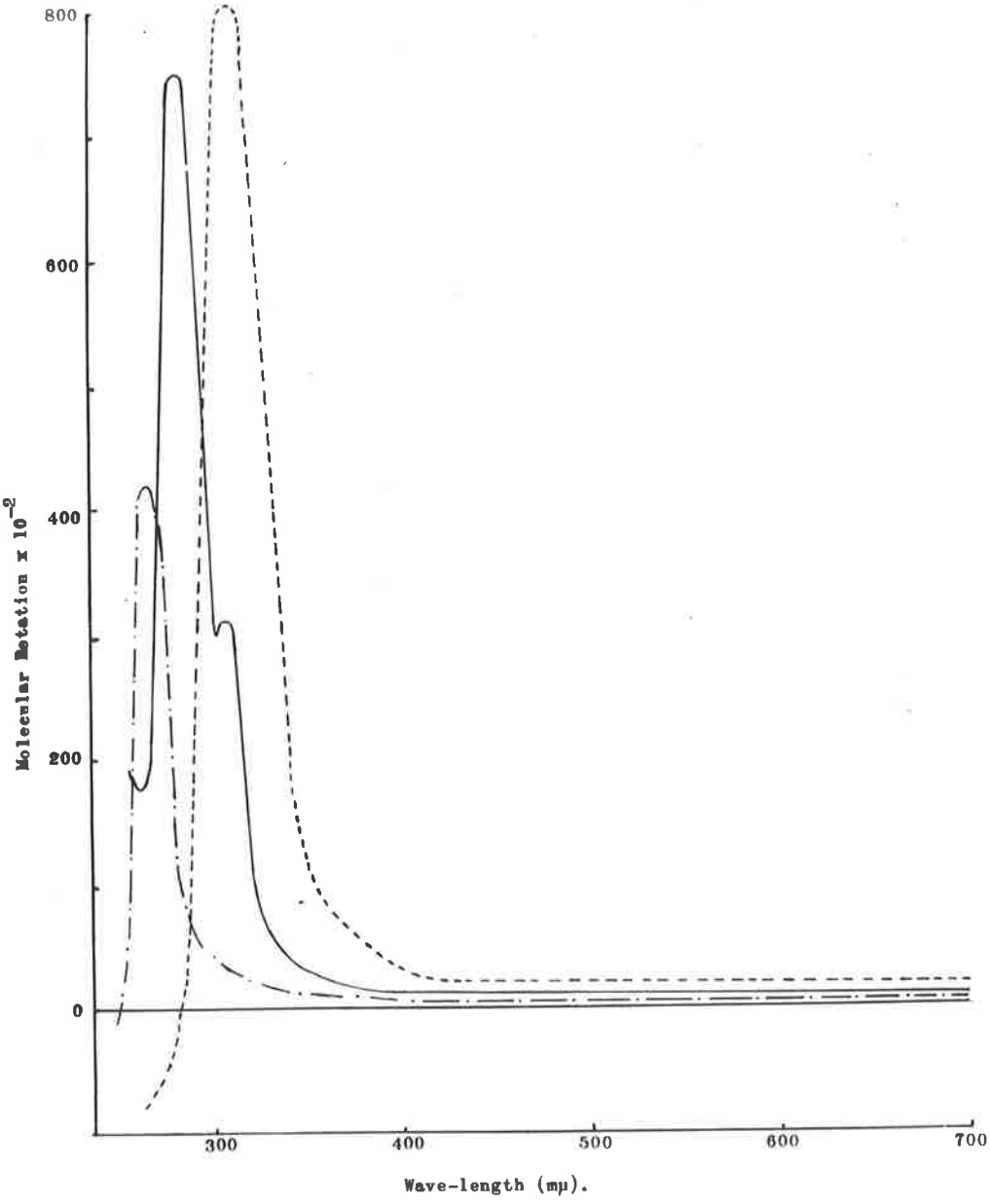
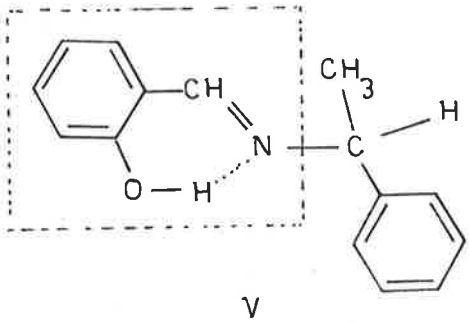


Fig.3.2e. Rotatory dispersion curves of N-p-dimethylaminobenzylidene-α-phenylethylamine (- - - - - -), N-p-nitrobenzylidene-α-phenylethylamine (————), and N-benzylidene-α-phenylethylamine (— · — · —).

(negative). This phenomenon can be tentatively attributed to the presence of hydrogen bonding in N-salicylidene-∝-phenylethylamine (V) and to the choice of preferred conformation. From the building of models, it appears most reasonable to consider the schiff base in its trans form, where the two benzene rings face each other at an angle of 90°, and lying perpendicular to the plane of the paper. When no ortho substituent is present in the aldehyde ring,



V

it can easily rotate around the C-C bond of >C-C=N-. However, when an ortho substituent is present, the rotation is slightly restricted. The amount of restriction depends on the size of the ortho substituent. The restriction appears to be caused by the azomethine nitrogen and the hydrogen of -CH=N-. With N-salicylidene-∝-phenylethylamine (V), hydrogen bonding between the phenolic hydrogen and the azomethine nitrogen can occur. As such, the most stable conformation for it would probably be one

where the atoms in the dotted line (V) are all in one plane, which is the plane of the paper.

When the o-substituent is o-methoxy, o-ethoxy, or o-nitro, hydrogen bonding can no longer take place. These substituents are larger than the hydroxy substituent. Thus the conformation suitable for N-salicylidene-α-phenylethylamine (V) will be unsuitable for the other anils. It appeared that the least hindered conformation for large o-substituents in the schiff bases would probably be one where the two benzene rings face each other at 90° and lie perpendicular to the plane of the paper. It has a different conformation to the one for N-salicylidene-α-phenylethylamine (V) as the aldehyde benzene ring has now rotated 90° or approximately 90°. As the schiff bases have different conformations, it is quite likely then that they possess different signs of rotations. The above explanation is applicable to all the other N-arylidene derivatives of p-substituted α-phenylethylamines.

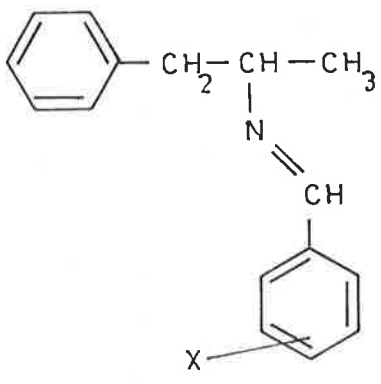
When one considers the schiff bases of (+)-amphetamine, the model appears to be more crowded around the -CH=N-C bonds. The two benzene rings now face each other at an angle of approximately 45°. The angle of rotation of the aldehyde ring is greatly reduced when an ortho-substituent is present. The ortho-substituted schiff bases now have a limited choice of 'preferred conformations'

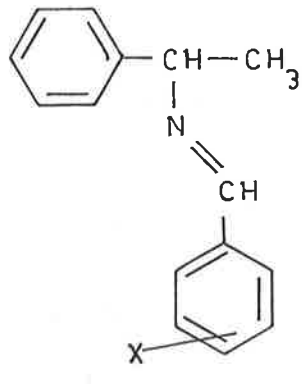
and probably very little difference would be observed between the available ones. Therefore all the o-substituted schiff bases of amphetamine have the same sign of rotation and dispersion curves.

With N-arylidene derivatives where the substituent in the aldehyde ring is in the p-position, apparently the preferred conformation is the same for amphetamine and ∝-phenylethylamine. These in turn are similar to that of N-salicylidene-∝-phenylethylamine. Studies of ∝-β unsaturated ketones[69] have shown a number of examples of inversion of multiple cotton effects which have been attributed to conformational (steric) effects.

Discussion of N-arylidene derivatives of (+)-amphetamine and (-)-∝-phenylethylamine.

The optical rotatory dispersion of both the N-salicylidene derivatives of (+)-amphetamine (I, X is o-OH), and (-)-∝-phenylethylamine (IIa, X is o-OH) are





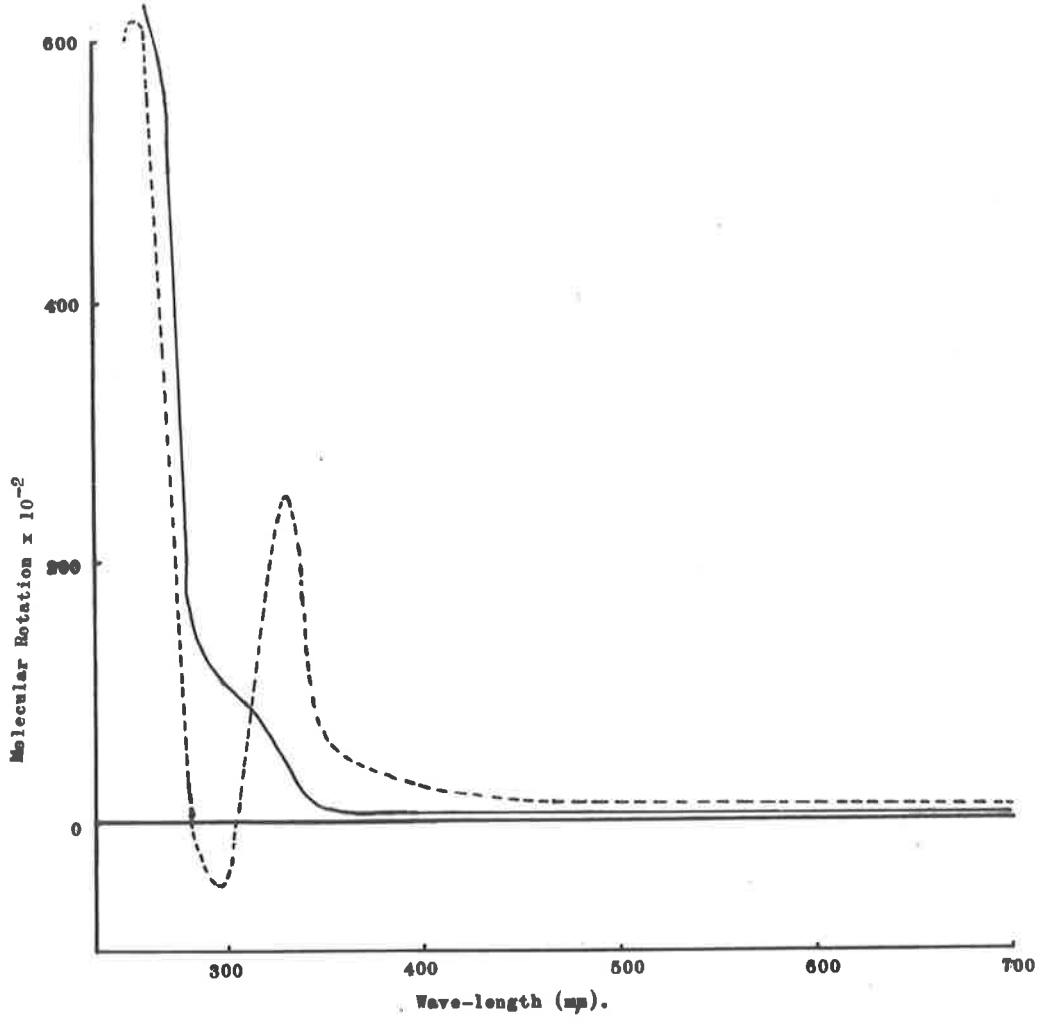


Fig.3.3a. Rotatory dispersion curves of N-o-nitrobenzylidene-amphetamine (————), and N-salicylidene-amphetamine (- - - - - - -).

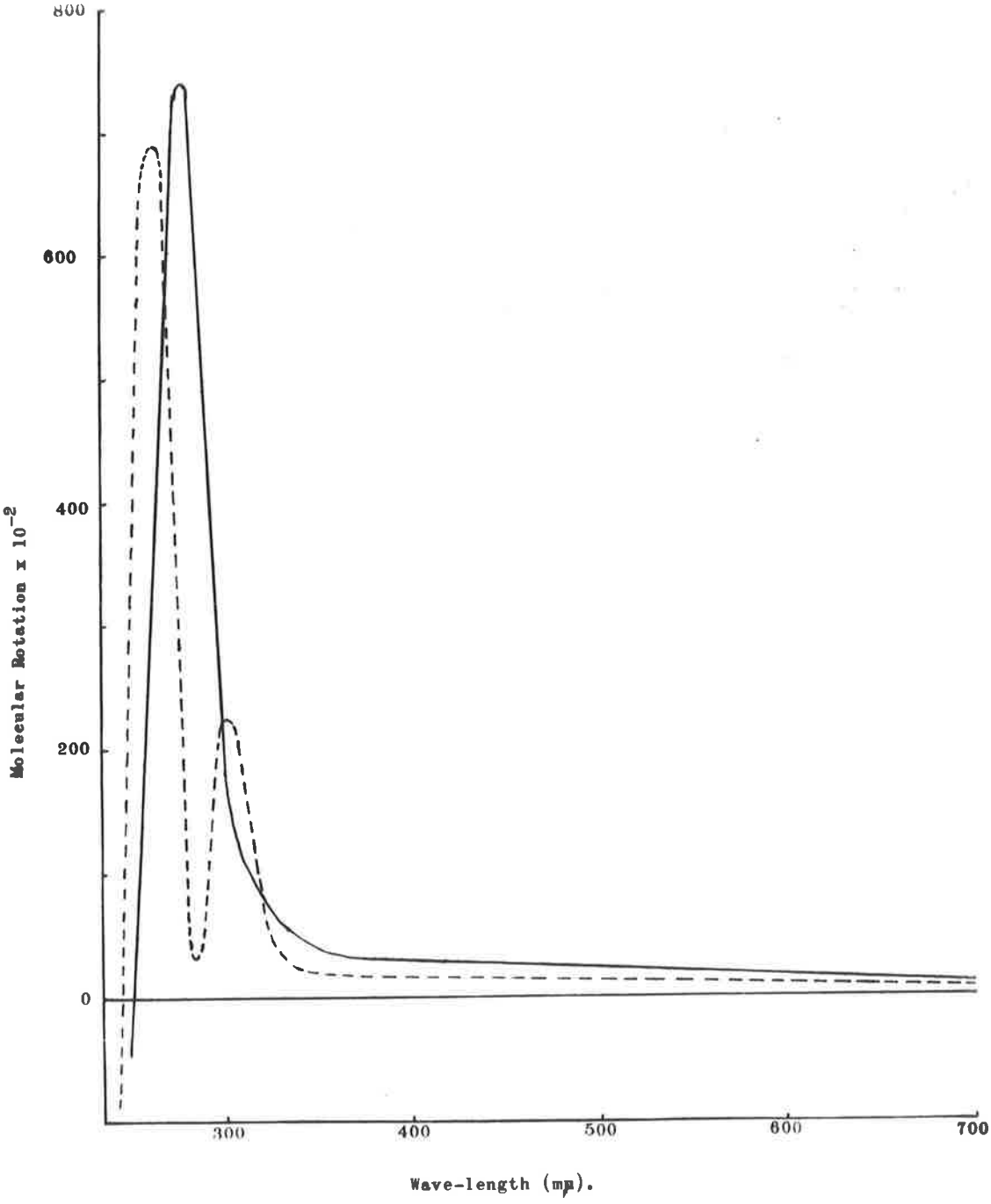


Fig.3.3b. Rotatory dispersion curves of N-o-methoxybenzylidene-amphetamine (- - - - - -), and N-p-methoxybenzylidene-amphetamine (————).

very alike. However, the rotatory dispersion curve of the former is more positive than that of the latter (Fig. 3.2a and 3.3a). This has been attributed to the optical rotatory dispersion of the latter schiff base (IIa) being superimposed on a negative background, as the amine (-)-α-phenylethylamine has a negative rotatory dispersion curve (Fig. 3.1a).

In N-o-methoxybenzylidene-α-phenylethylamine (IIa, X is o-OCH_3), the first extremum is negative while the other two are positive (Fig. 3.2b). The negative extremum is probably caused by the negative rotatory dispersion of the amine. Since the rotations in the visible region are small, the effect of the negative amine is probably greater. The rotations are large in the ultraviolet region, and as such the positive rotations mask the small, negative rotations of the amine. As a result the two positive peaks in N-o-methoxybenzylidene-α-phenylethylamine (IIa, X is o-OCH_3) can be compared to the two positive peaks observed in the optical rotatory dispersion of the corresponding schiff base from amphetamine. Similarly, in N-o-ethoxybenzylidene (IIa, X is o-OC_2H_3), a rotatory dispersion curve like the o-methoxy derivative (IIa, X is o-OCH_3) is observed (Fig. 3.2c).

The rotatory dispersion curves of N-o-nitrobenzylidene-α-phenylethylamine (IIa, X is o-NO_2, Fig. 3.2d),

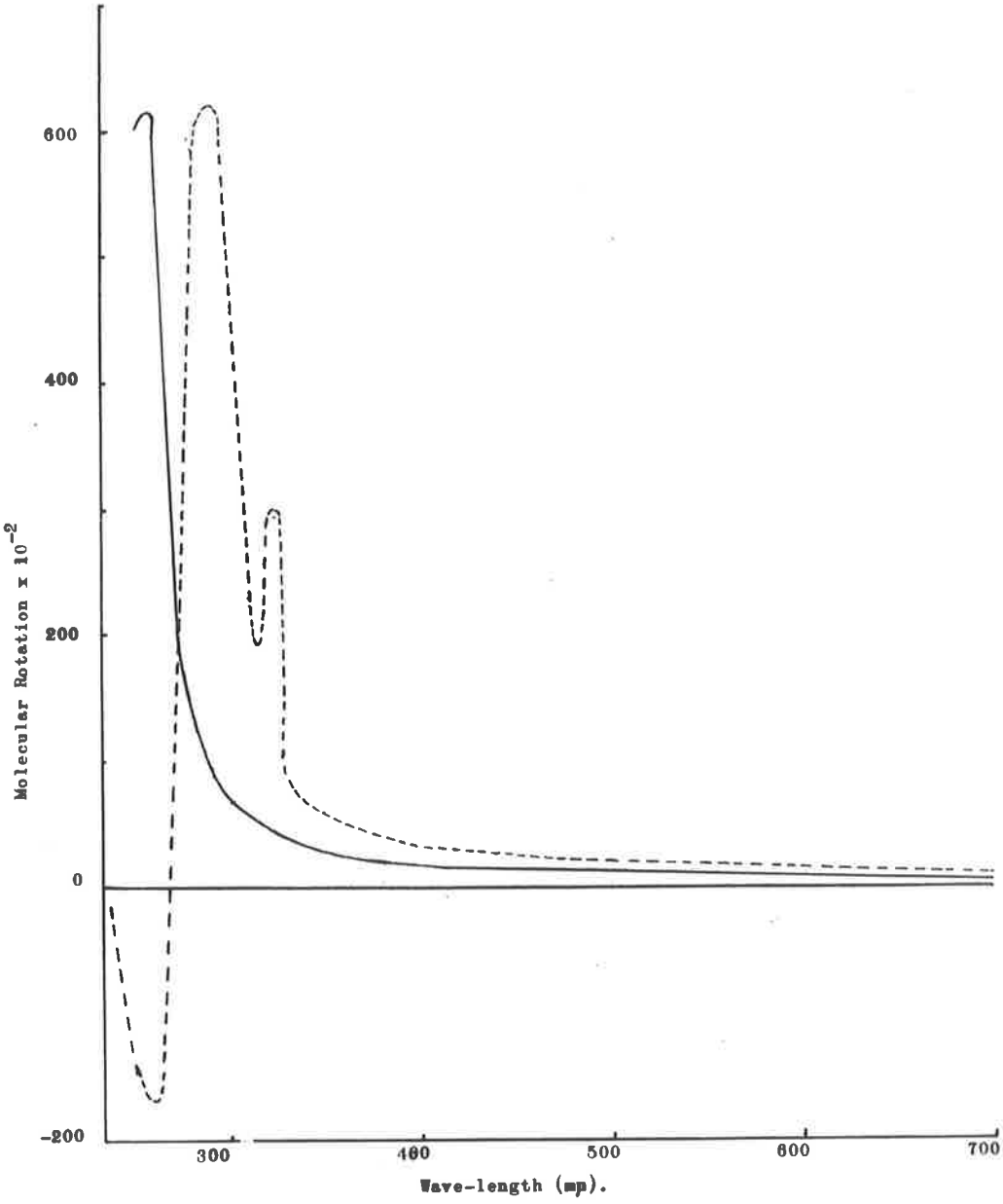


Fig.3.3c. Rotatory dispersion curves of N-p-nitrobenzylidene-amphetamine (- - - - - -), and N-benzylidene-amphetamine (————).

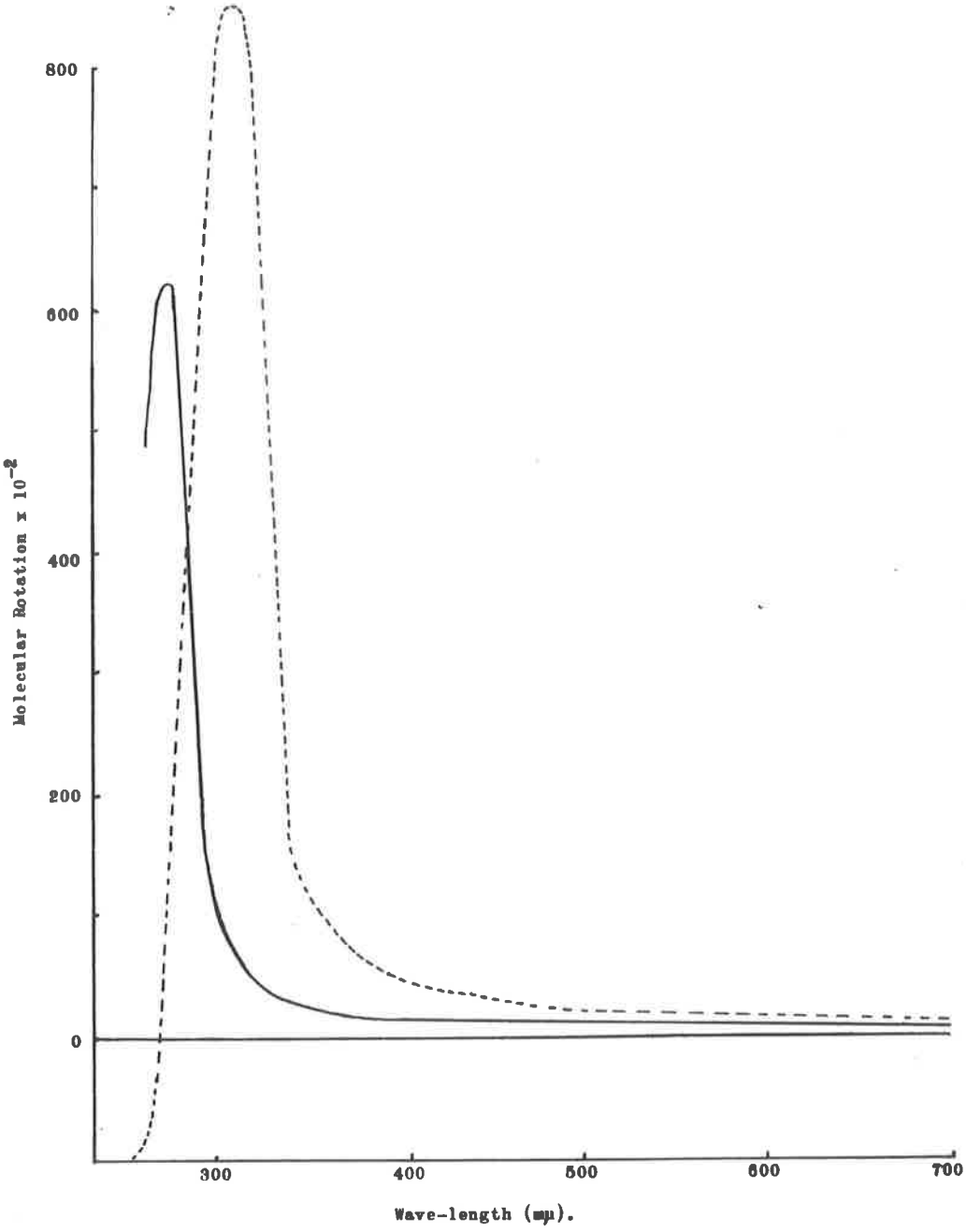


Fig.3.3d. Rotatory dispersion curves of N-p-dimethylaminobenzylidene-amphetamine (- - - - -), and N-p-methylbenzylidene-amphetamine (————).

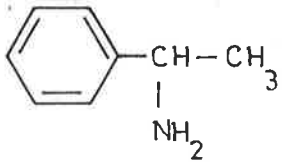
and N-o-nitrobenzylidene-amphetamine (I, X is o-NO_2, Fig. 3.3d) are different from their corresponding o-substituted derivatives. In α-phenylethylamine, the schiff base has a negative first extremum, followed by a plain curve with a slight inflection in the positive region. In amphetamine, the schiff base has a rotatory dispersion curve with an inflection at approximately 315 mμ. The ultraviolet absorption spectra of these two schiff bases do not exhibit the usual absorption at 320 mμ and 256 mμ characteristic of other o-substituted anils. Instead, an ultraviolet absorption spectra with an inflection at 305 mμ have been observed. It would appear that the two usual absorption maxima are superimposed on one another. This results in a plain curve (Fig. 3.2d). However, it is of interest to note that the rotatory dispersion of N-o-nitrobenzylidene-α-phenylethylamine (IIa, X is o-NO_2) still exhibits the negative extremum. This seems to indicate further that the negative rotatory dispersion of the amine (Fig. 3.1a) contributes to the dispersion curve of the schiff base, in particular in the visible and near ultraviolet regions.

In both N-p-nitrobenzylidene-α-phenylethylamine (IIa, X is p-NO_2) and N-p-nitrobenzylidene amphetamine (I, X is p-NO_2), an extra shoulder is observed (Fig. 3.2e and 3.3c). The extra shoulder could be due to the nitro

group itself. A nitro group (isolated) has spectral properties of its own (λ max. 270-280 mμ), and in conjunction with the aromatic ring, a broad absorption peak is observed. The absorption maximum is probably an addition of the absorption of the nitro group and the benzene absorption band superimposed on one another. Hence, the extra shoulder observed in the N-p-nitro-benzylidene derivatives can be attributed to the nitro chromophore being optically active.

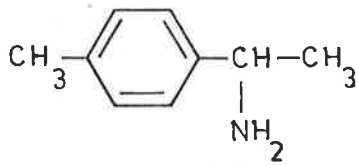
Discussion of N-arylidene derivatives of α-phenylethylamine and p-substituted α-phenylethylamines.

The optical rotations of α-phenylethylamine (IVa) and α-p-methylphenylethylamine (VIa) are negative, while the rotations for α-p-bromophenylethylamine (VIb) and α-p-methoxyphenylethylamine (VIc) are positive.



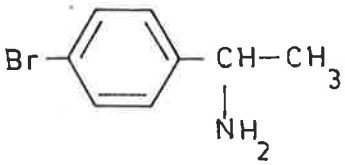
(-)

IVa



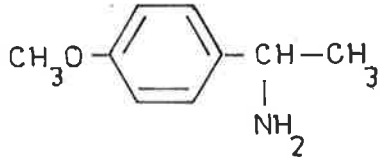
(-)

VIa



(+)

VIb



(+)

VIc

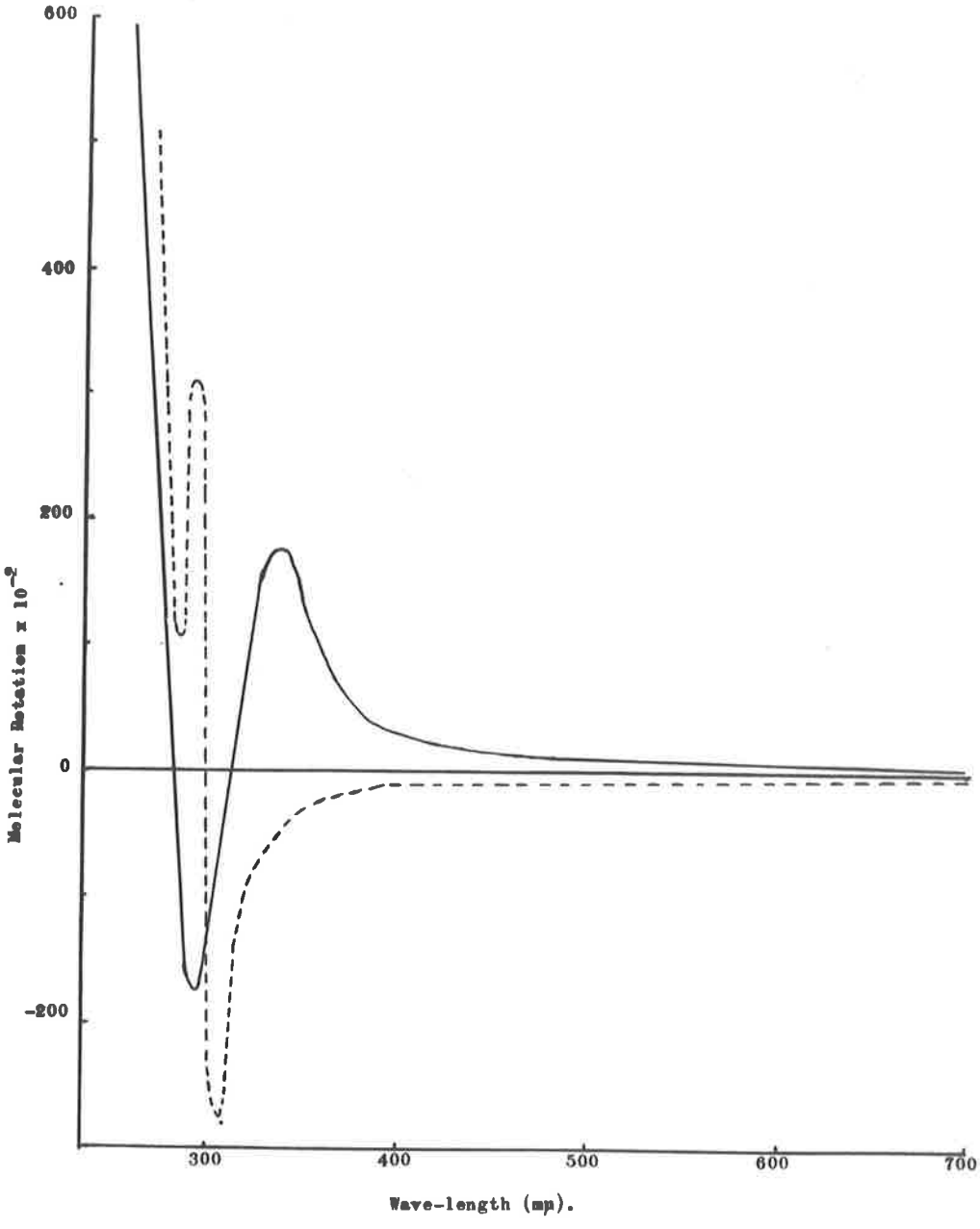


Fig.3.4a. Rotatory dispersion curves of N-salicylidene-α-p-methylphenylethylamine (————), and N-o-methoxybenzylidene-α-p-methylphenylethylamine (- - - - - -).

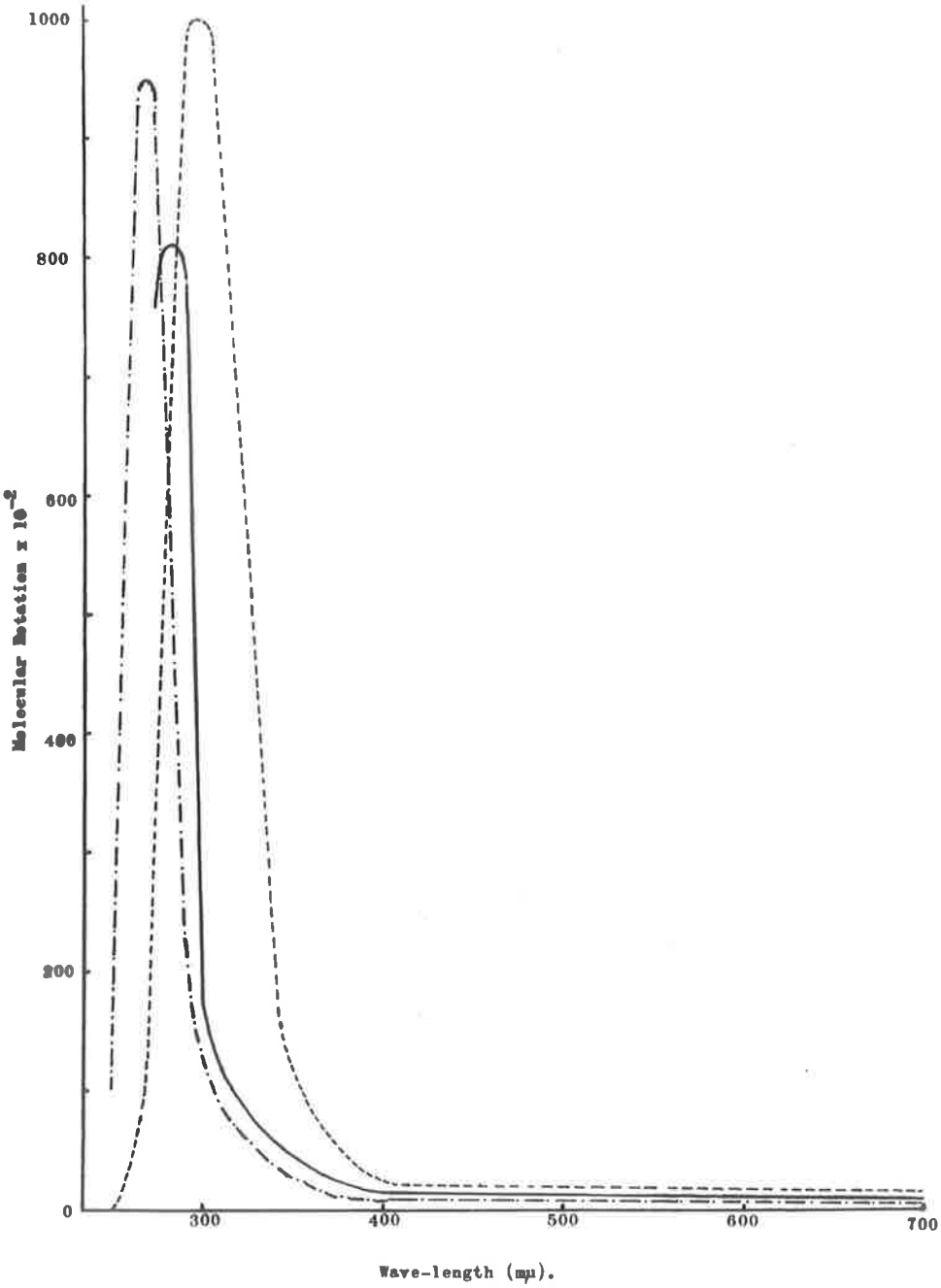


Fig.3.4b. Rotatory dispersion curves of N-p-dimethylaminobenzylidene-α-p-methylphenylethylamine (- - - - - -), N-p-methoxybenzylidene-α-p-methylphenylethylamine (————), and N-p-methylbenzylidene-α-p-methylphenylethylamine (- · - · - · -).

Since the absolute configuration of (-)- α-phenylethylamine is L, (+)- α-phenylethylamine should have the opposite configuration. It follows therefore that the two positive amines (VIb and VIc) would have the same absolute configuration as the (+)- α-phenylethylamine i.e. D. The rotatory dispersion curves of the two positive amines (VIb and VIc) are almost mirror images of the rotatory dispersion from the two negative amines (IVa and VIa) (Fig. 3.1).

The rotatory dispersion curves of N-arylidene derivatives from the two positive amines (VIb and VIc) appear to have an extra extremum (Fig. 3.5 - 3.6). The curves have a small trough followed by a large peak or positive rotations. This means that in several instances complete cotton effect curves are obtained even with schiff bases when the substituent is in the p-position of the aldehyde benzene ring. The mean of the wave-length of peak and trough corresponds quite well with the wave-length of maximal absorption and this further indicates the benzene absorption band to be optically active.

The optical rotatory dispersion curve of N-o-methoxybenzylidene schiff bases of the four amines (IVa and VIa - VIc) appear to be mirror images of the corresponding N-salicylidene derivatives (Fig. 3.2a

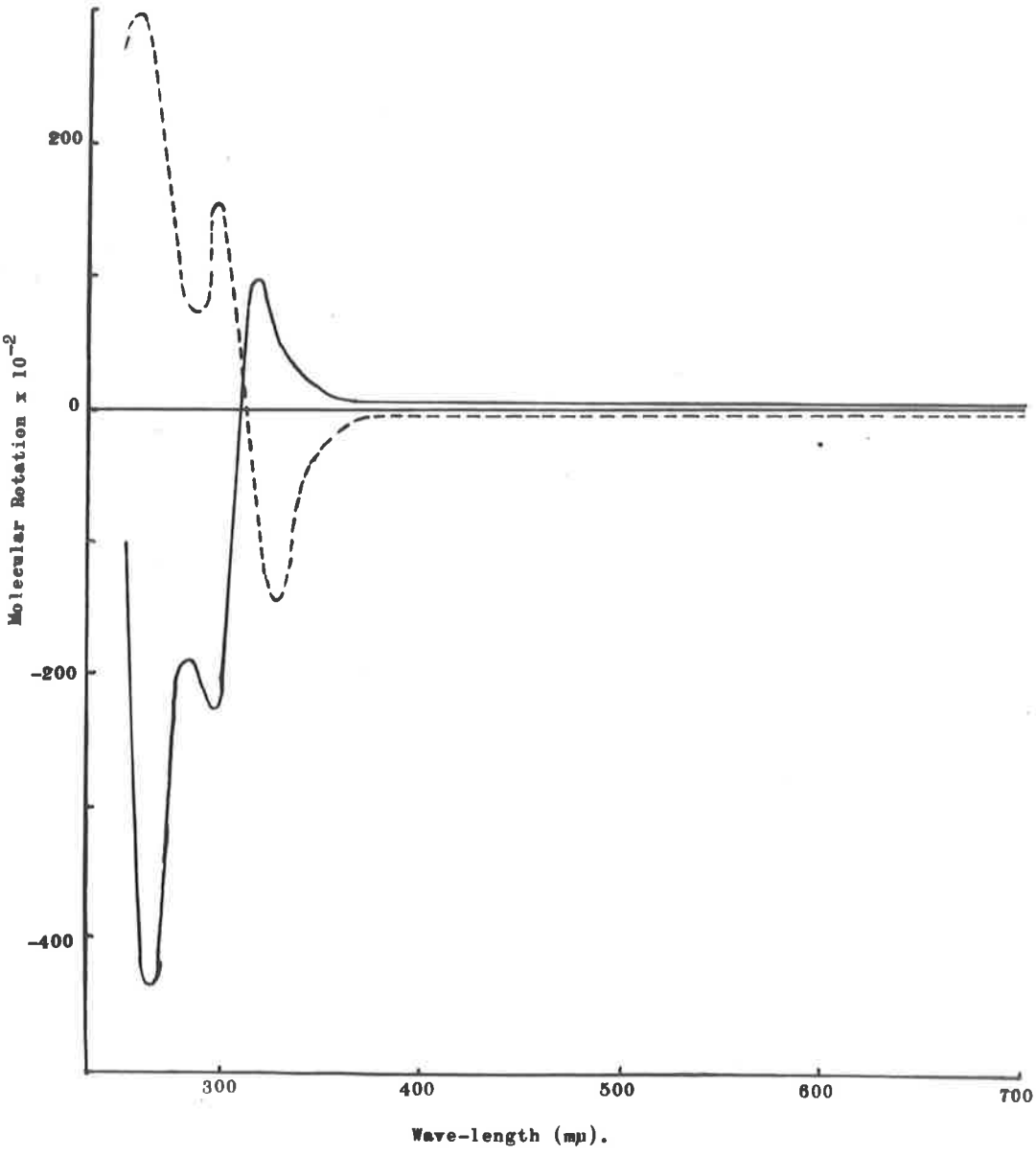


Fig.3.5a. Rotatory dispersion curves of N-o- methoxybenzylidene -α-p-bromophenylethylamine (————), and N- salicylidene-α-p-bromophenylethylamine (- - - - - -).

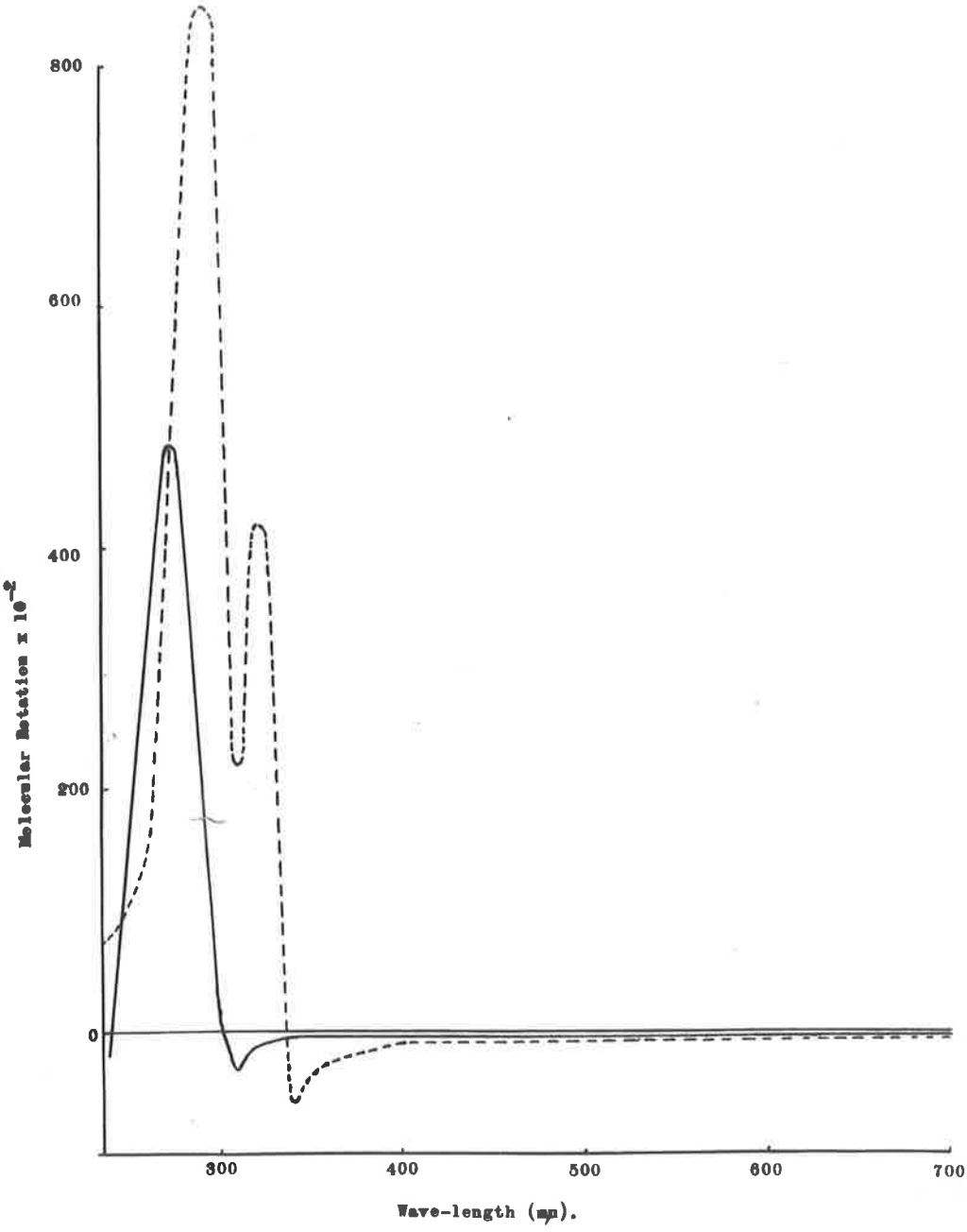
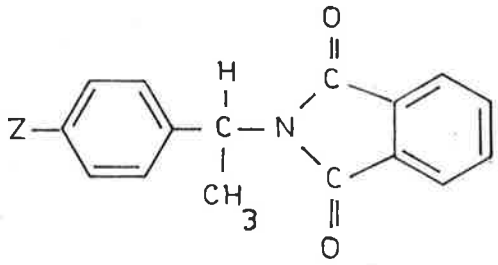


Fig.3.5b Rotatory dispersion curves of N-p-dimethylaminobenzylidene-S-p-bromophenylethylamine (- - - - - -), and N-p-methoxybenzylidene-p-bromophenylethylamine (————).

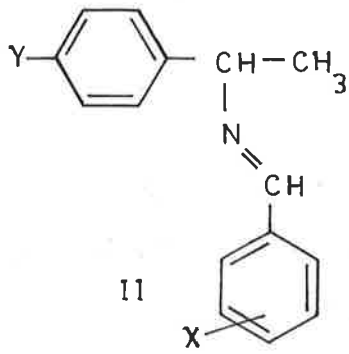
3.2b, 3.4a, 3.5a and 3.6a). It was further observed that all the N-p-substituted arylidene derivatives for the two amines with positive rotations (VIc and VId) have a dispersion curve (3.5-3.6) very similar to that of the N-o-methoxybenzylidene - (Fig. 3.2b and 3.4a) and N-o-ethoxybenzylidene (Fig. 3.2c) derivatives of the two amines with the negative rotations (IVa and VIa). It is indicative here that all these schiff bases probably have the same conformation. At the same time a similarity is seen between N-salicylidene derivatives (Fig. 3.2a and 3.4a) of α-phenylethylamine (IVa) and α-p-methylphenylethylamine (VIa), and the N-o-methoxybenzylidene derivatives (Fig. 3.5a and 3.6a) of the two positive amines (VIb and VIc). The interpretation of results here is very difficult as there is no reference in the literature of optical rotatory dispersions of schiff bases. From examples of other work,[70] mirror images are usually produced by enantiomers. Perhaps it would be better to indicate here that the schiff bases of each amine exist in two optical forms, one having the same optical properties as the amine, and the other the opposite. However, an inversion in the absolute configuration at the asymmetric carbon is unlikely.

A correlation between substituent effects and the position of the first extremum have been observed by

Brewster and Osman.[71] They found that the electronic properties of the substituent (Z) in phthalimides derived from ∝-phenylethylamine influence the position of the first extremum (VII). Electron donating substituents decrease the wave-length of the first extremum to shorter wave-length, while electron attracting substituents cause a bathochromic shift. Comparison of the effect of the substituent Y (II) on the position of the first extremum



VII



II

Z = p-NO_2, H, pBr and pOCH_3. Y = p-CH_3, p-OCH_3, H and p-Br.

and the rotatory dispersion curves of N-arylidene derivatives of substituted ∝-phenylethylamines, did not afford a relationship similar to that obtained by the above workers.[71] However, if one considers only the schiff bases where the substituent X (II) is in the para position, and the wave-length of the first positive extremum, a relationship is obtained (Table 3.1).

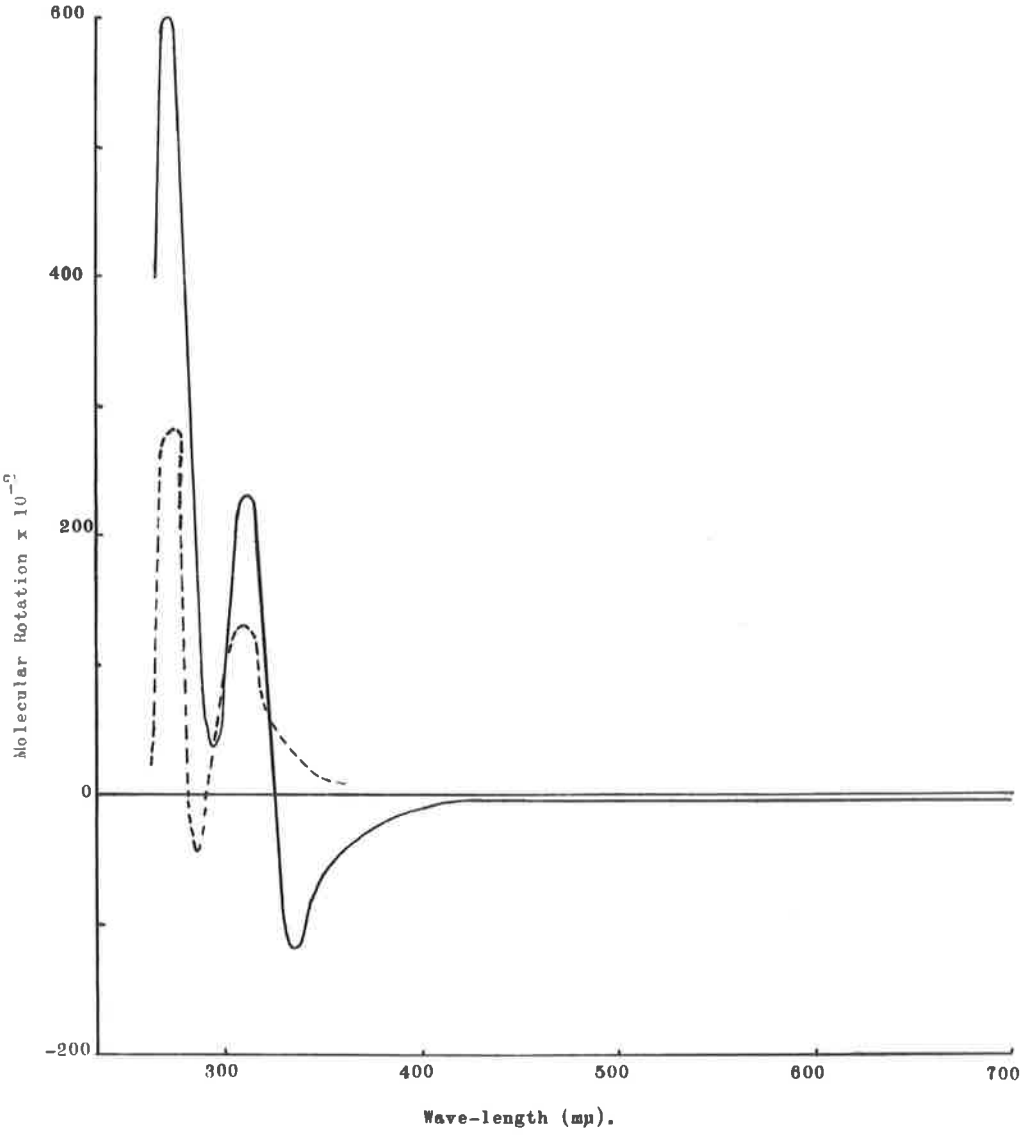


Fig.3.6a. Rotatory dispersion curves of N-salicylidene-α-p-methoxyphenylethylamine (————), and N-o-methoxybenzylidene-α-p-methoxyphenylethylamine (– – – –).

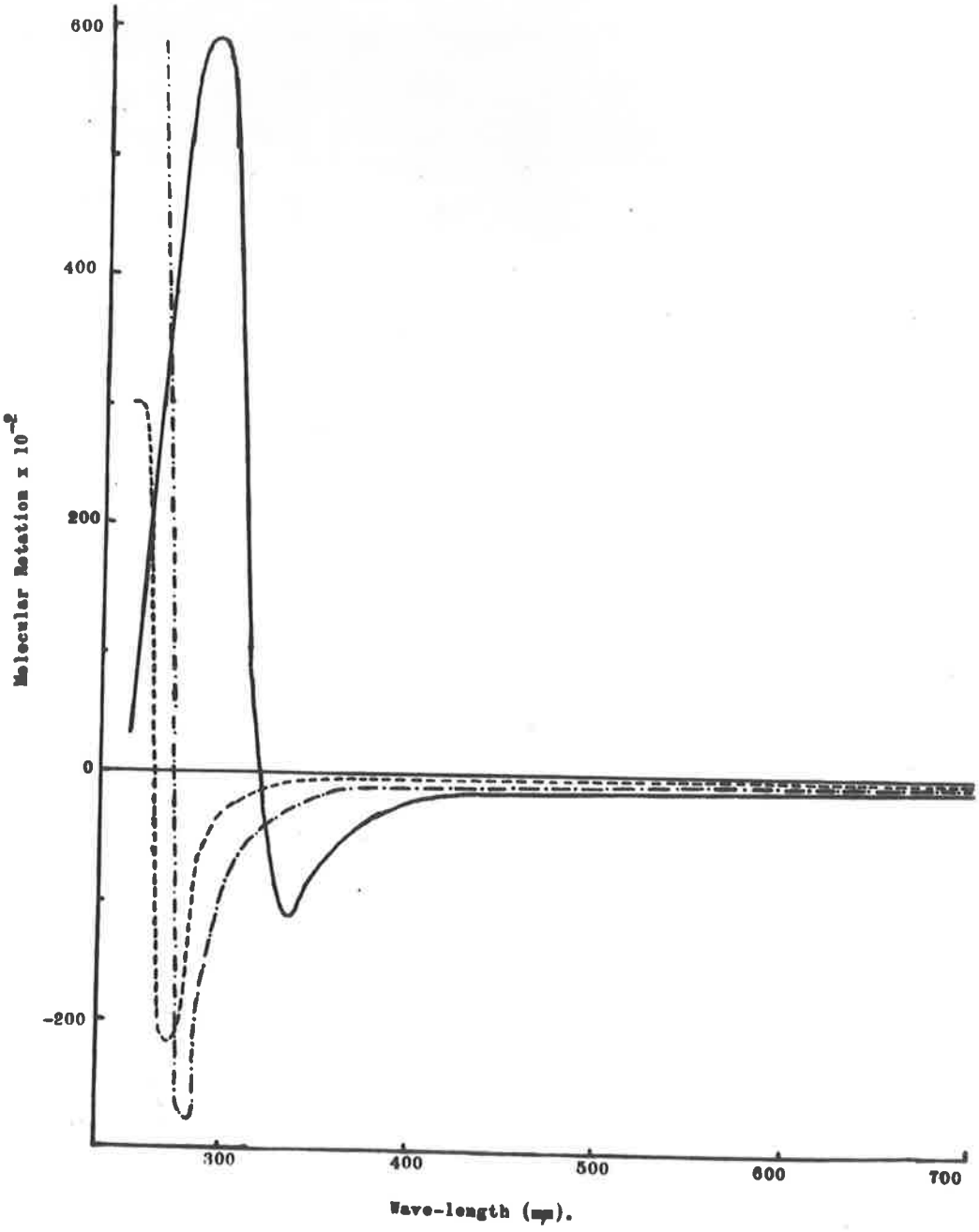


Fig.3.6b. Rotatory dispersion curves of N-p-dimethylaminobensylidene-α-p-methoxyphenylethylamine (————), N-p-methyl-α-p-methoxyphenylethylamine (– – – –), and N-p-methoxy-α-p-methoxyphenylethylamine (–·–·–·–).

Table 3.1

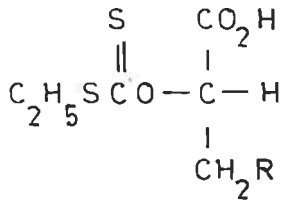
X	Y			
	H	p-CH_3	p-OCH_3	p-Br
p-OCH_3	270	270	265	272
p-CH_3	270	267	255	-
p-$N(CH_3)_2$	310	300	295	320

In comparison with the unsubstituted schiff base (II, Y = H) electron donating substituents (Y = p-CH_3, p-OCH_3), cause a hyposochromic shift to the first extremum, while electron attracting substituents (Y = Br) with very little electronic effects have a value very similar to that of the unsubstituted. Otherwise, there is very little relationship observed between the effect of the different substituent (Y) have on the rotatory dispersion curves of the N-arylidene derivatives of p-substituted α-phenylethylamines.

Part II

Many classes of organic compounds are optically active, but do not possess chromophores that absorb at a convenient wave-length of above 290 mμ. This limites the scope for structural as well as stereochemical conclusions as these compounds would probably exhibit a plain curve. The hydroxy function absorbs below 200 mμ and it is therefore not surprising that the optically active organic alcohols exhibit plain dispersion curves. However in many instances alcohols can be oxidised to the corresponding ketones or aldehydes whose anomalous rotatory dispersion curve can be employed.[72] The desirable point is an easily prepared derivative which has an optically absorption band in a convenient spectral region. Tschugaeff investigated several coloured dixanthates and dithiourethanes of alcohols, and observes anomalous dispersion.[73] The formation of xanthate α-hydroxy-acids were also found to be useful in correlation of configuration.[71] L(+)lactic acid and L(-)-malic acid are configurationally related,[72] though the respective rotations at the sodium D line differ in sign. It was subsequently demonstrated by Fredga[74] that L(+)lactic acid ethyl xanthate (VIII) still retains a positive rotation while the corresponding

derivative of L(-)malic acid (IX) is now positively rotating. The rotatory dispersion curves are shown in



VIII R = H

IX R = CO_2H

Fig. 3.7, the positive cotton effect in each case confirms their configurational relationship. Similarly the formation of dithiocarbamates[76] of α-amino acids served a useful tool for configurational assignments. L(+)alanine and L(-)proline both show positive cotton effect curves, but the amino acids show opposite rotations at the sodium D line.

(-)-α-Phenylethylamine and (+)-amphetamine both have the same absolute configuration,[66] but the amines have opposite rotations at the sodium D line. Their optical rotatory dispersion curves are different as well (Fig. 3.1a, Part I). However, the N-arylidene derivatives generally have the same sign of rotation. It was thought perhaps a derivative can be made of these two amines which would provide a chromophore in the visible region. These derivatives could then be used in comparing with similar

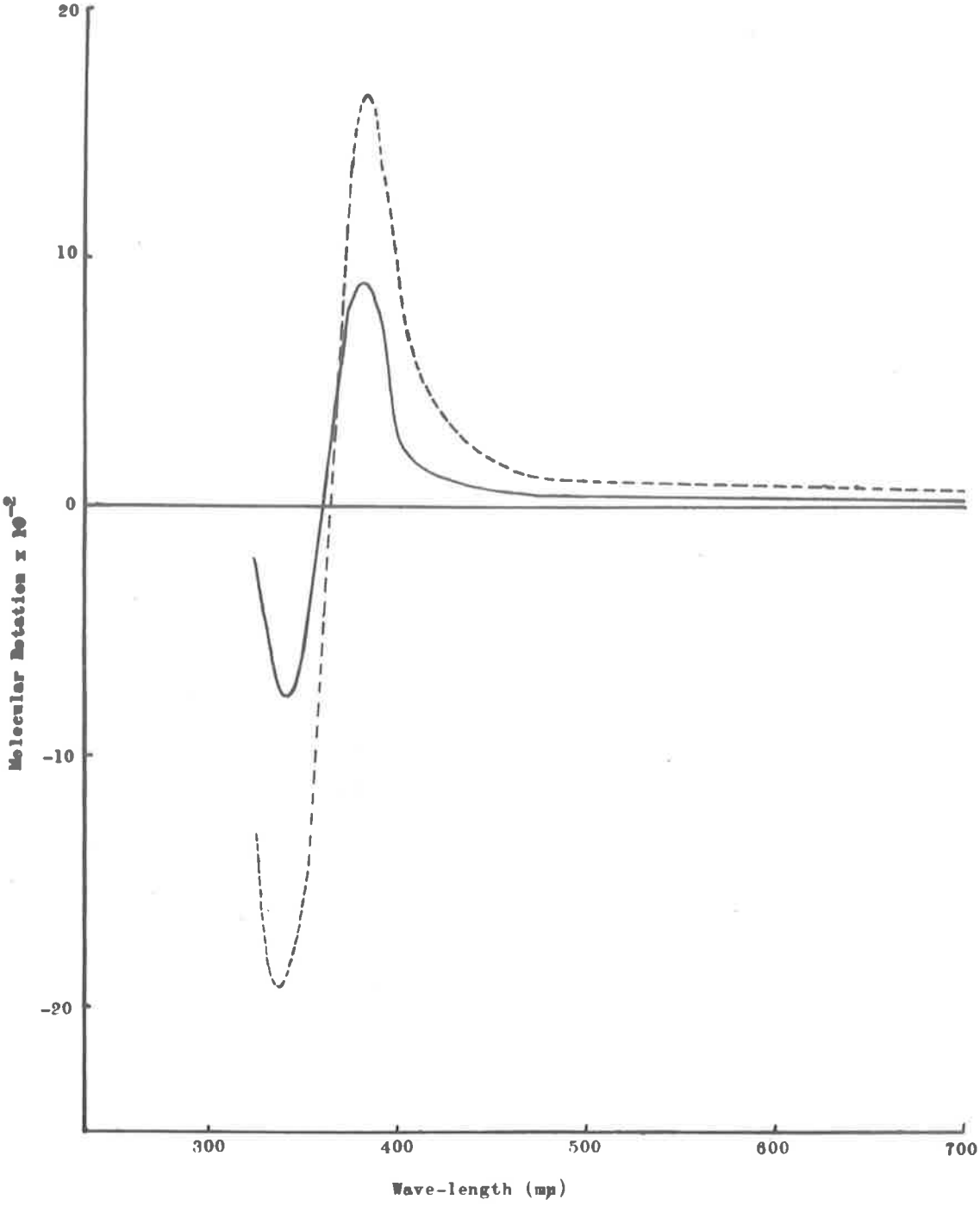
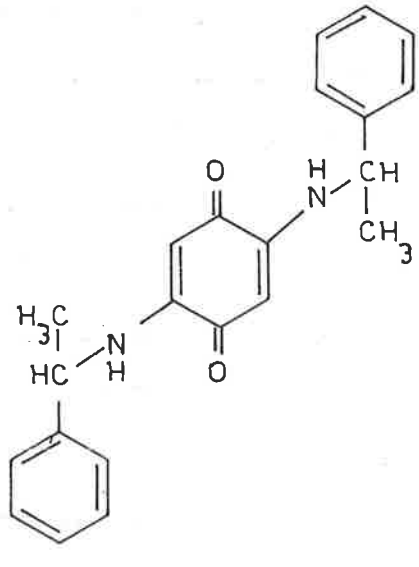


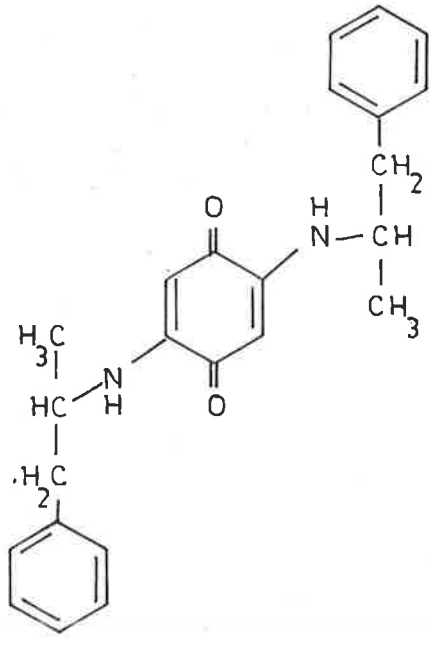
Fig.3.7. Rotatory dispersion curves (methanol) of L-(+)-lactic acid ethyl dithiocarbonate (VIII) and L-malic acid ethyl dithiocarbonate(IX).

derivatives from other amines or related compounds by comparing their rotatory dispersion curves.

Subsequently, it was found that a derivative could be formed from 1,4-benzoquinone and the amines. The product (red crystals) is highly absorbing and absorbs in the visible region. The 1,4-benzoquinone derivatives were prepared by mixing equimolecular proportions in ethanol. The red crystals obtained have sharp melting points and very high optical rotatory power at the sodium D line. The optical rotatory dispersion of the derivatives are shown in Fig. 2.8. Although ∝-phenylethylamine (X) has a negative rotation at the sodium D line, the benzoquinone derivative now has a positive cotton effect similar to the corresponding derivative of amphetamine (XI.)



X



XI

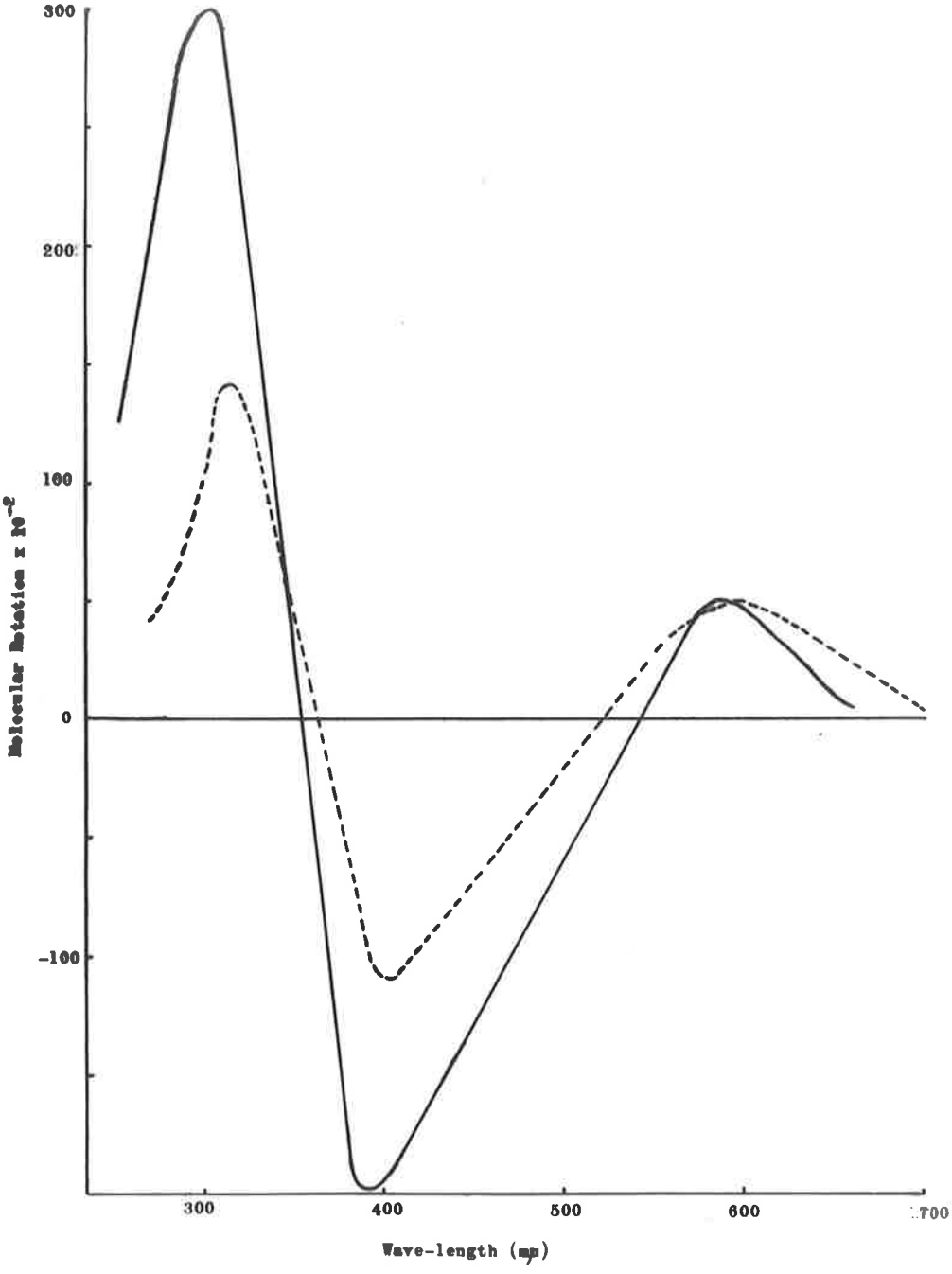


Fig.3.8. Rotatory dispersion curves (ethanol) of 2,5-di(α-phenylethylamino)-1,4-benzoquinone (————), and di-α-(benzylethylamino)-1,4-benzoquinone (- - - - -).

It is most likely then that other derivatives of benzoquinone should exhibit the same type of positive cotton effect curve if the compound has an absolute configuration similar to that of (-)-α-phenylethylamine and (+)-amphetamine. The first and second extrema occur in the visible region (600 mμ and 400 mμ). A complete positive cotton effect curve is therefore observed in the visible region. It can be used in the assignment of absolute configuration. In particular in cases where for instrumental reasons, measurements into the ultraviolet is not possible.

EXPERIMENTAL

Part I

Materials.

(a) Preparation of Amines. The amines were prepared by Leukart's synthesis for amines,[58] using the required ketone (1 mole) and excess ammonium formate (4 moles). Resolution of the amine was carried out by D-(+)-tartaric acid in methanol.[59] The salts were repeatedly recrystallized in methanol until a constant melting point and rotation was obtained. The following amines have been prepared this way.

(i) (-)-α-phenylethylamine: The optically pure amine was obtained in 20% yield, b.p. 105°/43 mm., $[\alpha]_D^{20}$ - 38° (pure liquid) (lit.[59] $[\alpha]_D$ - 36°).

(ii) (+)-α-benzylethylamine: The optically inactive amine was obtained commercially (B.D.H.). The optically pure amine was obtained in 15% yield, b.p. 110°/40 mm., $[\alpha]_D^{20}$ + 36.5° (pure liquid) (lit.[64] + 36.2°).

(iii) (-)-α-p-methylphenylethylamine: The ketone p-methyl acetophenone was prepared by Friedel-Crafts method for the preparation of ketones.[77] The amine (50% pure) was obtained in 10% yield, b.p. 110°/26 mm., $_D^{20}$ - 18.5 (pure liquid) (lit.[78] $[\alpha]_D^{18}$ - 36°).

(iv) (+)-α-p-Bromophenylethylamine: p-Bromoacetophenone was prepared by Friedel-Crafts method for ketones.[77] The amine was obtained in 50% yield, b.p. 114°/11 mm., $[\alpha]_D^{20}$ + 11.1 (c 6.69 in ethanol). The benzoyl derivative m.p. 149-151, $[\alpha]_D$ + 5.0 (c 1.0 in ethanol), was analysed.

Anal. Cald for $C_{15}H_{14}BrNO$: C, 59.22; H, 4.6.
Found: C, 59.59; H, 4.8.

(v) (+)-α-p-methoxyphenylethylamine: p-methoxy acetophenone was prepared by the method of Noller and Adams.[79] The amine (25% yield) was obtained 82.4% optically pure, b.p. 124°/17 mm., $[\alpha]_D^{20}$ + 18.6° (pure liquid) (lit.[80] b.p. 129°/25 mm., $[\alpha]_D$ + 22.7°).

(b) Aldehydes. The benzaldehydes were all obtained commercially. Solids were recrystallized, and liquids distilled under reduced pressure in nitrogen, just before use.

Preparation of optically active schiff bases.

The amine (0.005 mole), and the aldehyde (0.005 mole) were each dissolved in warm ethanol (5 cc), and mixed. The solid schiff bases were obtained by letting the mixture stand overnight. They were recrystallized from ethanol, or aqueous ethanol. The liquid schiff bases were obtained by boiling the mixture (2-4 hrs.). The ethanol was then evaporated. The residue obtained was

distilled under reduced pressure. The above method has been used in preparing all the schiff bases. Whenever possible, the rotations were corrected for the purity of the amine.

Schiff bases of α-phenylethylamine:

N-Benzylidene-(-)-α-phenylethylamine was obtained in 60% yield, b.p. 134°/0.25 mm., $[\alpha]_D^{20}$ + 77° (c 2.15 in ethanol) (lit.[65] $[\alpha]_D$ + 72.25° in ethanol).

N-p-methoxybenzylidene-(-)-α-phenylethylamine, b.p. 138-140°/0.05 mm., was collected in 79% yield. It solidified on standing (m.p. 34°), $[\alpha]_D^{20}$ + 109° (c 3.4 in ethanol) (lit.[65] $[\alpha]_D$ + 97.1° in ethanol).

N-salicylidene-(-)-α-phenylethylamine, m.p. 74-75° was obtained as bright yellow needles in 85% yield, $[\alpha]_D^{20}$ + 223.8° (c 2.25 in ethanol), + 200° (c 1.5 in benzene) (lit.[61] m.p. 76°, $[\alpha]_D$ + 187° in benzene).

N-p-dimethylaminobenzylidene-(-)-α-phenylethylamine, m.p. 83-84° was obtained as cream crystals in 75% yield, $[\alpha]_D^{20}$ + 222° (c 2.52 in ethanol), + 220° (c 1.7 in benzene) (lit.[61] m.p. 84°, $[\alpha]_D$ + 182° in benzene).

N-p-nitrobenzylidene-(-)-α-phenylethylamine was obtained from a mixture of the amine, and a slightly higher equivalent amount of aldehyde. The oil obtained on

evaporation of the ethanol was extracted with a saturated solution of sodium bisulphite to remove the excess aldehyde. It was obtained as a yellow oil, $[\alpha]_D^{20}$ + 120.6° (c 7.88 in ethanol), + 115° (c 6.0 in benzene) (lit.[61] $[\alpha]_D^{20}$ + 106.4 in benzene).

N-o-nitrobenzylidene-(-)-α-phenylethylamine, b.p. 160-161°/ 0.06 mm., $[\alpha]_D^{20}$ - 61.1° (c 1.08 in ethanol), - 70° (c 2.0 in benzene) (lit.[61] $[\alpha]_D$ - 89.5° in benzene).

N-p-methylbenzylidene-(-)-α-phenylethylamine, m.p. 95-96° was obtained as white needles in 81% yield, $[\alpha]_D^{20}$ + 86.1° (c 1.44 in ethanol).

Anal. Cald. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27.
Found: C, 86.18; H, 7.54; N, 6.42.

N-o-methoxybenzylidene-(-)-α-phenylethylamine, b.p. 110°/ 0.01 mm., was collected as a pale yellow liquid in 61% yield, $[\alpha]_D^{20}$ - 94.9° (c 1.92 in ethanol), n_D^{20} 1.5900.

Anal. Cald. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85.
Found: C, 79.92; H, 7.10; N, 6.03.

N-o-ethoxybenzylidene-(-)-α-phenylethylamine, m.p. 63-64° was obtained as white needles in 70% yield, $[\alpha]_D^{20}$ - 35° (c 2.02 in ethanol).

Anal. Cald. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53.
Found: C, 80.93; H, 7.58; N, 5.76.

(ii) Schiff bases of (+)-amphetamine[64] (Table 3.2).

(iii) Schiff bases of (-)-α-p-methylphenylethylamine (Table 3.3).

(iv) Schiff bases of (+)-α-p-bromophenylethylamine (Table 3.4).

Table 3.2.

Schiff bases of ∝-benzylethylamine

Substituent	m.p.	b.p.	n_D^{20}	$[\alpha]_D^{20}$	Yield %
p-NMe_2	64-65°	-	-	+ 280.5	70
p-OCH_3	-	145°/0.04 mm.	1.5791	+ 176	87
p-CH_3	-	145°/0.02 mm.	-	+ 228	65
p-Cl	-	128°/0.05 mm.	1.5780	+ 169.3	64
H	-	99°/0.025 mm.	1.5687	+ 225.5	50
o-OH	61-62°	-	-	+ 345.1	70
o-NO_2	-	154°/0.02 mm.	1.5840	+ 71.9	57
o-OCH_3	-	152°/0.1 mm.	1.5791	+ 176	87
o-Cl	-	135°/0.08 mm.	1.5807	+ 124.5	60
p-NO_2	80-81°	-	-	+ 300	55

Table 3.3

Schiff bases of (-)-α-p-methylphenylethylamine

Substituent	m.p. or b.p. (mm.)	$[\alpha]_D^{20}$	n_D^{20}	Yield %		Calculated %			Found %		
						C	H	N	C	H	N
OH	74-76°	+ 175.7°	-	98	Bright yellow needles	80.3	7.2	5.9	80.04	7.0	5.9
p-NMe_2	89-90°	+ 194.6°	-	87	Pale yellow needles	81.2	8.3	10.5	80.9	8.04	10.7
p-CH_3	98-99°	+ 75°	-	57	White needles	86.03	8.1	5.9	85.9	8.02	6.18
p-OCH_3	158° (0.1)	+ 85°	1.5220	71	Colourless liquid	84.6	7.6	5.5	80.2	7.6	5.7
o-OCH_3	159° (0.15)	- 38°	1.5851	64	Yellow liquid	80.6	7.6	5.5	80.7	7.6	5.6

Table 3.4

Schiff bases of (+)-α-p-Bromophenylethylamine

Substituent	m.p. or b.p. (mm.)	$[\alpha]_D^{20}$	n_D^{20}	Yield %		Calculated %			Found %		
						C	H	N	C	H	N
OH	65-66°	- 53.7°	-	85	Bright yellow needles	59.2	4.6	4.6	59.3	4.7	4.4
p-NMe_2	94-96°	- 75.2°	-	73	White needles	61.6	5.8	8.5	61.6	5.7	8.2
p-OCH_3	61-62° or 185° (0.8)	- 37.3°	-	56	White needles	60.4	5.1	4.4	60.4	5.0	4.1
o-OCH_3 [x]	179° (0.9)	+ 19°	1.5900	72	Yellow liquid	60.4	5.1	4.4	59.8	5.0	4.15

[x] The analysis for carbon is slightly too low for the calculated value. However, since the hydrogen and nitrogen values are correct, and the method of isolation of the schiff base unambiguous, the compound obtained is assumed to be the one indicated.

Schiff bases of (+)-α-p-methoxylphenylethylamine.

N-salicylidene-(+)-α-p-methoxyphenylethylamine, m.p. 64-65° was obtained in 96% yield, $[\alpha]_D^{20}$ - 71.7 (c 1.845 in ethanol), -88° (c 1.265 in benzene) (lit.[80] m.p. 66°, $[\alpha]_D^{20}$ - 139.8° in benzene).

N-p-dimethylaminobenzylidene-(+)-α-p-methoxyphenylethylamine, m.p. 104-105° was obtained in 72% yield, $[\alpha]_D^{20}$ - 172° (c 1.166 in ethanol), -162° (c 1.05 in benzene) (lit.[80] m.p. 105°, $[\alpha]_D^{20}$ - 172° in benzene).

N-p-methylbenzylidene-(+)-α-p-methoxyphenylethylamine, m.p. 89-90° was obtained as white needles in 79.4% yield, $[\alpha]_D^{20}$ - 31.3° (c 1.98 in ethanol).

Anal. Cald. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53.
Found: C, 80.84; H, 7.58; N, 5.54.

N-p-methoxybenzylidene-(+)-α-p-methoxyphenylethylamine, b.p. 175°/0.05 mm. was collected as a colourless liquid in 67% yield. It solidified on standing, m.p. 42-43°, $[\alpha]_D^{20}$ - 42.7° (c 2.205 in ethanol), n_D^{20} 1.6720,

Anal. Cald. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20.
Found: C, 76.13; H, 7.38; N, 5.21.

N-o-methoxybenzylidene-(+)-α-p-methoxyphenylethylamine, b.p. 173-174°/0.05 mm. was obtained as a pale yellow viscous liquid in 62% yield, $[\alpha]_D^{20}$ + 23.6 (c 1.125 in ethanol), n_D^{20} 1.6351.

Anal. Cald. for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11.
Found: C, 75.74; H, 7.30.

Optical Rotatory Dispersion Measurement.

The measurements were carried out in a Rudolf photo-electric spectropolarimeter. It consists of four parts: (a) a Rudolf circular scale high precision polarimeter (model 80); (b) a Beckman quartz monochromator (with light sources of mercury and Zenon); (c) a photovolt multiplier photometer (model 520-M) with interchangeable photomultiplier tubes RCA IP21 (for the visible), and RCA IP28 (for the ultraviolet).

The amine or schiff base (0.001 mole) was dissolved in spectroscopically pure cyclohexane (10 ml.). The measurements were carried out in a polarimeter tube (1 dm.) with special quartz end-plates. For every measurement the tube was placed in the same position in the polarimeter trough i.e. very close to the polariser prism. The angle setting was left permanently at 5°. The optical rotatory dispersion was first measured with the emission lines of the mercury lamp, and then the Zenon lamp was used to fill in the necessary points. Whenever necessary the solution was diluted to allow transmission. However readings were large enough for accurate measurement, and were outside the experimental error of $\pm 0.01^{\circ}$. Readings were measured at large intervals in the visible region (25-50 mμ) and closer at the ultraviolet. At the

extrema, the interval of measurements were as close as 2.5 mμ. A blank run of solvent was carried out each time.

Ultraviolet measurements.

The absorption spectra of the schiff bases and the amines were carried out in spectroscopically pure cyclohexane in an Optica CF_4 recording spectrophotometer.

Infrared measurements.

These were carried out in a Perkin-Elmer Infracord spectrometer with 0.5 mm. cells in chloroform solutions.

Rotatory Dispersion of the Amines.

(a) (-)-α-phenylethylamine: (Fig. 3.1a) $[\phi]_{580}$ - 25°, $[\phi]_{546}$ - 50°, $[\phi]_{275}$ - 380°, $[\phi]_{265}$ - 150°, $[\phi]_{255}$ - 1000°, $[\phi]_{248}$ - 250°.

(b) (+)-α-benzylethylamine (amphetamine): (Fig. 3.1a) $[\phi]_{580}$ + 22°, $[\phi]_{300}$ + 370°, $[\phi]_{248}$ + 2750°.

(c) (-)-α-p-methylphenylethylamine: (Fig. 3.1b) $[\phi]_{580}$- 52°, $[\phi]_{350}$ - 120°, $[\phi]_{300}$ - 200°, $[\phi]_{295}$ - 50°, $[\phi]_{265}$ - 1200°, $[\phi]_{248}$ - 20°.

(d) (+)-α-p-bromophenylethylamine: (Fig. 3.1b) $[\phi]_{580}$ + 24°, $[\phi]_{280}$ + 1100°, $[\phi]_{254}$ + 500°.

(e) (-)-α-p-methylphenylethylamine: (Fig.3.1b) $[\phi]_{580}$ + 24°, $[\phi]_{300}$ + 250°, $[\phi]_{285}$ + 4000°, $[\phi]_{240}$ + 500°

Rotatory Dispersion of Schiff bases.

(a) Schiff bases of α-phenylethylamine.

(i) N-salicylidene-α-phenylethylamine: (Fig. 3.2a) $[\phi]_{589}$ + 265°, $[\phi]_{335}$ + 20480, $[\phi]_{314}$ 0, $[\phi]_{285}$ - 13000, $[\phi]_{274}$ 0, $[\phi]_{263}$ + 34000, $[\phi]_{258}$ + 71 [λ max 257 mμ (log ε 4.14), 321 mμ (log ε 3.57)]

(ii) N-o-methoxybenzylidene-α-phenylethylamine: (Fig. 3.2b) $[\phi]_{589}$ - 150, $[\phi]_{317}$ - 7200, $[\phi]_{307}$ 0, $[\phi]_{300}$ + 47,000, $[\phi]_{280}$ + 11,000, $[\phi]_{265}$ + 41,000, $[\phi]_{240}$ - 23,500 [λ max 256 mμ (log ε 4.178) 304 mμ (log ε 3.74)].

(iii) N-p-methoxybenzylidene-α-phenylethylamine: (Fig. 3.2b), $[\phi]_{589}$ + 277, $[\phi]_{275}$ + 71,000, $[\phi]_{252}$ 0, $[\phi]_{240}$ - 36,000. [λ max 266 mμ (log ε 4.44), 297 mμ (log ε 3.70)].

(iv) N-o-ethoxybenzylidene-α-phenylethylamine: (Fig. 3.2c), $[\phi]_{589}$ + 130, $[\phi]_{325}$ - 5,500, $[\phi]_{315}$ 0, $[\phi]_{290}$ + 32,000, $[\phi]_{275}$ + 20,000, $[\phi]_{265}$ + 45,500, $[\phi]_{248}$ - 10. [λ max 254 mμ (log ε 4.31), 308 mμ (log ε 3.87)].

(v) N-p-methylbenzylidene-α-phenylethylamine: (Fig. 3.2c), $[\phi]_{589}$ + 170, $[\phi]_{265}$ + 53,000, $[\phi]_{248}$ + 10. [λ max 256 mμ (log ε 4.34)].

(vi) N-o-nitrobenzylicene-α-phenylethylamine: (Fig. 3.2d), $[\phi]_{589}$ - 84, $[\phi]_{315}$ - 7,000, $[\phi]_{507}$ 0, $[\phi]_{265}$ + 43,000. [λ shoulder 305 mμ (log. ε 2.505)]

(vii) N-p-dimethylaminobenzylidene-α-phenylethylamine: (Fig. 3.2e), $[\phi]_{589}$ + 301°, $[\phi]_{310}$ + 81,000, $[\phi]_{277}$ 0,

$[\phi]_{258}$ - 20,000. [λ max. 305-312 mμ (log ε 4.395)].

(viii) N-benzylidene-α-phenylethylamine: (Fig. 3.2e) $[\phi]_{589}$ + 177, $[\phi]_{270}$ + 42,000, $[\phi]_{250}$ 0. [λ max. 247 mμ (log ε 4.354)].

(ix) N-p-nitrobenzylidene-α-phenylethylamine (Fig. 3.2e) $[\phi]_{589}$ + 190°, $[\phi]_{305}$ + 31,000, $[\phi]_{280}$ + 75,000, $[\phi]_{258}$ + 18,000. [λ max. 280 mμ (log ε 4.288)].

(b) Schiff bases of (+)-α-benzylethylamine (amphetamine).

(i) N-salicylidene-(+)-amphetamine: (Fig. 3.3a), $[\phi]_{589}$ + 540, $[\phi]_{330}$ + 25,000, $[\phi]_{305}$ 0, $[\phi]_{295}$ - 6,500, $[\phi]_{280}$ 0, $[\phi]_{263}$ + 64,000, $[\phi]_{248}$ 0. [λ max. 256 mμ (log ε 4.22), 317 mμ (log ε 3.60)].

(ii) N-o-nitrobenzylidene-(+)-amphetamine: (Fig. 3.3a) $[\phi]_{589}$ + 170, $[\phi]_{290}$ 14,000, $[\phi]_{260}$ 630,000. [λ max. 250 mμ (log ε 4.314)].

(iii) N-o-methoxybenzylidene-(+)-amphetamine: (Fig. 3.3b) $[\phi]_{589}$ + 290, $[\phi]_{300}$ + 23,000, $[\phi]_{283}$ + 3,000, $[\phi]_{260}$ + 69,000, $[\phi]_{245}$ 0. [λ max. 256 mμ (log ε 4.25), 304 mμ (log ε 3.85)].

(iv) N-p-methoxybenzylidene-(+)-amphetamine: (Fig. 3.3b) $[\phi]_{589}$ + 430, $[\phi]_{272}$ + 70,300, $[\phi]_{248}$ - 6,000. [λ max. 266 mμ (log ε 4.45), 302 mμ (log ε 3.85)].

(v) N-benzylidene-(+)-amphetamine: (Fig. 3.2c) $[\phi]_{589}$ + 336, $[\phi]_{258}$ + 67,000, $[\phi]_{254}$ + 54,000. [λ max. 247 mμ (log ε 4.09)].

(vi) N-p-nitrobenzylidene-(+)-amphetamine: (Fig. 3.2c) $[\phi]_{589}$ + 700, $[\phi]_{324}$ + 30,000, $[\phi]_{317}$ + 18,500, $[\phi]_{290}$ + 62,000, $[\phi]_{265}$ 0, $[\phi]_{258}$ - 17,000. [λ max. 284 mμ (log ε 4.21)]

(vii) N-p-dimethylaminobenzylidene-(+)-amphetamine: (Fig. 3.3d), $[\phi]_{589}$ + 750, $[\phi]_{310}$ + 86,000, $[\phi]_{270}$ 0, $[\phi]_{258}$ - 14,000. [λ max. 307-313 mμ (log ε 4.38)]

(viii) N-p-methylbenzylidene-(+)-amphetamine: (Fig. 3.3d) $[\phi]_{589}$ + 420, $[\phi]_{270}$ + 62,000, $[\phi]_{260}$ + 40,000. [λ max. 256 mμ (log ε 4.398.)]

(c) Schiff bases of (-)-α-p-methylphenylethylamine:

(i) N-salicylidene-(-)-α-p-methylphenylethylamine: (Fig. 3.4a), $[\phi]_{589}$ + 330, $[\phi]_{335}$ + 18,920, $[\phi]_{310}$ 0, $[\phi]_{295}$ - 18,108, $[\phi]_{275}$ 0, $[\phi]_{248}$ + 108,100. [λ max. 258 mμ (log ε 4.23), 314 mμ (log ε 3.77)].

(ii) N-o-methoxybenzylidene --: (Fig. 3.4a), $[\phi]_{589}$ - 54, $[\phi]_{305}$ - 27,500, $[\phi]_{297}$ 0, $[\phi]_{293}$ + 31,000, $[\phi]_{280}$ + 11,000, $[\phi]_{265}$ + 59,500. [λ max. 254 mμ (log. ε 4.38), 307 mμ (log ε 3.98)].

(iii) N-p-methoxybenzylidene --: (Fig. 3.4b), $[\phi]$ + 380, $[\phi]_{280}$ + 81,000. [λ max. 267 mμ (log ε 4.55)].

(iv) N-p-dimethylaminobenzylidene --: (Fig. 3.4b), $[\phi]_{589}$ + 540, $[\phi]_{300}$ + 105,000, $[\phi]_{254}$ + 2,000. [λ max. 300-310 mμ (log. ε 4.58)]

(v) N-p-methylbenzylidene —: (Fig. 3.4b), $[\phi]_{589}$ + 400, $[\phi]_{270}$ + 95,000, $[\phi]_{248}$ + 4,000 [λ max 256 mμ (log ε 4.505)].

(d) Schiff bases of (+)-α-p-bromophenylethylamine.

(i) N-salicylidene --: (Fig. 3.5a), $[\phi]_{589}$ - 160, $[\phi]_{324}$ - 15,000, $[\phi]_{313}$ 0, $[\phi]_{295}$ + 16,000, $[\phi]_{285}$ + 7,000, $[\phi]_{260}$ + 300. [λ max 258 mμ (log. ε 4.28), 322 mμ (log. ε 3.70)].

(ii) N-methoxybenzylidene --: (Fig. 3.5a), $[\phi]_{589}$ + 61, $[\phi]_{315}$ + 10,000, $[\phi]_{292}$ + 23,000, $[\phi]_{278}$ - 19,000, $[\phi]_{262}$ - 43,000, $[\phi]_{258}$ - 15,000. [λ max 254 mμ (log ε 4.03), 304 mμ (log ε 3.49)].

(iii) N-p-dimethylaminobenzylidene --: (Fig. 3.5b), $[\phi]_{589}$ - 249, $[\phi]_{338}$ - 6,000, $[\phi]_{335}$ 0, $[\phi]_{317}$ + 42,000, $[\phi]_{310}$ + 22,000, $[\phi]_{290}$ + 85,000, $[\phi]_{250}$ + 11,000. [λ max 314 mμ (log ε 4.33)].

(iv) N-p-methoxybenzylidine --: (Fig. 3.5b), $[\phi]_{589}$ - 118, $[\phi]_{305}$ + 3,500, $[\phi]_{300}$ 0, $[\phi]_{273}$ + 48,000, $[\phi]_{240}$ + 4,000. [λ max 266 mμ (log ε 4.43), 296.5 mμ (log. ε 3.64)].

(e) Schiff bases of (+)-α-p-methoxyphenylethylamine.

(i) N-salicylidene --: (Fig. 3.6a), $[\phi]_{589}$ - 190, $[\phi]_{335}$ - 12,700, $[\phi]_{310}$ + 23,700, $[\phi]_{295}$ + 3,600, $[\phi]_{267}$ + 61,200. [λ max 254 mμ (log ε 4.10), 314 mμ (log ε 3.42)].

(ii) N-o-methoxybenzylidene -- (Fig. 3.6a) $[\phi]_{589}$ + 60, $[\phi]_{305}$ + 13,000, $[\phi]_{289}$ - 4,000, $[\phi]_{275}$ + 30,000, $[\phi]_{265}$ + 12,000. [λ max 255 mμ (log ε 4.326), 307 mμ (log ε 3.85)].

(iii) N-p-dimethylaminobenzylidene -- (Fig. 3.6b), $[\phi]_{589}$ - 494, $[\phi]_{330}$ - 12,200, $[\phi]_{293}$ + 60,000, $[\phi]_{265}$ + 18,000. [λ max 327-330 mμ (log ε 4.50)].

(iv) N-p-methoxybenzylidene --: (Fig. 3.6b), $[\phi]_{589}$ - 14, $[\phi]_{280}$ - 28,000, $[\phi]_{258}$ + 74,000. [λ max 272 mμ (log ε 4.36)].

(v) N-p-methylbenzylidene --: (Fig. 3.6b), $[\phi]_{589}$ -80, $[\phi]_{272}$ - 23,000, $[\phi]_{262}$ 0, $[\phi]_{254}$ + 29,000. [λ max 256 mμ (log ε 4.44)].

Part II

Materials.

(a) (+)-Amphetamine and (-)-α-phenylethylamine were each prepared as for Part I.

(b) 1,4-Benzoquinone was obtained commercially (B.D.H.) but was recrystallized for X4/Benzene mixture before use.

Benzoquinone derivatives.

The amine (0.01 mole), and an equivalent amount of benzoquinone (0.01 mole) were mixed in ethanol (10 mls.). The reaction is exothermic. On boiling gently for 2 hours, the mixture was left to stand aside. On cooling a red solid was obtained. For purification, the red solid was dissolved in benzene and chromatographed on alumina and eluted with benzene. The benzoquinone was left on the column and the benzene fractions collected contained pure product.

(a) 2,5-Di(α-phenylethylamino)-1,4-benzoquinone was obtained as red needles m.p. 188-189°, $[\alpha]_D^{25}$ + 1177 (c 0.0476 in ethanol, l = 4).

Anal. Cald. for $C_{22}H_{22}N_2O_2$ require: C, 76.3; H, 6.4; N, 8.1.

Found: C, 76.0; H, 6.6; N, 8.45.

(b) 2,5-Di(α-benzylethylamino)-1,4-benzoquinone was obtained as red needles m.p. 157-158°, $[\alpha]_D^{25}$ + 1202 (c 0.042

in ethanol, l = 4).

Anal.Cald. for $C_{24}H_{26}N_2O_2$ require: C, 76.97; H, 7.0; N, 7.5

Found: C, 77.2; H, 6.9; N, 7.9.

Optical Rotatory Dispersion measurements.

The optical rotatory dispersion were carried out in the same way as for Part I. The benzoquinone derivative (0.001 M) was dissolved in S.V.R. alcohol. The solution was diluted accordingly. Rotations were measured at close intervals at the peaks and troughs and the rotations measured were all larger than the experimental error of ± 0.01°.

Rotatory Dispersion of 2,5-di(∝-phenylethylamino)1,4-benzoquinone: (Fig. 3.8), $[\phi]_{600}$ + 4,000, $[\phi]_{540}$ 0, $[\phi]_{390}$ - 21,000, $[\phi]_{335}$ 0, $[\phi]_{300}$ + 48,000, $[\phi]_{253}$ + 24,000. [λ max 345 mμ (log ε 4.47), 495-500 mμ (log ε 2.44)].

Rotatory Dispersion of 2,5-di(∝-benzylethylamino)1,4-benzoquinone: (Fig. 3.8), $[\phi]_{600}$ + 4500, $[\phi]_{517}$ 0, $[\phi]_{400}$ - 16,000, $[\phi]_{360}$ 0, $[\phi]_{310}$ + 20,000, $[\phi]_{253}$ + 5,000. λ max 345 mμ (log ε 4.47), 495-500 mμ (log ε 2.44).

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