Preparation and Some Reactions of 2,2-Diaryl-2*H*-imidazole 1-Oxides

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The acid-catalysed condensation of diphenylmethyleneamines with various α-hydroxyimino-ketones (1a—f) gave 2,2-diphenyl-2*H*-imidazole 1-oxides [(2a—f), and (8)]. These compounds react as nitrones with lithium aluminium hydride, methylmagnesium iodide, and dimethyl acetylenedicarboxylate. However, the reaction of 4-methyl-2,2-diphenyl- and 2,2,4-triphenyl-2*H*-imidazole 1-oxides with sodium borohydride gave the corresponding 2*H*-imidazoles. Curtius rearrangement of 5-methyl-2,2-diphenyl-2*H*-imidazole-4-carbonyl azide 3-oxide (6) gave 7-methyl-5,5-diphenylimidazo[1,5-*b*][1,2.4]oxadiazol-2(5*H*)-one (14).

FEW examples of 2*H*-imidazoles have been reported. Weiss described[1] the preparation of a series of 4,5-diphenyl-2*H*-imidazoles from benzil, a ketone, and ammonium acetate, and pointed out their instability to heat and acid. More recently, 2*H*-imidazole 1-oxides have been obtained by reaction of α-dioximes with certain aldehydes or ketones and subsequent treatment with alkali.[2]

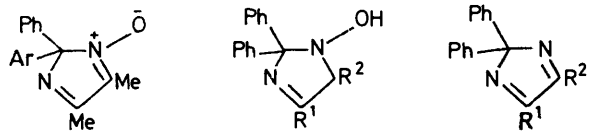
Here we report the preparation of 2,2-diphenyl-2*H*-imidazole 1-oxides (2a—f) *via* acid-catalysed condensation of diphenylmethyleneamine with various α-hydroxyimino-ketones (1a—f). Substituted diphenylmethyleneamines also reacted with diacetyl mono-oxime (1c) to give the substituted-phenyl compounds (8). The reaction of carbonyl compounds with imines has been

(1)

a; R^1 = Me, R^2 = H
b; R^1 = Ph, R^2 = H
c; R^1 = Me, R^2 = Me
d; R^1 = Ph, R^2 = Ph
e; R^1 = Me, R^2 = COMe
f; R^1 = Me, R^2 = CO_2Et

(2a-f)

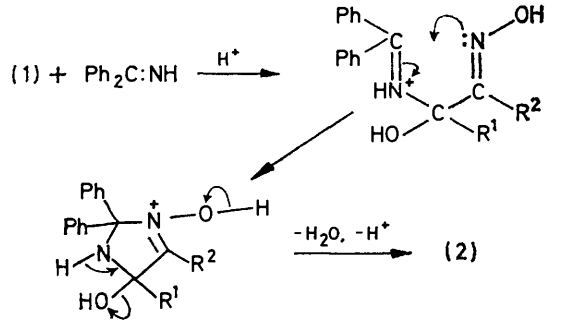
(3) R^1 = Me, R^2 = CH(OH)Me
(4) R^1 = Me, R^2 = C(:NOH)Me
(5) R^1 = Me, R^2 = CO_2H
(6) R^1 = Me, R^2 = CON_3
(7) R^1 = Me, R^2 = NCO



(8) (9) (10)

Ar = *p*-ClC_6H_4
Ar = *m*-$CF_3 \cdot C_6H_4$
Ar = *p*-$MeO \cdot C_6H_4$

used in the synthesis of imidazoles[1,3] and oxazoles.[4] We envisage that formation of the 2*H*-imidazoles (2a—f) and (8) occurs by initial condensation of the imine with the ketone, followed by intramolecular cyclisation and subsequent dehydration (Scheme).



SCHEME

α-Hydroxyimino-ketones, with the exception of benzil mono-oxime (1d), were obtained in only one geometric form. Reaction of either the *E*- or the *Z*-isomer of benzil mono-oxime with diphenylmethyleneamine gave the 2*H*-imidazole 1-oxide (2d), indistinguishable from the compound obtained by oxidation of the known[1] 2,2,4,5-tetraphenyl-2*H*-imidazole (10d) with *m*-chloroperbenzoic acid. Ethyl 5-methyl-2,2-diphenyl-2*H*-imidazole-4-carboxylate 3-oxide (2f) was isolated in two crystalline forms with different m.p.s. and solid phase i.r. spectra, but indistinguishable n.m.r. and solution i.r. spectra. They were hydrolysed to the same acid (5), which was decarboxylated to 4-methyl-2,2-diphenyl-2*H*-imidazole 1-oxide (2a), also obtained from diphenylmethyleneamine and 1-hydroxyimino-acetone (1a).

The n.m.r. and mass spectra were consistent with the assigned structures, but were ineffective in distinguishing between *N*-oxides (2a—f), and the corresponding 6*H*-1,2,5-oxadiazines (11). The mass spectra of all compounds investigated exhibited, as well as a molecular ion, fragments at *m/e* 165 and 166 in high abundance. No intense $M - 16$ or $M - 17$ peaks, frequently observed with heterocyclic *N*-oxides,[5] were apparent, in accord with findings in the pyrroline 1-oxide series.[6] The i.r. spectra of compounds (2a—f) and (8), which may be

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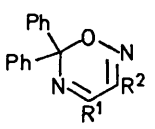
regarded as conjugated nitrones, all show strong absorptions in the regions 1 600—1 620 (C:N) and 1 150—1 200 cm^{-1} ($N^+–O^-$) characteristic of nitrones.[7] The assignment of imidazole 1-oxide structures is further supported by their reactions.

Nitrones are reduced by metal hydrides to hydroxylamines.[8] The 2*H*-imidazole 1-oxides (2a—d) reacted with lithium aluminium hydride at room temperature to give 1-hydroxy-Δ^3-imidazolines (9a—d). At higher



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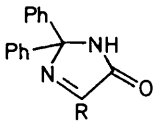

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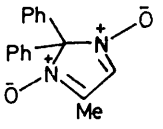

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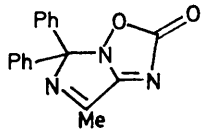

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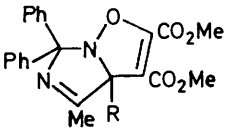

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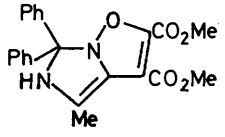

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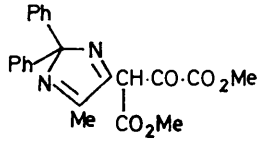

(17)

temperatures the tetraphenylimidazole 1-oxide (2d) was deoxygenated to the 2*H*-imidazole (10d), whereas the dimethyl compound (2c) again gave the cyclic hydroxylamine (9c). The *N*-hydroxy-compounds (9; R^2 = H) were, surprisingly, converted into 2*H*-imidazoles (10) by sodium borohydride; no reaction was apparent when R^2 was not H. Similarly, reduction of the 2*H*-imidazole 1-oxides (2a and b) with sodium borohydride gave 2*H*-imidazoles (10a and b), respectively, but when R^2 was not H the nitrone function was retained. Thus with the dimethyl compound (2c) no reaction was observed, and the carbinol (3) was obtained from the 5-acetyl derivative (2e).

The 2*H*-imidazoles (10a and b) were oxidised by peroxy-acid to the corresponding imidazolones (12). Although no mono-*N*-oxidation products were isolated, a di-*N*-oxide (13) was also obtained from the imidazole (10a). The imidazolones (12) could not be further oxidised by peroxy-acid, and the imidazole 1-oxides (2a and c) were unchanged when similarly treated.

4-Methyl-2,2-diphenyl-2*H*-imidazole 1-oxide (2a) reacted with methylmagnesium iodide to give the expected 1-hydroxyimidazoline (9c). Sodium cyanide and (2a) in dimethyl sulphoxide at 100 °C gave the imidazolone (12; R = Me), possibly *via* hydroxide-ion displacement[9] of the intermediate 2*H*-imidazole-4-carbonitrile (10; R^1 = Me, R^2 = CN).

2,2,4,5-Tetraphenyl-2*H*-imidazole 1-oxide (2d) was converted into 1,2,4,5-tetraphenyl-1*H*-imidazole when heated with triphenylphosphine at 300 °C. Deoxygenation of (2d) may have taken place prior to rearrangement since 2*H*-imidazoles have been reported to undergo thermal rearrangement to the 1*H*-isomers.[1] No deoxygenation product was obtained when (2d) was heated with triphenylphosphine at lower temperatures.

The imidazole 1-oxide (2c) did not undergo the usual reactions exhibited by heterocyclic *N*-oxides[10] with either acetic anhydride or phosphoryl chloride. Failure to prepare a 5-chloro-derivative prevented the introduction of an amino-substituent by conventional procedures. Attempts to prepare a 5-amino-2*H*-imidazole *via* Curtius rearrangement of the acid azide (6) resulted in formation of the novel imidazo[1,5-*b*][1,2,4]-oxadiazole system. The azide, when heated in ethanol, benzene, or water, gave a single product whose elemental analysis, n.m.r. spectrum, and molecular ion were consistent with the isocyanate structure (7). The i.r. spectrum lacked the characteristic isocyanate (2 240—2 275 cm^{-1}) and nitrone (1 150—1 200 cm^{-1}) absorptions, and the presence of a strong carbonyl absorption at 1 770 cm^{-1} (γ-lactam) indicated that intramolecular cyclisation of the intermediate isocyanate (7) to 7-methyl-5,5-diphenylimidazo[1,5-*b*][1,2,4]oxadiazol-2-(5*H*)-one (14) had taken place. Attempted Beckmann rearrangement of a mixture of *E*- and *Z*-oximes (4) of the acetyl compound (2e) resulted in extensive decomposition.

The reaction of the imidazole 1-oxides (2a and c) with a dipolarophile also depended upon the nature of the 5-substituent. The adduct (15; R = Me) was obtained when the 4,5-dimethylimidazole 1-oxide (2c) was treated with dimethyl acetylenedicarboxylate. The product obtained from the 4-methylimidazole 1-oxide (2a) and dimethyl acetylenedicarboxylate in cold chloroform exists in the tautomeric form (16) of (15; R = H). The 2*H*-imidazole (17) was obtained when this reaction was carried out in hot benzene. Rearrangement products of this type have been reported in the 1-methylbenzimidazole 1-oxide series.[11]

The diarylimidazole 1-oxides (2a—f) and (8) were insoluble in all aqueous media. The methyl compounds (2a and c) did not form salts in ethereal hydrogen chloride and attempted quaternisation of (2c) was unsuccessful.

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The n.m.r. spectrum of (2c) was not significantly changed by addition of trifluoroacetic acid.

EXPERIMENTAL

Physical and spectroscopic data for all new compounds are available as Supplementary Publication No. SUP 21428 (6 pp).*

Diarylmethyleneamines.—These compounds were prepared from benzonitrile and a (substituted) phenylmagnesium bromide by the method of Pickard and Tolbert.[12]

α-Hydroxyimino-ketones.— 1-Hydroxyiminoacetone (1a),[13] 2-hydroxyiminoacetophenone (1b),[14] biacetyl mono-oxime (1c),[15] benzil mono-oxime (1d),[16] 3-hydroxyimino-pentane-2,4-dione (1e),[17] and ethyl 2-hydroxyiminoaceto-acetate (1f),[18] were prepared according to published procedures.

2,2-*Diaryl*-2H-*imidazole* 1-*Oxides* (*General Procedure*).—Equimolar proportions of diarylmethyleneamine and α-hydroxyimino-ketone in toluene or xylene containing a few drops of methanesulphonic acid were heated under reflux for 7—23 h. Water formed was removed by azeotropic distillation. The cooled solution was washed successively with aqueous 5% sodium hydrogen carbonate and water, dried, and concentrated. Addition of ether to the residue resulted in crystallisation of the 2H-*imidazole* 1-*oxides* (2a—f) and (8).

The *N*-oxide (2a) was also obtained (60%) by heating the acid (5) at 140 °C and triturating the solid residue with ether.

2,2,4,5-Tetraphenyl-2*H*-imidazole 1-oxide (2d) was also obtained (40%) from 2,2,4,5-tetraphenyl-2*H*-imidazole [1] (1.0 g) and *m*-chloroperbenzoic acid (0.5 g) in dichloromethane (15 ml) at room temperature for 3 days.

Reduction of the 2H-*Imidazole* 1-*Oxides* (2a—d) *with Lithium Aluminium Hydride* (*General Method*).—The *N*-oxide (1.0 g) in tetrahydrofuran (15 ml) was added to a stirred suspension of lithium aluminium hydride (0.1—0.15 g) in tetrahydrofuran (10 ml). Stirring was continued for 1—1.5 h. The mixture was diluted with water, filtered, and extracted with ether to give the N-*hydroxyimidazolines* (9a—d).

1-Hydroxy-4,5-dimethyl-2,2-diphenyl-Δ³-imidazoline (9c) was also obtained (30%) by the addition of the Grignard reagent from methyl iodide (3.0 g) and magnesium (0.5 g) in ether to 4-methyl-2,2-diphenyl-2*H*-imidazole 1-oxide (2a) (1.4 g) in dioxan (25 ml) and refluxing the mixture for 1 h.

Reduction of (2d) in hot dioxan afforded 2,2,4,5-tetraphenyl-2*H*-imidazole, m.p. 201—203° (lit.,[1] 199—201°).

The 2,2-*Diphenyl*-2H-*imidazoles* (10a *and* b).—The 2*H*-imidazole 1-oxide (2a or b) or the corresponding 1-hydroxy-Δ³-imidazoline (9a or b) and sodium borohydride (0.5 mol. equiv.) in ethanol were heated under reflux for 4 h. The solution was concentrated and water was added to the residue. The resulting solid was filtered off and dissolved in ether. Concentration of the dried solution gave the *imidazole* (10a or b).

4,5-Dimethyl-2,2-diphenyl-2*H*-imidazole 1-oxide and 1-hydroxy-4,5-dimethyl-2,2-diphenyl-Δ³-imidazoline were unchanged when similarly treated with sodium borohydride.

5-(1-*Hydroxyethyl*)-4-*methyl*-2,2-*diphenyl*-2H-*imidazole* 1-*Oxide* (3).—5-Acetyl-4-methyl-2,2-diphenyl-2*H*-imidazole 1-oxide (5.84 g), sodium borohydride (0.38 g), and tetrahydrofuran (100 ml) were heated under reflux for 2.5 h. The mixture was diluted with water and extracted with ether to afford the *carbinol*.

4-*Methyl*-2,2-*diphenyl*-Δ³-*imidazolin*-5-*one* (12; R = Me).—4-Methyl-2,2-diphenyl-2*H*-imidazole (6.0 g), *m*-chloroperbenzoic acid (6.0 g), and dichloromethane (200 ml) were kept at room temperature for 7 days. Trituration of the crude product with ether gave the *imidazolinone*.

The residual oil obtained from the extraction with ether was treated with ethanol to give a solid, which afforded 4-*methyl*-2,2-*diphenyl*-2H-*imidazole* 1,3-*dioxide* (13).

The imidazolinone (12; R = Me) was also obtained by heating 4-methyl-2,2-diphenyl-2*H*-imidazole 1-oxide (1.0 g) with sodium cyanide (1.0 g) in dimethyl sulphoxide (50 ml) for 4.5 h at 100 °C. The mixture was poured into water and extracted with ether to give 0.2 g of product.

2,2,4-*Triphenyl*-Δ³-*imidazolin*-5-*one* (12; R = Ph).—This *compound* was prepared from 2,2,4-triphenyl-2*H*-imidazole and *m*-chloroperbenzoic acid as described above.

1,2,4,5-*Tetraphenyl*-1H-*imidazole*.—2,2,4,5-Tetraphenyl-2*H*-imidazole 1-oxide (3.8 g) and triphenylphosphine (2.6 g) were heated gradually until reaction commenced. The cooled residue was triturated with ethanol to give the 1*H*-imidazole (1.95 g, 54%), m.p. 220—222° (from ethanol) (lit.,[19] 219—223°), indistinguishable (i.r., mixed m.p.) from an authentic sample.[19]

5-*Methyl*-2,2-*diphenyl*-2H-*imidazole*-4-*carboxylic Acid* 3-*Oxide* (5).—Ethyl 5-methyl-2,2-diphenyl-2*H*-imidazole-4-carboxylate 3-oxide (1.5 g), methanol (10 ml), and aqueous 40% sodium hydroxide (50 ml) were heated on a water-bath for 0.5 h. The solution was acidified and the precipitated *acid* N-*oxide* collected.

5-*Methyl*-2,2-*diphenyl*-2H-*imidazole*-4-*carbonyl Azide* 3-*Oxide* (6).—Triethylamine (2.52 g) in acetone (5 ml) was added to the acid (5) (6.24 g) in acetone (15 ml). Ethyl chloroformate (2.98 g) in acetone (10 ml) was then added, keeping the temperature at 0 °C. After 0.5 h sodium azide (2.12 g) in water (8 ml) was added (< 5 °C) and stirring was continued for 1 h. The mixture was poured into cold water and the precipitate was collected and dissolved in ether. The dried solution was concentrated to give the *azide* (3.4 g).

7-*Methyl*-5,5-*diphenylimidazo*[1,5-b][1,2,4]*oxadiazol*-2-(5H)-*one* (14).—The azide, when heated on a water-bath in ethanol, benzene, or water afforded the *imidazo*[1,5-b]-[1,2,4]*oxadiazol*-2-*one*.

Dimethyl 3a,6-*Dihydro*-3a,4-*dimethyl*-6,6-*diphenylimidazo*-[1,5-b]*isoxazole*-2,3-*dicarboxylate* (15; R = Me).—4,5-Dimethyl-2,2-diphenyl-2*H*-imidazole 1-oxide (1.32 g), dimethyl acetylenedicarboxylate (0.71 g), and benzene (50 ml) were refluxed for 2 h. The mixture was filtered and the filtrate was concentrated to give an oil (2.0 g) which could not be further purified.

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

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Dimethyl 5,6-Dihydro-4-methyl-6,6-diphenylimidazo[1,5-b]*isoxazole-2,3-dicarboxylate* (16).—4-Methyl-2,2-diphenyl-2*H*-imidazole 1-oxide (1.0 g) and dimethyl acetylenedicarboxylate (0.57 g) in chloroform (25 ml) were kept at room temperature for 3 days. The mixture was concentrated to give an oil, which produced a solid on trituration with ethanol. Recrystallisation from ethanol gave the *imidazo*[1,5-b]*isoxazole* as yellow fibres.

Dimethyl (5-*Methyl-2,2-diphenyl-*2H-*imidazol-4-yl*)*oxalacetate* (17).—4-Methyl-2,2-diphenyl-2*H*-imidazole 1-oxide (0.75 g) and dimethyl acetylenedicarboxylate (0.43 g) in benzene (50 ml) were refluxed for 2 h. The mixture was filtered and the filtrate concentrated to give an oil. Trituration with petroleum (b.p. 40—60°) gave the *imidazole*.

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