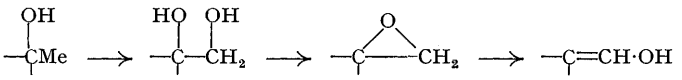
144. *The Condensation of Benzamidine with α-Diketones.*

By J. W. Cornforth and H. T. Huang.

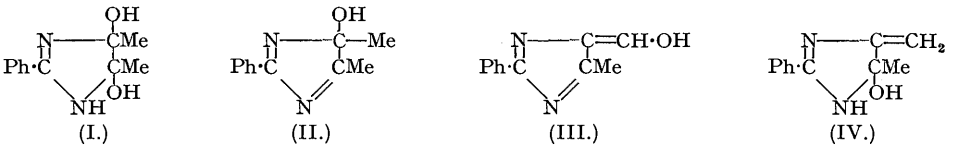
An inquiry into the nature of a substance described as 2-phenyl-4-methyliminazole has led to a general examination of the subject indicated in the title.

It has been reported by Diels and Schleich (*Ber.*, 1916, **49**, 1711) that benzamidine hydrochloride and diacetyl in aqueous solution with sodium acetate gave the hydrochloride of an addition product, $C_{11}H_{14}O_2N_2$, formulated as (I); this lost water when heated with hydrochloric acid, and gave the hydrochloride of a new base, $C_{11}H_{12}ON_2$. The structure (II) was ascribed to this base; its oxidation with nitric acid led to a pseudo-acidic substance having the reactions of an aldehyde or ketone. Since such a substance could not be derived from (II)

without a rearrangement, the structure (III) was proposed, together with the following mechanism of oxidation :



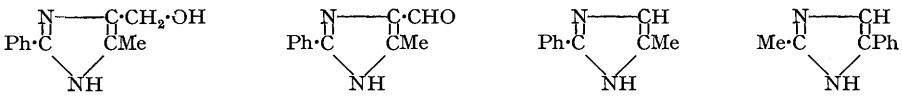
While there seemed no reason to doubt that the adduct $C_{11}H_{14}O_2N_2$ was correctly formulated as (I), it appeared likely that this substance on dehydration would tend to form the stabilised iminazole nucleus. A primary dehydration product might well be (IV), anionotropic rearrangement of which would furnish 2-phenyl-5-methyl-4-hydroxymethyliminazole (V).



(I.) (II.) (III.) (IV.)

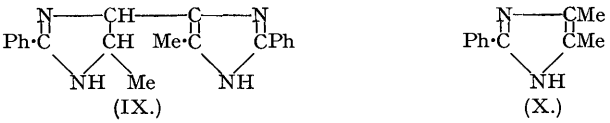
If this were the structure of the base $C_{11}H_{12}ON_2$, its oxidation would be a straightforward process leading to 2-phenyl-5-methyliminazole-4-carboxyaldehyde (VI). The known iminazole-4-aldehyde is not reported to be pseudo-acidic, but in the case of (VI) there should be marked stabilisation of the anion by distribution of the negative charge over both rings. It is probably not necessary to write the aldehyde in the tautomeric form (III); the normal state of the molecule may well be a (hybridised) dipolar form of (VI).

Diels and Schleich (*loc. cit.*) heated the base $C_{11}H_{12}ON_2$ in ethyl malonate, whereby it was converted into a substance, m. p. 293°, formulated as 2-phenyl-4-methyliminazole (VII). We had prepared, by methods to be reported later, a substance which was undoubtedly (VII), and it was this circumstance which drew our attention to the work of Diels and Schleich; for our substance had no resemblance to the product, m. p. 293°, but rather appeared to be identical with the 2-phenyl-4-methyliminazole (m. p. 181—182°) of John (*Ber.*, 1935, **68**, 2290). It may be mentioned that the compound, m. p. 159°, prepared by Lewy (*ibid.*, 1888, **21**, 2192), and reported in Beilstein's " Handbuch " (3rd ed.; Vol. **27**, 58) as (VII), is clearly 4-phenyl-2-methyliminazole (VIII).



(V.) (VI.) (VII.) (VIII.)

The high melting point and low solubility of the product, m. p. 293°, suggest that it may be a dimer such as (IX); other structures of the di-iminazolyl or di-iminazolylmethane type are not, however, excluded, as their composition is not greatly different. The low value for the molecular weight as determined cryoscopically in phenol may well be due to salt formation by one of the two basic centres in a molecule of type (IX).

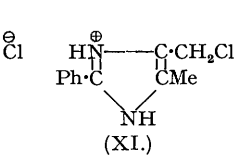


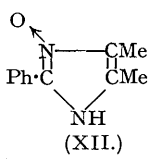
(IX.) (X.)

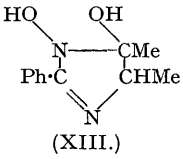
The essential parts of the experimental work of Diels and Schleich have been repeated and confirmed. It was found that on catalytic hydrogenation of the aldehyde $C_{11}H_{10}ON_2$, the basic alcohol $C_{11}H_{12}ON_2$ was regenerated. Since the structure (II) could only arise from reduction of (III) by a mechanism as strange as that proposed for the reverse process of oxidation, the formulation of the basic alcohol as (V) could be regarded as established, provided that the alcohol was indeed a hydroxy-derivative of 2-phenyl-4 : 5-dimethyliminazole (X). This point was cleared up by Clemmensen reduction of the aldehyde, which gave (X) in low yield, and also by conversion (thionyl chloride) of the basic alcohol into *2-phenyl-5-methyl-4-chloromethyliminazole hydrochloride* (XI), which was smoothly reduced to (X) by zinc dust and acetic acid.

The specimen of (X) for comparison was prepared by zinc dust–acetic acid reduction of " 2-phenyl-4 : 5-dimethyldioxydihydroiminazol " (Diels, *Ber.*, 1918, **51**, 965; Diels and Salomon, *ibid.*, 1919, **52**, 51). We consider that this substance (obtained from diacetyl-monoxime, benzaldehyde, and ammonia) is to be regarded as a hydrate of the *N*-oxide (XII) rather than

the hydroxylamine (XIII) (cf. Cornforth, *J.*, 1947, 96); the identity of the reduction product is not, however, in doubt.

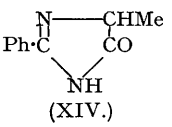

(XI.)

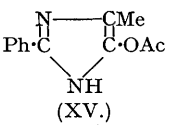

(XII.)

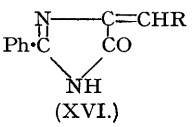

(XIII.)

Attempts to synthesise (V) or one of its derivatives from 2-phenyl-4-methyliminazole were unsuccessful. No useful products were obtained by the action of formaldehyde, formaldehyde–hydrogen chloride, or *N*-methylformanilide–phosphoryl chloride. Evidently the phenyl group deactivates the iminazole nucleus. It was found that the aldehyde (VI) could not be oxidised smoothly to the corresponding carboxylic acid; this behaviour is also characteristic of iminazole-4-carboxyaldehyde.

Since a simple and general synthesis of 4-hydroxymethyliminazoles could be of considerable importance for the preparation of histidine and its analogues, the condensation of benzamidine hydrochloride and methylglyoxal was studied. When the reactants were mixed in aqueous solution (best in the presence of a little potassium hydroxide) a crystalline hydrochloride separated which after recrystallisation from dilute hydrochloric acid gave no precipitate with phenylhydrazine acetate and appeared to be the hydrochloride monohydrate of a base $C_{10}H_{10}ON_2$, for on treatment with aqueous sodium picrate the picrate of the anhydrous base was obtained. The base itself was prepared by the action of potassium carbonate on the hydrochloride. It appeared that if a compound analogous to (I) was produced it had suffered dehydration under the conditions of the experiment. The product, however, was not 2-phenyl-4-hydroxymethyliminazole, for on hydrolysis with either acid or alkali it yielded benzoic acid, ammonia, and an α-amino-acid (evidently alanine). The substance was therefore *5-keto-2-phenyl-4-methyl-4 : 5-dihydroiminazole* (XIV) apparently produced by simple dehydration of a glycol of type (I). The identity of the substance was confirmed by synthesis from benziminomethyl ether and *dl*-alanine ethyl ester (cf. Finger, *J. pr. Chem.*, 1907, **76**, 24). Among the derivatives prepared for comparison was the nicely crystalline monoacetyl compound; this was sufficiently basic to dissolve in dilute acetic acid and to form a picrate, and was therefore most probably *5-acetoxy-2-phenyl-4-methyliminazole* (XV).


(XIV.)

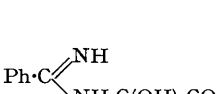

(XV.)

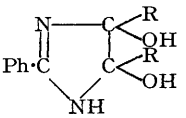

(XVI.)

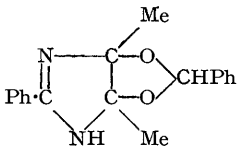
Attention was directed to a series of papers by Ekeley, Ronzio, and their collaborators (*J. Amer. Chem. Soc.*, 1935, **57**, 1353; 1936, **58**, 163; 1937, **59**, 1118) in which the addition product benzamidine–glyoxal was studied. Our experience with methylglyoxal and the internal evidence of these papers led to the conclusion that the compounds produced by condensing benzamidine–glyoxal with aromatic aldehydes were probably 5-keto-2-phenyl-4-arylidene-4 : 5-dihydroiminazoles (XVI); and the few simple experiments necessary to test this hypothesis had already been carried out before it was discovered that the American workers (Williams, Symonds, Ekeley, and Ronzio, *ibid.*, 1945, **67**, 1157) had eventually reached and established this conclusion themselves, having been guided by some experiments on the condensation of phenylglyoxal with benzamidine and with urea (Fisher, Ekeley, and Ronzio, *ibid.*, 1942, **64**, 1434; Waugh, Ekeley, and Ronzio, *ibid.*, p. 2029).

We chose phenyl-benzylidene-, -*p*-methoxybenzylidene- and -furfurylidene-iminazolones as the test substances, for these three iminazolones had been prepared from the corresponding oxazolones by Erlenmeyer (*Annalen*, 1904, **337**, 266, 280, 298), and the decomposition points given by him for all three differed from the melting points given by Ekeley and Ronzio (*J. Amer. Chem. Soc.*, 1935, **57**, 1353). Erlenmeyer's method was slightly modified to bring the isolation procedure into line with that of Ekeley and Ronzio, and the three iminazolones were compared with the products obtained from benzamidine–glyoxal and the appropriate aldehydes. The identity of the two series was established directly by mixed melting point; decomposition was slight except in the furfurylidene derivatives. In no case was an appreciable difference in melting point observed between an iminazolone prepared by Erlenmeyer's method and the

corresponding substance from benzamidine–glyoxal. This contrasts with the statement of Williams *et al.* (*loc. cit.*) that the melting point of phenylbenzylideneiminazolone varies according to the method of preparation. We were unable to confirm the melting points given by Ekeley and Ronzio for any of the three substances prepared by their method.


(XVII.)


(XVIII.)


(XIX.)

The general structure (XVII) rather than (XVIII) has been ascribed by Ekeley and Ronzio to the addition products of benzamidine with glyoxal and with diacetyl; ultra-violet absorption curves were given which were claimed to support this view. These curves, which are merely end absorptions showing no characteristic maximum, can hardly be used in support of either interpretation; nor is the fact that the addition reaction is reversible of any significance in deciding between the two formulæ. There are two pieces of evidence available which support structure (XVIII), at least for the diacetyl adduct. First, Diels and Schleich (*loc. cit.*) prepared a benzylidene compound from this adduct which from its composition and properties would seem to be (XIX). Secondly, when one of the carbonyl groups in diacetyl was blocked, as in diacetyl monoxime (Ekeley and Elliott, *J. Amer. Chem. Soc.*, 1936, **58**, 163), the addition compound had the composition 2 molecules of oxime : 1 molecule of benzamidine. Neither of these facts is decisive but both are significant.

Experimental.

2-Phenyl-5-methyl-4-hydroxymethyliminazole (V).—Prepared according to the procedure of Diels and Schleich (*loc. cit.*), this product after 2 recrystallisations from methanol formed clusters of shiny prisms, m. p. 204° (Found : C, 69·9; H, 6·3. Calc. for $C_{11}H_{12}ON_2$: C, 70·2; H, 6·4%). The *picrate* crystallised from methanol in light yellow prisms, m. p. 181° (Found : C, 48·8; H, 3·6; N, 16·7. $C_{11}H_{12}ON_2,C_6H_3O_7N_3$ requires C, 48·9; H, 3·6; N, 16·8%).

2-Phenyl-5-methyliminazole-4-carboxyaldehyde (VI).—Oxidation of the foregoing alcohol with nitric acid (Diels and Schleich, *loc. cit.*) gave the aldehyde monohydrate, m. p. 108°. The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in tiny dark red rhombs (decomp. at 310°) (Found : C, 55·8; H, 4·0. $C_{17}H_{16}O_4N_6$ requires C, 55·4; H, 4·3%).

Hydrogenation of (VI).—The aldehyde monohydrate (1 g.) and a trace of ferric chloride were dissolved in methanol (15 c.c.) and hydrogenated at room temperature and pressure, using platinum oxide catalyst (50 mg.) until 1 mol. of hydrogen had been absorbed. The filtered solution on concentration gave the hydroxymethyliminazole (VII), m. p. and mixed m. p. 203—204° after 2 crystallisations from methanol.

Clemmensen Reduction of (VI).—The monohydrate (2 g.) and amalgamated zinc (5 g.) were refluxed vigorously in concentrated hydrochloric acid (7 c.c.) for 24 hours, with addition of fresh acid (1 c.c.) at 6-hour intervals. The clear solution was precipitated with ammonia, and the resulting solid reprecipitated from solution in 2N-hydrochloric acid by ammonia, dried, and sublimed at 160—200°/1 mm. The sublimate on crystallisation from aqueous ethanol gave small white prisms (150 mg.), m. p. 236°, raised to 241° by further sublimation and crystallisation. The mixed m. p. with 2-phenyl-4 : 5-dimethyliminazole was 240—241°.

2-Phenyl-4-methyl-5-chloromethyliminazole Hydrochloride (XI).—Thionyl chloride (5 c.c.; pure) was added cautiously to a suspension of 2-phenyl-5-methyl-4-hydroxymethyliminazole (2 g.) in dry benzene (5 c.c.). Refluxing was continued for 20 minutes after the initial reaction had subsided. The mixture was evaporated under reduced pressure, and the evaporation twice repeated after addition of fresh benzene (5 c.c. each time). The residue was dissolved in ethanolic hydrogen chloride (20 c.c. of 10%) and dry ether (20 c.c.) added; the *iminazole hydrochloride* then separated as a white powder (2·3 g.), m. p. 182—183° after drying in a vacuum over phosphoric oxide (Found : C, 54·5; H, 5·3; Cl, 28·3. $C_{11}H_{11}N_2Cl,HCl$ requires C, 54·3; H, 5·0; Cl, 29·2%).

Reduction of the (XI).—The foregoing hydrochloride (0·5 g.) was dissolved in acetic acid (6 c.c.), and zinc dust (0·8 g.) added gradually with shaking. When the evolution of gas seemed to have stopped the mixture was refluxed for 6 hours. The product (200 mg.) was isolated and purified as described in the succeeding experiment, giving 2-phenyl-4 : 5-dimethyliminazole, m. p. 240—241° undepressed by admixture with authentic material.

2-Phenyl-4 : 5-dimethyliminazole (X).—This base was prepared by modifying slightly the conditions given by Diels (*Ber.*, 1918, **51**, 965). "2-Phenyl-4 : 5-dimethyldioxydihydroiminazol" (16 g.) mixed with zinc dust (30 g.) was treated cautiously with glacial acetic acid (60 c.c.). After refluxing vigorously for 6 hours the solution was filtered hot, diluted with an equal volume of water, and evaporated under reduced pressure. The syrupy residue was dissolved in water, and the iminazole (11 g.; m. p. 230—235°) precipitated by addition of excess of ammonia. Purification by sublimation (160—200°/1 mm.) gave shiny prisms, m. p. 241° (Diels and Salomon, *loc. cit.*, gave m. p. 242°) (Found : C, 76·9; H, 7·2; N, 16·3. Calc. for $C_{11}H_{12}N_2$: C, 76·7; H, 7·0; N, 16·3%).

Condensation of Benzamidine Hydrochloride with Methylglyoxal.—Methylglyoxal (4 c.c.; crude, undistilled, acetone-free product prepared according to Riley, *J.*, 1932, 1875) was added to a solution of benzamidine hydrochloride (5 g.) in water (15 c.c.). Potassium hydroxide (2 c.c. of 2N) was dropped into the mixture, which after thorough shaking was left overnight in a refrigerator. The crystalline solid was collected and dissolved in a minimum amount of 2N-hydrochloric acid. After removal of some coagulated selenium by filtration the cooled solution deposited the *hydrochloride monohydrate* of 5-keto-2-phenyl-4-methyl-4 : 5-dihydroiminazole (2·6 g.) as clusters of long thin needles, m. p. 170—172° after softening at 130° (Found : C, 53·0; H, 5·8; N, 12·0; Cl, 15·7. $C_{10}H_{10}ON_2,HCl,H_2O$ requires C, 52·7; H, 5·5; N, 12·3; Cl, 15·6%). On addition of aqueous sodium picrate to a solution of the hydrochloride the *iminazolone picrate* was deposited; it crystallised from water–ethanol in light yellow silky needles, m. p. 169—171° (Found : C, 47·6; H, 3·25; N, 17·9. $C_{10}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 47·7; H, 3·25; N, 17·4%). Heating the hydrochloride monohydrate in 10% hydrochloric acid for periods as long as 14 hours produced no change in the composition of the product which separated on cooling.

The hydrochloride monohydrate (0·5 g.) was heated with acetic anhydride (1·5 c.c.) on a steam-bath for 20 minutes. After cooling, concentrated aqueous ammonia was added; an oil separated and soon crystallised. Recrystallisation from benzene gave the *monoacetyl* derivative [probably (XV)]; massive shining rhombs (0·47 g.), m.p. 170—172° (Found : C, 66·4; H, 5·5; N, 13·0. $C_{12}H_{12}O_2N_2$ requires C, 66·6; H, 5·6; N, 13·0%). The substance developed a smell of acetic acid when kept in air.

The hydrochloride monohydrate (2·1 g.) was suspended in aqueous potassium carbonate (10 c.c.; saturated) and warmed on a steam-bath with vigorous stirring. The oil which separated gradually solidified; the light brown granular solid after trituration was collected and washed with a little cold water (yield, 1·2 g.). Recrystallisation from benzene gave 5-*keto*-2-*phenyl*-4-*methyl*-4 : 5-*dihydroiminazole* (XIV) in small rhombs, m. p. 167—168° raised to 170° by sublimation at 160°/15 mm. and recrystallisation from benzene (Found : C, 69·3; H, 5·7; N, 16·3. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%). The compound was easily soluble in chloroform and ethanol, moderately so in water, less so in benzene. It gave with aqueous silver nitrate a white precipitate which rapidly darkened; no coupling was observed with diazobenzenesulphonic acid in sodium carbonate solution.

Degradation and Synthesis of the Iminazolone (XIV).—An attempt at reduction led to hydrolysis. The free base (0·5 g.) was refluxed with phosphoric acid (2·7 c.c. of 85%), red phosphorus (0·2 g.), potassium iodide (0·06 g.), and water (0·3 c.c.) for 6 hours. On cooling, benzoic acid separated; it was removed by ether extraction and identified. The aqueous acid solution was filtered from phosphorus and made strongly alkaline with sodium hydroxide (2N). On warming, ammonia was evolved; it was boiled off and a portion of the residual liquor brought to pH 7 and warmed with a few crystals of ninhydrin. A deep purple colour was developed. Essentially the same result was obtained by heating the iminazolone with 20% potassium hydroxide. Oxidation of the iminazolone with 10% nitric acid also gave benzoic acid and ammonia.

Benziminomethyl ether (5·8 g.) and *dl*-alanine ethyl ester (5·03 g.), both freshly distilled, were mixed. After 25 hours at room temperature the crystalline product was ground well with benzene and collected (4·8 g.). A further quantity (2·4 g.) separated during 3 weeks from the benzene filtrate. Recrystallisation from benzene gave the iminazolone (XIV), m. p. 170° undepressed by admixture with the benzamidine–methylglyoxal product (Found : C, 69·0; H, 5·7. Calc. for $C_{10}H_{10}ON_2$: C, 69·0; H, 5·8%). The picrates and acetyl derivatives were also compared and showed no differences.

Condensation of Benzamidine–Glyoxal with Aldehydes.—A satisfactory polyglyoxal preparation was obtained by oxidising paraldehyde with dilute nitric acid in the known manner, removal of excess of nitric acid by 2 or 3 evaporations with water, neutralisation of the slightly diluted residue by calcium carbonate, precipitation of calcium salts by alcohol, and evaporation of the alcoholic filtrate to a thick syrup. The condensation with benzamidine was carried out according to Ekeley and Ronzio (*loc. cit.*); equally good results were, however, obtained when a solution of potassium hydroxide equivalent in amount to the benzamidine hydrochloride was added all at once, with good stirring. The benzamidine-glyoxal was condensed with benzaldehyde, with anisaldehyde, and with furfuraldehyde according to the general direction of the American authors, and the products purified by precipitation with acetic acid from alcoholic alkaline solution, followed by crystallisation from butyl acetate. The purification treatment did not in any case raise the m. p. more than 2—3°.

The iminazolones were obtained by dissolving the corresponding oxazolone (0·5 g.) in dioxan (2 c.c.) and warming with aqueous ammonia (1 c.c.; *d* 0·88). A clear solution was obtained after about a minute; most of the ammonia was then boiled off and potassium hydroxide (0·5 g.) added. After boiling for 30 seconds the solution was diluted with alcohol to 10 c.c. and acidified with glacial acetic acid; the iminazolone then crystallised out. The iminazolones were purified as described above, their melting points changing even less than before. The melting points were taken with a freshly calibrated thermometer; the same values were found in an electrically heated block as in a paraffin bath. The following m. p.s were found for iminazolones prepared by either method : 2-phenyl-4-benzylidene-, 272—273°; 2-phenyl-4-*p*-methoxybenzylidene-, 289—290°; 2-phenyl-4-furfurylidene-, 266—267°. There was no depression of m. p. on mixing corresponding members of the two series.

The authors' thanks are due to the British Council for enabling one of them to take part in this investigation.

Dyson Perrins Laboratory, Oxford University.
National Institute for Medical Research, Hampstead. [*Received, June 2nd,* 1947.]