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THE ISOMERISM OF 1,5-DIPHENYL-3-HYDROXY-METHYL-1,2,4-TRIAZOLE

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Abstract—The isomers of 1,5-diphenyl-3-hydroxymethyl-1,2,4-triazole are described. The isomerism is shown to arise at the molecular level of organization. Chemical and physical data suggest that the isomers differ by conformation or that the unstable isomer has the structure of a charged exocyclic hydroxymethylene compound.

THE reduction of 1,5-diphenyl-3-carbomethoxy-1,2,4-triazole (I) by lithium aluminium hydride affords the expected alcohol (II)[1,2] in two modifications (IIA and IIB), with the melting points 132–133° and 153–154° respectively. The unsharp melting points of mixtures vary between 131° and 150°. Both the ultra-violet and infra-red spectra of IIA and IIB are different; hence isomerism is due to molecular differences and not to different crystal forms.

The labile form IIA has been obtained in a pure state twice only; other preparations gave IIA rapidly changing to the stable form IIB. The transformation of IIA into IIB occurs slowly in neutral polar solvents, but fast in the presence of acid. The conversion of IIA in methanolic solution to IIB over a period of 48 hours is shown by the changing ultra-violet absorption spectra (Fig. 1). Curve V is substantially identical with the

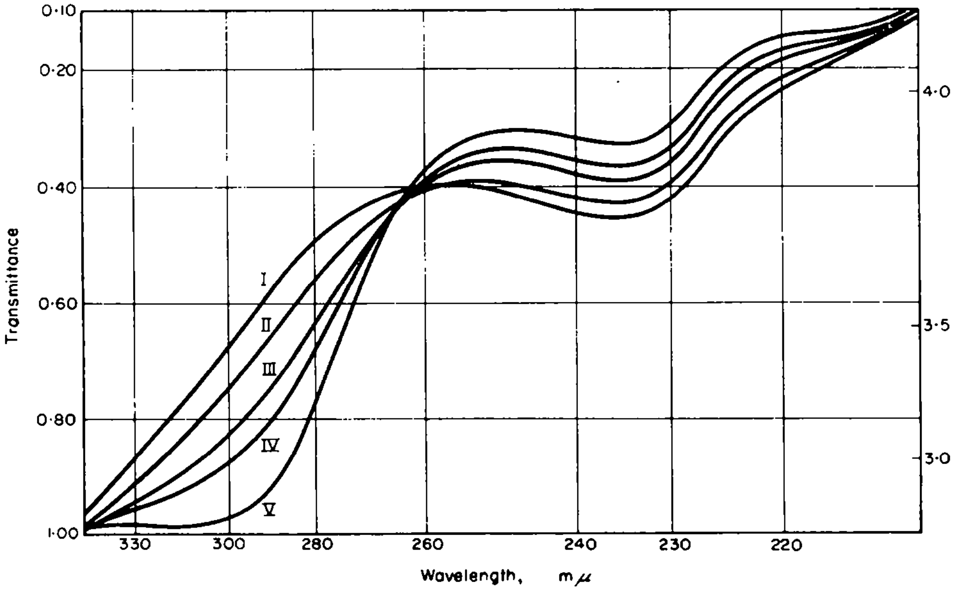

FIG. 1. Ultra-violet absorption spectra of the unstable isomer (IIA) of 1,5-diphenyl-3-hydroxymethyl-1,2,4-triazole (15 mg/litre in methanol) and its transformation products at different times: I, initial curve; II, 2 hr; III, 5 hr; IV, 8 hr; V, 23 hr and 48 hr.

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[1] E. J. Browne and J. B. Polya, *Chem. & Ind.* 1086 (1960).

[2] E. J. Browne and J. B. Polya, *J. Chem. Soc.* in course of publication.

absorption of IIB. Figures 2 and 3 display the infra-red regions where significant differences between IIA and IIB can be observed.

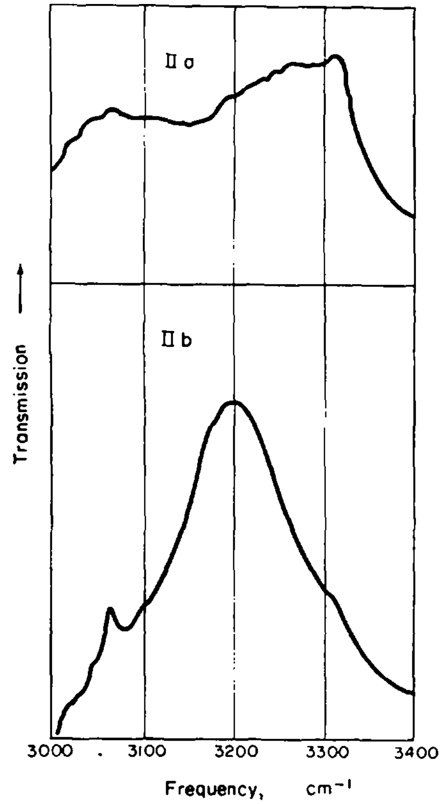

Fig. 2. Infra-red absorption spectra of isomers of 1,5-diphenyl-3-hydroxymethyl-1,2,4-triazole (3000–3400 cm^{-1}) in KBr disc.

The bands due to OH-stretching vibrations in the region 3100–3400 cm^{-1} (Fig. 2) are very strong and of comparable intensities for both IIA and IIB, but the band system of IIA is broader and, in part, displaced to higher frequencies. The low band of IIB at 3060 cm^{-1} is ascribed to C—H stretching vibrations of an aromatic ring, and is present in all the 1,5-diaryl-1,2,4-triazoles. The corresponding band system in IIA is broader, and may be due to the overlapping of bands of different origin.

The bands at 1050 cm^{-1} and around 1350 cm^{-1} are commonly found in alcohols. The isomers do not differ in respect of the band at 1050 cm^{-1}. As regards other features, IIB has the spectral characteristics of six other alcohols in the same series, and it is IIA that must be regarded as anomalous.

The stable form is monomeric and has the higher melting point. Thus one must either reject the hypothesis that IIA and IIB differ in grade of polymerization, or accept the unlikely alternative that polymerization of a stable substance affords an unstable, spontaneously depolymerized, polymer with a sharp but lower melting point.

The two isomers must have identical structures. They have the same empirical analyses and give the same acetyl derivative and the same aldehyde or acid on oxidation. The opposite view, that they are structural isomers undergoing transformation in the course of acetylation or oxidation, can be disproved on chemical and physical evidence. There is no doubt of the structure of the stable IIB, related by simple reactions to known substances such as I[1,3,4] and the corresponding acid (III)[3,4] or 1,5-diphenyl-1,2,4-triazole[5] obtained by the decarboxylation of III. These and many other 1,5-diaryl-1,2,4-triazoles[1,2] have a common background of infra-red bands (on which we propose to report later). If IIA differed structurally from IIB, it would have arisen by the modification of the 1,2,4-triazole ring of either I or II. The common infra-red band-system for I, IIA and IIB makes this unlikely, but we can survey other hypotheses.

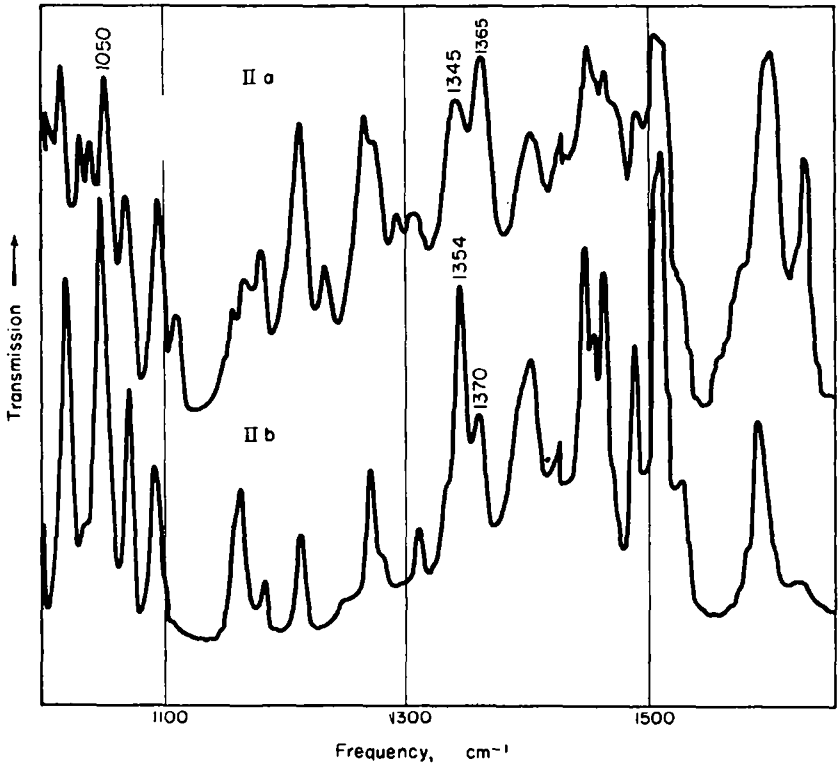

Fig. 3. Infra-red absorption spectra of isomers of 1,5-diphenyl-3-hydroxymethyl-1,2,4-triazole (1000–1650 cm^{-1}) in KBr discs.

Identification of IIA with the aldehydes (IVa and IVb) derived from dihydrotriazoles would imply uptake of energy compensating for the loss of resonance energy. Energetic conditions invariably afford IIB, and chemically IIA behaves like an alcohol, not like an aldehyde.

Acyclic acylamidrazones as precursors of 1,2,4-triazoles are known[1,2,6,7] but they

[3] J. A. Bladin, *Ber. Dtsch. Chem. Ges.* **22**, 796 (1889).

[4] G. W. Sawdey, *J. Amer. Chem. Soc.* **79**, 1955 (1957).

[5] G. Young, *J. Chem. Soc.* **67**, 1063 (1895).

[6] V. K. Kuskov, *Zh. Obshch. Khim.* **21**, 152 (1951).

[7] I. Ya. Postovskii and N. N. Vereshchagina, *Zh. Obshch. Khim.* **29**, 2139 (1959).

have significantly different spectra and a composition different from IIA and IIB. Rational acyclic structures obtained from such acylamidrazones by withdrawal of one molecule of water cannot be written; but one could consider cyclization to the unlikely strained structure V, the pyrazole-derivative VI and the dihydro-1,2,4-triazine derivative VII. The normal 1,5-diaryl-1,2,4-triazole background of the infra-red spectrum of IIA excludes V and VI. The rearrangement of VI or VII to IIB not only lacks drive but is most unlikely to occur without byproducts, whereas the transformation of IIA affords pure IIB.

Having excluded differences of aggregation, polymerism and structure, we can consider the stereochemical alternatives implied by either a planar or a buckled triazole nucleus. A planar triazole nucleus allows stereochemical differences of two kinds: those arising out of the relative rotations of the triazole nucleus and the phenyl rings, and those arising out of the rotation of the hydroxymethyl group. Simple calculations based on covalent, interatomic distances or reference to models show that all the three rings cannot be coplanar without excessive distortion of normal bond-angles. Even one phenyl and one methyl group in the 1 and 5 positions interfere.[8] The 5-phenyl may conjugate with the triazole nucleus but not the 1-phenyl (i.e. neglecting canonic structures with charge separation); hence it is more likely that the 1-phenyl group is "deflected". The less likely deflection of the 5-phenyl cannot account for the existence of IIA, which, on the evidence of ultra-violet spectra, appears to be more effectively conjugated than IIB. The extreme stereochemical effects of the rotation of the hydroxymethyl group would be due to hydrogen bond formation with N_2 or N_4 (VIII or IX), presumably the latter, if the process may be regarded analogous with quaternization.[9] The hypsochromic shift in the ultra-violet from IIA to IIB (12 mμ) suggests an energetic difference of 4–5 kcal/mole, greater than the bond-energy of mesomerically stabilized hydrogen bonds, hence much greater than the difference between the bond-energies of two hydrogen bonds not thus stabilized.

Buckling of the 1,2,4-triazole nucleus would direct the bonds joining the phenyl and hydroxymethyl groups to the triazole towards the front or back of a plane defined by three arbitrarily chosen centres of the five constituting the nucleus. In this sense any two of the three bonds in question could be "cisoid" or "transoid". For steric reasons the two phenyl groups must be transoid, and the hydroxymethyl group necessarily cisoid to one of the phenyl groups and transoid to the other, If the hydroxymethyl group is cisoid in relation to the 1-phenyl group, it could be in one of, or oscillate between, the hydrogen bonded structures VIII and IX. These are expected to have energies[9,10,11] similar within RT cal/mole, hence difficult to detect at room temperature. If, on the other hand, the 1-phenyl and 3-hydroxymethyl groups are transoid, further conformational possibilities X or XI arise. If the energy difference between the planar (or insignificantly buckled, 1,3 cisoid) and buckled (1,3 transoid) forms is comparable with that between the chair and boat forms of cyclohexane, the energy difference of 4–5 kcal/mole between IIA and IIB becomes reasonable. In further accordance with this hypothesis the OH stretching frequencies of IIA are found in broader bands than those of IIB and shifted to higher frequencies (by 120 cm^{-1} in Nujol or 110 cm^{-1} in

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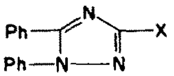
[8] M. R. Atkinson, E. A. Parkes and J. B. Polya, *J. Chem. Soc.* 4256 (1954).

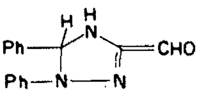
[9] G. F. Duffin, J. D. Kendall and H. R. J. Waddington, *J. Chem. Soc.* 3799 (1959).

[10] M. R. Atkinson and J. B. Polya, *J. Chem. Soc.* 3319 (1954).

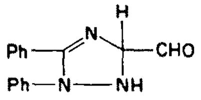
[11] L. E. Orgel, T. L. Cottrell, W. Dick and L. E. Sutton, *Trans. Faraday Soc.* 47, 113 (1951).



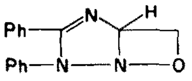
X = CO_2Me (I)
= CH_2OH (II)
= CO_2H (III)



IVa



IVb



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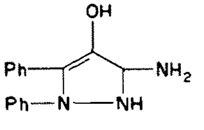

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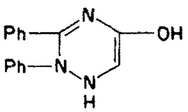
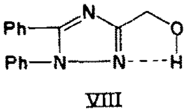
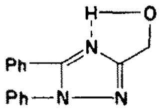


VII



VIII



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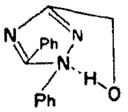
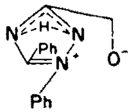


X



XI

potassium bromide; (Fig. 2), indicating more diffuse bonding and weaker by 2–3 kcal/mole.[12a] A number of 1,5-diaryl-1,2,4-triazoles with different substituents in the 3-position[1,2] have an infra-red band of medium to strong intensity at 1365–1370 cm^{-1}, corresponding to the C—N stretching vibration of uncharged tertiary aromatic amines (1310–1360 cm^{-1}).[12b] In IIA alone is this band lowered as expected on the hypothesis of X or XI.

Except for the sensitivity of IIA to acid which points to XI, evidence in hand does not permit a distinction between X and XI. The hypothesis of a markedly buckled triazole nucleus requires confirmation by other methods. A resolution of expected antipodes of IIA or IIB is almost certain to fail for the same reason as that of asymmetrical tertiary amines. X-ray and electron diffraction methods could decide the issue. The hypothesis does not explain the hitherto unobserved isomerism of other 1,5-diaryl-3-hydroxymethyl-1,2,4-triazoles, except for a doubtful observation in the case of 1-*p*-methoxyphenyl-5-phenyl-3-hydroxymethyl-1,2,4-triazole. The absence of the phenomenon in the case of the 1-*o*-tolyl and 1-*m*-tolyl analogues could be explained by the increased steric interaction of the 1- and 5-aryl groups, but this *ad hoc* explanation does not apply when the 1-aryl group has *p*-substituents.

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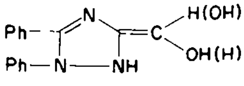
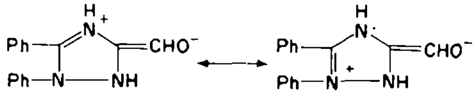
[12] L. J. Bellamy, *The infra-red spectra of complex molecules.* [a] p. 95, [b] p. 249. Methuen, London (1960).

Although the energetic difference between IIA and IIB is slight, there may be a double-peaked energy-barrier between the two forms, as the conversion of IIA and IIB appears irreversible by irradiation or sudden freezing of an equilibrated melt.



XII



XIII

The tautomer XII of II, if existent, has two geometrical isomers and three possible hydrogen bonded states. The infra-red spectra and the isosbestic point seen in Fig. 1 are consistent with the hypothesis of XII being the structure of the unstable alcohol. On the other hand XII is tautomeric with the more likely aldehyde structure IVa excluded before. Stable heterocyclic hydroxymethylene compounds with an exocyclic double bond do not appear to have been isolated before; in the somewhat analogous and well investigated case of iminazole-4-aldehyde[13] spectroscopic evidence excludes the hydroxymethylene structure. To assert that the isomerism under discussion is due to the otherwise unusual stability of the hydroxymethylene structure implies one of two alternatives. The formation of stable IIB from the ester followed by rearrangement to labile IIA, then by rearrangement to the original IIB, is absurd. The other alternative is 1,4- reduction by lithium aluminium hydride, which is considered unusual.[14] The mesomeric ion-pair structure XIII is more likely than the uncharged tautomer XII.[13] However imidazole-4-aldehyde has some aldehydic properties and thus differs from IIA.

It appears that the explanation of the isomerism of 1,5-diphenyl-3-hydroxymethyl-1,2,4-triazole must rest on one of two unusual alternatives: the buckling of the 1,2,4-triazole nucleus or the mesomerically stabilized twin ion of an exocyclic hydroxymethylene compound. While a definite choice cannot be made, the latter alternative may appear more attractive at present.

EXPERIMENTAL

1,5-*Diphenyl*-3-*hydroxymethyl*-1,2,4-*triazole*

IIA: To a suspension of old $LiAlH_4$ (0·3 g) in dry ether (50 ml) was added 1,5-diphenyl-3-carbomethoxy-1,2,4-triazole (I, 2.2 g) in dry ether (50 ml). The mixture was refluxed for 5 hr. Aqueous methanol (20%, 2 ml) was added and heating continued for 5–10 min. The inorganic precipitate was filtered off and washed with ether. The combined filtrates were concentrated and cooled to give (IIA, 1·6 g, 80%). IIA Recrystallized from aqueous ethanol or, preferably, benzene and light petroleum, as white prisms, m.p. 132–3°. (Found: C, 71·8; H, 5·6; N, 16·0. $C_{15}H_{13}N_3O$ requires: C, 71·7; H, 5·2; N, 16·7%).

IIB: Most subsequent reactions, conducted substantially as above, gave rise to IIB, as white prisms from aqueous ethanol, or benzene and light petroleum, m.p. 153–154°. . (Found: C, 71·6; H, 5·2; N, 15·9. $C_{15}H_{13}N_3O$ requires: C, 71·7; H, 5·2; N, 16·7%).

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[13] R. A. Turner, *J. Amer. Chem. Soc.* **71**, 3472 (1949).

[14] F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.* **70**, 3738 (1948).

Mol wt (Rast): 249:250. Theoretical 251. When fresh, active preparations of $LiAlH_4$ were used in the reduction, IIB was the only product isolated; IIB was also the only product isolated from the reduction of I with $LiBH_4$ in ether.

1,5-*Diphenyl*-3-*acetoxymethyl*-1,2,4-*triazole*

An excess of acetyl chloride was added dropwise to a sample of IIA (0·3 g). When the vigorous exothermic reaction had ceased the mixture was heated for 5 min on a water bath. Excess acetyl chloride was evaporated off, 5 ml water were added, and the solution neutralized with aqueous K_2CO_3. The precipitate was filtered off, charcoaled, and recrystallized from benzene and light petroleum as white plates (0·2 g), m.p. 110–111°. (Found: C, 70·0; H, 5·5; N, 14·3. $C_{17}H_{15}N_3O_2$ requires: C, 69·6; H, 5·2; N, 14·3%).

Treatment of IIB with acetyl chloride, as described, gave the same substance as the only isolated product.

Ultra-violet spectra were determined in methanol solution, using a Perkin–Elmer 4000 A Spectracord.

Infra-red spectra were obtained from KBr discs or Nujol mulls, on a Perkin–Elmer double beam spectrophotometer No. 221.

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