Triad Prototropic Systems. Part III. The Effect of Substituents on the Mobility of the Azomethine System.*

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Aliphatic and aromatic α-amino-acids are easily degraded to carbonyl compounds containing one less carbon atom, when heated with aldehydes and ketones in which the carbonyl group is preferably directly attached to, or conjugated with, electron-attracting groups (see preceding paper); the corresponding azomethines from the same aldehydes and ketones and aliphatic amines do not tautomerise except in the case of isatin ethylimine. Anomalous results are obtained with the imines formed from the *o*-nitrobenzaldehydes.

However, most of the Schiff's bases derived from benzylamine tautomerise, though generally much less than the corresponding azomethinecarboxylic acids. When some of the corresponding esters are subjected to the same treatment, practically no tautomerism takes place, which shows that decarboxylation is the main factor responsible for the high mobility of the acids.

THE azomethine system is known to be immobile except in the presence of a strong nucleophilic reagent such as sodium ethoxide (cf. Ingold *et al.*, *J.*, 1922, **121**, 2381; 1929, 1199; Shoppee, *J.*, 1931, 1225; 1932, 696). Mobility is promoted by aryl groups, but in (I) and (II) (R = H or alkyl) it requires the presence of alkali at an elevated temperature and appears to be unidirectional.

$$\text{(I)}\quad \mathrm{Ph{\cdot}\overset{\gamma}{C}H_2{\cdot}N{:}\overset{\alpha}{C}HR} \longrightarrow \mathrm{Ph{\cdot}\overset{\gamma}{C}H{:}N{\cdot}\overset{\alpha}{C}H_2R}\quad \text{(II)}$$

In the present investigation we have studied the mobility of the Schiff's bases R·CH:N·R', where R is a substituted phenyl group and R' is ethyl, *iso*propyl, *cyclo*hexyl, or benzyl, in an attempt to compare them with the corresponding azomethinecarboxylic acids. The experiments were carried out in boiling dry pyridine in a stream of dry carbon dioxide (cf. Part II).

With the exception of those from *o*-nitrobenzaldehydes, which behaved anomalously, the Schiff's bases Ar·CH:NR' are relatively immobile when R' is ethyl, *iso*propyl or *cyclo*hexyl, mobility decreasing in that order: *e.g.*, the base from isatin and ethylamine isomerised but those from isatin and *iso*propylamine or *cyclo*hexylamine did not; *o*-chlorobenzylidene*cyclo*hexylamine was stable even when refluxed with alcoholic sodium ethoxide for 5 hours (cf. Baddar, *J.*, 1950, 136). This may be due to the fact that the negative charge created on the α-carbon atom of the *iso*propylimine or *cyclo*hexylimine by the inductive effect (+*I*) of the methyl or methylene groups is greater in these cases than with the ethyl group. However, the stability of the *iso*propyl- and *cyclo*hexyl-imines cannot be due to the

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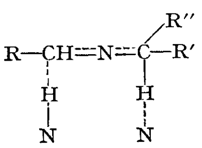
* Part II, preceding paper.

preferential recombination of the proton at the α-carbon atom because this will not explain why the corresponding azomethinecarboxylic acids undergo appreciable interconversion (cf. Part II), even at a lower temperature.

The mobility of the system increased very greatly when R′ of Ar·CH:NR′ was changed from alkyl to benzyl: this, by the —*E* effect of the phenyl group, lowered the energy required for the removal of the proton from the α-carbon atom. Conversion of Ar·CH:N·CH_2Ph into Ar·CH_2·N:CHPh was also facilitated by the introduction of electron-attracting groups, especially in the *o*- and the *p*-position of the group Ar.

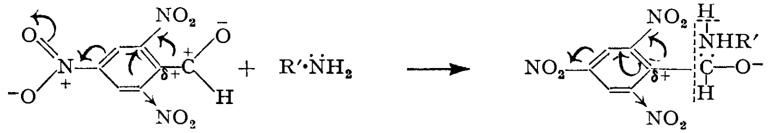
Steric factors may play an important role in explaining some of the ambiguous results obtained. Thus, if we accept the termolecular mechanism of prototropy advanced by Lowry (*J.*, 1927, 2554; Ossorio and Hughes, *J.*, 1952, 426) we can understand why the interconversion of *o*-nitro- and 2 : 4 : 6-trichlorobenzylidenebenzylamine was lower than that of *p*-nitro- and *o*-chlorobenzylidenebenzylamine, respectively, in spite of the fact that all these Schiff's bases are easily formed when the constituents are mixed. According to this mechanism pyridine and its conjugate acid attack the molecule at both the α- and the γ-carbon atom simultaneously. This will be influenced by steric factors, which are developed with the increase in bulk of the groups R′ and R″ in (III) or with the introduction of *o*-substituents into R.



(III)

Such a phenomenon was not observed with α-amino-acids, because here the change is governed by decarboxylation of the intermediate azomethinecarboxylic acid—a process which is hardly affected by steric factors.

Although steric factors may be partly responsible, the low conversion of amines into carbonyl compounds by 2 : 4 : 6-trinitrobenzaldehyde may be mainly due to the ready reaction of 2 : 4 : 6-trinitrobenzaldehyde with amines to give *s*-trinitrobenzene (cf. Secareanu, *Ber.*, 1931, **64**, 837; *Bull. Soc. chim.*, 1932, **51**, 591), which seems to take place as follows:



The broken line indicates the fate of electron pairs forming the covalent bonds which were broken.

Azomethinecarboxylic esters (IV) were found to be substantially immobile and they were almost unchanged by our treatment, possibly owing to competition between the azomethine (IV*a*) and the keto–enol system (V*b*). Therefore, even if the proton is extracted by the catalyst, recombination may take place preferentially at the oxygen atom to give

(IV)

(V)

$$\text{(IV)}\quad \text{Ar}\cdot\text{CH}{:}\text{N}\cdot\underset{\text{Ph}\ \ \text{H}}{\text{C}}\text{—}\underset{\text{OEt}}{\text{C}}{:}\text{O} \rightleftharpoons \text{Ar}\cdot\text{CH}{:}\text{N}\cdot\underset{\text{Ph}}{\text{C}}{=}\underset{\text{OEt}}{\text{C}}\cdot\text{OH}\quad \text{(V)}$$

(V) which on hydrolysis with dilute acids regenerates phenylglycine ethyl ester. Brewer and Herbst (*J. Org. Chem.*, 1941, **6**, 867) noticed that the amino-group of a transaminating system moves to, or remains attached to, that side of the system which carries the protected carboxyl group. The authors believe, however, that the reaction between carbonyl compounds and esters needs further investigation.

The results obtained in the present work showed clearly that the ease of prototropy in the case of azomethinecarboxylic acids, compared with that of the azomethines and azomethinecarboxylic esters, is mainly due to the decarboxylation in the first system.

EXPERIMENTAL

N-(2-*Chloro*-5-*nitrobenzylidene*)*ethylamine*.—2-Chloro-5-nitrobenzaldehyde (Erdmann, *Annalen*, 1893, **272**, 148) (1·8 g.) was left with anhydrous ethylamine (5 c.c.) overnight at room temperature, then diluted with water, and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4), and evaporated to a brownish yellow solid (*ca.* 2·0 g.), which was crystallised from light petroleum (b. p. 40—60°), to give N-(2-*chloro*-5-*nitrobenzylidene*)*ethylamine* as pale lemon-yellow aggregates, m. p. 47—48°, depressed on admixture with the original aldehyde (Found: C, 51·0; H, 4·2; N, 12·6; Cl, 16·6%; *M*, 188. $C_9H_9O_2N_2Cl$ requires C, 50·8; H, 4·2; N, 13·2; Cl, 16·7%; *M*, 212·5).

Isatin iso*Propylimine*.—Isatin (1·1 g., 1 mol.) dissolved exothermally in *iso*propylamine (5 c.c.). Next morning the excess of amine was evaporated off. The residual *isatin* iso*propylimine* (1·3 g.) crystallised from benzene–light petroleum (b. p. 60—80°) as pale yellow crystals, m. p. 185—186°, depressed on admixture with isatin (Found: C, 70·0; H, 6·4; N, 14·7%; *M*, 175. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%; *M*, 188).

N-(p-*Nitrobenzylidene*)iso*propylamine*.—A suspension of *p*-nitrobenzaldehyde (1·5 g.) in ether (50 c.c.) was left with *iso*propylamine (3 c.c.) overnight, then washed with 2% aqueous acetic acid solution, 3% sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Evaporation and crystallisation from light petroleum (b. p. 40—60°) gave N-(p-*nitrobenzylidene*)-iso*propylamine* (crude, *ca.* 1·75 g.) as yellowish prismatic needles, m. p. 54—55°, depressed on admixture with the original aldehyde (Found: C, 62·6; H, 6·3; N, 14·5%; *M*, 165. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·25; N, 14·6%; *M*, 192).

N-(2-*Chloro*-5-*nitrobenzylidene*)iso*propylamine*.—2-Chloro-5-nitrobenzaldehyde (2·0 g.) was left with *iso*propylamine (10 c.c.) at room temperature overnight, and then evaporated in a vacuum at room temperature. The residual N-(2-*chloro*-5-*nitrobenzylidene*)iso*propylamine* (2·4 g.) crystallised from light petroleum (b. p. 60—80°) as colourless crystals, m. p. 94—95°, depressed on admixture with the original aldehyde (Found: C, 53·3; H, 4·85; N, 11·8; Cl, 15·2. $C_{10}H_{11}O_2N_2Cl$ requires C, 53·0; H, 4·9; N, 12·4; Cl, 15·7%).

Other Imines.—Reactions similar to the above gave *isatin* cyclo*hexylimine*, brownish-yellow (from benzene), m. p. 157—158° (1·6 g. from 1·5 g. of isatin) (Found: C, 73·9; H, 6·9; N, 12·2%; *M*, 212. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·0; N, 12·3%; *M*, 228), N-(2 : 4-*dinitrobenzylidene*)-cyclo*hexylamine*, pale orange, m. p. 80—81° (Found: C, 56·3; H, 5·2; N, 15·2%; *M*, 249, 293. $C_{13}H_{15}O_4N_3$ requires C, 56·3; H, 5·4; N, 15·2%; *M*, 277), N-(2-*chloro*-5-*nitrobenzylidene*)cyclo*hexylamine*, pale yellow, m. p. 112° (Found: C, 58·5; H, 5·6; N, 10·5; Cl, 13·2%; *M*, 243. $C_{13}H_{15}O_2N_2Cl$ requires C, 58·5; H, 5·6; N, 10·5; Cl, 13·3%; *M*, 266·5), N-(p-*chlorobenzylidene*)-cyclo*hexylamine* (crystallised from light petroleum at −5° to −7°), almost colourless needles, m. p. 57—58° (Found: C, 70·5; H, 7·0; N, 6·6; Cl, 16·6%. $C_{13}H_{16}NCl$ requires C, 70·4; H, 7·2; N, 6·3; Cl, 16·0%), N-(*piperonylidene*)cyclo*hexylamine* (crystallised at <0°), very pale yellow rhombs, m. p. 65—66° (Found: C, 72·9; H, 7·5; N, 6·2%; *M*, 206. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·1%; *M*, 231), N-(p-*hydroxybenzylidene*)cyclo*hexylamine* (crystallised from benzene), colourless leaflets, m. p. 175—176° (2·3 g. from 2·3 g. of aldehyde) (Found: C, 76·7; H, 8·4; N, 6·9%; *M*, 199. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·4; N, 6·9%; *M*, 203), N-(2 : 4-*dinitrobenzylidene*)*benzylamine* [crystallised from benzene–light petroleum (b. p. 60—80°)], light brown needles, m. p. 85—86° (Found: C, 59·2; H, 4·1; N, 14·6%; *M*, 271. $C_{14}H_{11}O_4N_3$ requires C, 59·0; H, 3·9; N, 14·7%; *M*, 285), N-(2-*chloro*-5-*nitrobenzylidene*)*benzylamine* [crystallised from benzene–light petroleum (b. p. 60—80°)], pale yellow rhombs, m. p. 73—74° (Found: C, 60·9; H, 4·1; N, 10·3; Cl, 13·0%; *M*, 281. $C_{14}H_{11}O_2N_2Cl$ requires C, 61·2; H, 4·1; N, 10·2; Cl, 13·0%; *M*, 274·5), N-(2 : 4 : 6-*trichlorobenzylidene*)*benzylamine*, pale yellow silky needles, m. p. 50—51° (Found: C, 56·0; H, 3·35; N, 4·65; Cl, 35·5. $C_{14}H_{10}NCl_3$ requires C, 56·3; H, 3·35; N, 4·7; Cl, 35·7%), N-*piperonylidenebenzylamine* [crystallised from benzene–light petroleum (b. p. 60—80°)], colourless needles, m. p. 73—74° (Found: C, 75·1; H, 5·6; N, 5·8%; *M*, 225. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·5; N, 5·85%; *M*, 239), N-(p-*hydroxybenzylidene*)*benzylamine* (mostly precipitated from the ethereal solution of the reactants; crystallised from acetone), colourless cubes, m. p. 209—210° (Found: C, 79·6; H, 6·3; N, 6·0%; *M*, 186. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2; N, 6·6%; *M*, 211), N-(o-*nitrobenzylidene*)-*benzylamine*, a pale yellow oil (decomposed on distillation in a vacuum) (Found: C, 69·5; H, 5·2; N, 11·5%; *M*, 225. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0; N, 11·7%; *M*, 240), *ethyl* α-p-*nitrobenzylideneamino*-α-*phenylacetate* [crystallised from benzene–light petroleum (b. p. 40—60°)], pale yellow, unstable if impure, m. p. 75—76° (Found: C, 65·8; H, 5·1; N, 8·65%; *M*, 312. $C_{17}H_{16}O_4N_2$ requires C, 65·4; H, 5·2; N, 9·0%; *M*, 312), *ethyl* α-m-*nitrobenzylideneamino*-α-*phenylacetate* [crystallised from benzene–light petroleum (b. p. 40—60°)], colourless, m. p. 87—88° (Found: C, 65·7; H, 5·4; N, 8·7%; *M*, 298), *ethyl* α-2-*chloro*-5-*nitrobenzylideneamino*-α-*phenylacetate* [crystallised from benzene–light petroleum (b. p. 60—80°)], colourless, m. p. 129—130° (Found: C, 58·8; H, 4·1; N, 8·7; Cl, 9·6. $C_{17}H_{15}O_4N_2Cl$ requires C, 58·9; H, 4·3; N, 8·1; Cl, 10·2%), *ethyl* α-2 : 5-*dichlorobenzylideneamino*-α-*phenylacetate* [crystallised from benzene–light petroleum (b. p. 40—60°)], colourless, m. p. 54—55° (Found: C, 61·0; H, 4·5; N, 4·2; Cl, 20·9%; *M*, 298. $C_{17}H_{15}O_2NCl_2$ requires C, 60·7; H, 4·5; N, 4·2; Cl, 21·1%; *M*, 336), and *ethyl* α-p-*hydroxybenzylideneamino*-α-*phenylacetate* (crystallised from benzene), colourless, m. p. 151—152° (Found: C, 72·0; H, 5·9; N, 4·2. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·0; N, 4·9%).

Reactions with 2 : 4 : 6-*Trinitrobenzaldehyde.*—An ethereal solution of this aldehyde (Secareanu, *loc. cit.*) (2·0 g., 1 mol.) and *cyclo*hexylamine (0·82 g., 1 mol.) or benzylamine (0·9 g., 1 mol.) was left at room temperature for 2 days. Evaporation of the blood-red solution left a dark brown solid (*ca.* 2·0 g.) which, crystallised from dilute alcohol, gave 1 : 3 : 5-trinitrobenzene as colourless plates, m. p. 121—122°, undepressed on admixture with an authentic specimen (Found: C, 34·2, 33·7; H, 1·2, 1·5; N, 19·3, 20·1%; *M*, 212. Calc. for $C_6H_3O_6N_3$: C, 33·8; H, 1·4; N, 19·7%; *M*, 213).

2 : 4-*Dinitrophenylhydrazones.*—The following 2 : 4-*dinitrophenylhydrazones* were prepared in the usual manner, and were crystallised from acetic acid.

Benzaldehyde deriv.	Hydrazone, colour	m. p.	Formula	Found (%)				Required (%)			
				C	H	N	Cl	C	H	N	Cl
2-Chloro-5-nitro- ...	yellow	275—277°	$C_{13}H_8O_6N_5Cl$	42·9	2·4	19·3	9·6	42·7	2·2	19·2	9·7
2 : 4 : 6-Trichloro-...	orange	237—238	$C_{13}H_7O_4N_4Cl_3$	40·4	2·0	14·4	27·7	40·1	1·8	14·4	27·3
2 : 5-Dichloro-	yellow	242—243	$C_{13}H_8O_4N_4Cl_2$	43·9	2·2	15·6	20·1	43·9	2·25	15·8	20·0

Interconversion of the Ethylimines and iso*Propylimines.*—The imine (*ca.* 0·0021 mole) or a mixture of the carbonyl compound (0·0021 mole) and ethyl- or *iso*propyl-amine (0·0021 mole) was refluxed with dry pyridine (10 c.c.) in an oil-bath at 120° ± 2° in a stream of dry carbon dioxide. The experiments were carried out in the apparatus used in the degradation of the corresponding α-amino-acids (cf. preceding paper). The mixture was acidified with dilute hydrochloric acid and refluxed for *ca.* 20 min.

When 50% aqueous glycerol, at 145° ± 5°, was used instead of dry pyridine, acidification was omitted.

The liberated acetaldehyde and acetone were estimated as their 2 : 4-dinitrophenylhydrazones and identified by m. p. and mixed m. p. with authentic specimens.

From the weight of the hydrazones, the percentages of interconversion were calculated, the correction factors recorded in the preceding paper being used. The results are summarised in the annexed Table.

Interconversion (%).

Carbonyl compound	NH_2Et		NH_2Pr^i		$[CH_2]_5{>}CH{\cdot}NH_2$		$CH_2Ph{\cdot}NH_2$	
	P	G	P	G	P	G	P	Procedure
Isatin	42·8 *	24·6 * [1]	0	0	0	0	79·6 † [4]	(i)
2 : 4 : 6-Trinitrobenzaldehyde †	8·3	9·6	9·4	11·3	Trace	Trace	29·5 [5]	(i), (ii)
2 : 4-Dinitrobenzaldehyde ...	8·0 *	18·1 *	0 *	46·3 * [3]	0	Trace	63·2	(ii)
p-Nitrobenzaldehyde	0 ‡	0 ‡	0	0	0 ‡	0 ‡	38·2 [6]	(ii)
o-Nitrobenzaldehyde	0 *	18·6 * [2]	0 *	7·3 *	0 †	Trace †	17·1	(ii)
m-Nitrobenzaldehyde	—	—	—	—	0 †	—	5·0	(ii)
2-Chloro-5-nitrobenzaldehyde	0	0	0	0	0	0	23·5	(ii)
2 : 4 : 6-Trichlorobenzaldehyde	—	—	—	—	—	—	9·6	(iii*b*)
2 : 5-Dichlorobenzaldehyde...	—	—	—	—	0 †	—	22·8 †	(iii*b*)
o-Chlorobenzaldehyde	0 ‡	0 ‡	—	—	0 ‡	0 ‡	16·0 †	(iii*b*)
m-Chlorobenzaldehyde	—	—	—	—	0 †	—	5·7	(iii*b*)
p-Chlorobenzaldehyde	—	—	—	—	0	—	0	(iii*b*)
Piperonaldehyde	—	—	—	—	0	—	0	(i)
p-Hydroxybenzaldehyde [7] ...	—	—	—	—	0	—	0	(i)

P = pyridine, G = glycerol.
* The crude Schiff's base was used without purification.
† An equimolecular mixture of the carbonyl compound and the amine was used.
‡ Baddar's results (*J.*, 1950, 136).

[1] 11·3% when the product was hydrolysed without being refluxed. [2] 8·0% at 120° ± 2°. [3] Nil at 115° ± 2°. [4] 74·8% on a boiling-water bath. When benzylamine was mixed with isatin and left at room temperature for ½ hr., then decomposed with dilute hydrochloric acid, benzaldehyde was obtained (*ca.* 18·0%). [5] When the mixture was left at room temperature for ½ hr. and worked up as usual, the apparent interconversion was 8·5%. [6] 20·6% on a boiling-water bath. [7] Traces of benzaldehyde were obtained when the imine was heated for ½ hr. in quinoline 165° ± 5°. No benzaldehyde was formed when benzylamine alone was similarly treated.

In the case of 2 : 4 : 6-trinitrobenzaldehyde, the acidified reaction mixture was extracted with ether, and the residue (0·2 g.) left on the evaporation of the solvent was crystallised from dilute alcohol, to give 1 : 3 : 5-trinitrobenzene, identified by m. p. and mixed m. p.

Interconversion of the cyclo*Hexylimines.*—Reaction mixtures were heated as above for 3 hr., then acidified with dilute hydrochloric acid, refluxed for *ca.* 20 min., and distilled. The distillate was treated with 2 : 4-dinitrophenylhydrazine solution, and the precipitated hydrazones were filtered off and dried. The amount of the *cyclo*hexanone derivative in the mixture was estimated by extraction with hot alcohol, and the percentage of interconversion was calculated with the correction factors recorded in the preceding paper. In most cases the m. p. of the precipitated 2 : 4-dinitrophenylhydrazone indicated that it was that of the original carbonyl compound, and no depression took place on admixture with an authentic specimen. The results are summarised in the Table.

In the case of 2 : 4 : 6-trinitrobenzaldehyde, the mixture was found to contain 1 : 3 : 5-trinitrobenzene.

Interconversion of the Benzylimines.—After treatment as above (3 hr.), the mixture was acidified with dilute hydrochloric acid, and the benzaldehyde formed was estimated by the procedures adopted in the degradation of phenylglycine, the same correction factors being used. The results are summarised in the Table.

Attempted Interconversion of α-Benzylideneamino-α-phenylacetic Esters.—A solution of the azomethinecarboxylic ester (ethyl α-*p*-nitro-, -*m*-nitro-, -2-chloro-5-nitro, -2 : 5-dichloro-, and -*p*-hydroxybenzylideneamino-α-phenylacetate) (0·0021 mole) in dry pyridine (10 c.c.) was refluxed on an oil-bath at 120° ± 2°, in a stream of dry carbon dioxide for 3 hr., then treated with aldehyde-free 95% alcohol (100 c.c.) and concentrated hydrochloric acid (15 c.c.). Treatment with a boiling solution of 2 : 4-dinitrophenylhydrazine hydrochloride gave the hydrazone (m. p. and mixed m. p.) of the original aldehyde.

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