Heterocyclic Synthesis from *o*-Halogeno-acids. Part III.[1] Synthesis of 2-Methylindole-4-carboxylic Acid and Related Compounds and of Some Derivatives of 3-Phenylisoquinolin-1(2*H*)-one

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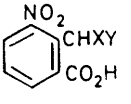
Condensation of 2-bromo-3-nitrobenzoic acid with acetylacetone in the presence of copper(II) acetate and ethanolic sodium ethoxide gives 2-acetylacetonyl-3-nitrobenzoic acid. Deacetylation with water–dimethyl sulphoxide at 170 °C yields 3-methyl-5-nitroisocoumarin, which is converted by catalytic hydrogenation and alkaline hydrolysis into 2-methylindole-4-carboxylic acid. Similar condensation and reduction reactions yield related compounds including dimethyl 2-methylindole-3,4-dicarboxylate. Tricyclic products are obtained by heating *o*-phenacylbenzoic acid with 2-amino-1-phenylethanol, ethane-1,2-diamine, and *o*-phenylenediamine. *o*-Phenacylbenzoic acid is also converted into 2-substituted 3-phenylisoquinolin-1(2*H*)-ones, which are cyclised to form dibenzo[*a*,*g*]-quinolizin-8-one derivatives and/or oxazolo[2,3-*a*]isoquinolinylium salts.

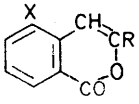
HURTLEY [2] showed that *o*-bromobenzoic acid condensed with carbanions in the presence of copper or a copper(II) salt, and this reaction has recently been studied thoroughly.[3-5] We have been examining the application of the reaction to the synthesis of heterocyclic compounds [1,6] and report here the preparation of substituted indole-4-carboxylic acids from 2-bromo-3-nitrobenzoic acid [7,8] and of some fused ring compounds from *o*-phenacylbenzoic acid.

Condensation of 2-bromo-3-nitrobenzoic acid with acetylacetone, benzoylacetone, and ethyl acetoacetate by using sodium ethoxide in ethanol and copper(II) acetate catalyst gave the corresponding acids (Ia—c). This condensation of acetylacetone apparently fails [5] under the conditions recently recommended for these reactions [excess of β-dicarbonyl compound, sodium hydride, and copper(I) bromide catalyst].[5] As Hurtley [2] observed, copper(II) acetate is a more vigorous catalyst than copper; his original reaction conditions may therefore still be of value in some condensations of this type and copper(I) salts may not necessarily be the most effective catalysts in all cases. Reaction of the bromo-nitro-acid with methyl acetoacetate, methanolic sodium methoxide, and copper(II) acetate, however, gave poor results, but the use of methyl acetoacetate with sodium hydride and copper(I) bromide [5] gave (Id) in moderate yield. Attempts to remove one acetyl group from compound (Ia) by either acidic or alkaline hydrolysis gave tarry products, presumably owing to displacement or condensation reactions of the nitro-group. The degradation of β-oxo-esters to ketones by heating with sodium chloride–water–dimethyl sulphoxide [9] was applied to the oxo-ester (Ic) to give the isocoumarin



(I)

a ; X = Y = Ac
b ; X = Ac, Y = Bz
c ; X = Ac, Y = CO_2Et
d ; X = Ac, Y = CO_2Me



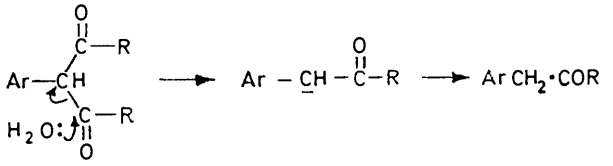
(II)

a ; R = Me, X = NO_2
b ; R = Ph, X = NO_2
c ; R = Me, X = NH_2
d ; R = Ph, X = NH_2

(IIa), the enol lactone of the required oxo-acid. The 1,3-diketones (Ia and b) were also deacetylated efficiently under these conditions to give the isocoumarins (IIa and b). The presence of sodium chloride was later found to be unnecessary, in agreement with recent reports [10] that the reaction involved is simply hydrolysis. Conversion of (Ia and b) into (IIa and b) by water–dimethyl sulphoxide represents a novel process for the neutral, hydrolytic degradation of 1,3-diketones to ketones (as the corresponding enol lactones), but experiments with simpler 1,3-diketones showed that the method was not a general one; it presumably depends on the strongly electron-withdrawing nitroaryl system to stabilise the intermediate carbanion (Scheme). Thus

[1] Part II, D. E. Ames and O. Ribeiro, *J.C.S. Perkin I*, 1975, 1390.
[2] W. R. H. Hurtley, *J. Chem. Soc.*, 1929, 1870.
[3] K. A. Ciriguttis, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1974, **27**, 2209; R. G. R. Bacon and J. C. F. Murray, *J.C.S. Perkin I*, 1975, 1267.
[4] *Cf.* D. W. Brown, S. F. Dyke, M. Sainsbury, and G. Hardy, *J. Chem. Soc.* (*C*), 1971, 3219.
[5] A. Bruggink and A. McKillop, *Tetrahedron*, 1975, **31**, 2607; *Angew. Chem. Internat. Edn.*, 1974, **13**, 340.
[6] D. E. Ames and W. D. Dodds, *J.C.S. Perkin I*, 1972, 705.
[7] F. C. Whitmore, P. J. Culhane, and H. T. Neher, *Org. Synth.*, Coll. Vol. I, 1941, p. 56; P. J. Culhane, *ibid.*, p. 125.
[8] M. S. Newman and M. C. V. Zwan, *J. Org. Chem.*, 1973, **38**, 319.
[9] A. P. Krapcho and A. J. Lovey, *Tetrahedron Letters*, 1973, 957.
[10] A. P. Krapcho, E. G. E. Jahngen, and A. J. Lovey, *Tetrahedron Letters*, 1974, 1091; C. L. Liotta and F. L. Cook, *ibid.*, p. 1095.

o-acetylacetonylbenzoic acid with water–dimethyl sulphoxide at 170 °C gave 4-acetyl-3-methylisocoumarin by cyclisation without deacetylation. It was also found that conversion of the acid (Ia) into the isocoumarin

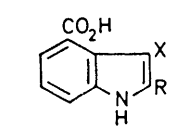


SCHEME

(IIa) could be effected, though in lower yield, by heating at 170 °C in dry dimethyl sulphoxide, presumably by intramolecular attack by the carboxy-group analogous to the hydrolysis scheme.

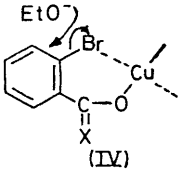
The nitro-lactones (IIa and b) were catalytically hydrogenated to the amino-lactones (IIc and d), which, on hydrolysis with alkali and then acidification, gave the 2-substituted indole-4-carboxylic acids (IIIa and b) by cleavage of the lactone ring and recyclisation of the oxo-amine. This route provides a short and convenient synthesis of 2-substituted indole-4-carboxylic acids.[11] Catalytic reduction of the intermediate diketone (Ia) yielded 3-acetyl-2-methylindole-4-carboxylic acid (IIIc), and the ester acid (Ic) gave the 3-ethyl ester of 2-methylindole-3,4-dicarboxylic acid (IIId). The ester-acid (Id) was esterified with diazomethane and then reduced to dimethyl 2-methylindole-3,4-dicarboxylate.

The products obtained by the Hurtley reaction of *o*-bromobenzoic acid with benzoylacetanilide, ethyl phenylsulphonylacetate, and phenylsulphonylacetone are described in the Experimental section. Only in the last case did simultaneous deacylation occur. When *o*-bromobenzoylacetone was treated with ethanolic sodium ethoxide and *o*-bromobenzoic acid, no condensation with the bromo-acid occurred but some *o*-ethoxybenzoylacetone was formed. Omission of the



(III)

a ; R = Me, X = H
b ; R = Ph, X = H
c ; R = Me, X = Ac
d ; R = Me, X = CO_2Et

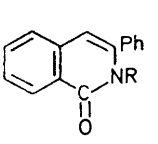


(IV)

a ; X = CHAc
b ; X = O

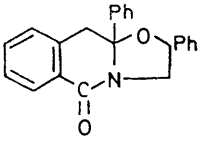
bromo-acid resulted in formation of the ethoxy-diketone, in good yield, but no reaction took place in the absence of copper(II) catalyst. This suggests that the mechanism of the displacement reaction [see (IVa)] is analogous to that of the Hurtley reaction [see (IVb)] [or to that involving copper(I) salt catalysis recently proposed [5]].

o-Phenacylbenzoic acid, which is readily obtained by Hurtley's method,[2] was also used for the synthesis of some isoquinolin-1-one derivatives.[4] Thus reaction of the oxo-acid with 2-amino-1-phenylethanol and acetic acid in ethanol gave 2-(2-hydroxy-2-phenylethyl)-3-phenylisoquinolin-1(2*H*)-one (Va). When less than one molar proportion of acetic acid was used, a second product was also obtained, and this is believed to be 2,3,10,10a-tetrahydro-2,10a-diphenyloxazolo[3,2-*b*]isoquinolin-5-one (VI). The formation of an analogous tricyclic compound by reaction of *o*-benzoylbenzoic acid with 2-aminoethanol has been reported.[12] Only 2-(2-hydroxyethyl)-3-phenylisoquinolin-1(2*H*)-one (Vb) could be isolated after treatment of *o*-phenacylbenzoic acid

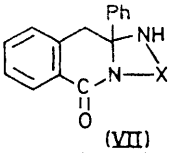


(V)

a ; R = $CH_2 \cdot CH(OH)Ph$
b ; R = $CH_2 \cdot CH_2 \cdot OH$
c ; R = $CH_2 \cdot CH{:}CH_2$
d ; R = $CH_2 \cdot CMe{:}CH_2$
e ; R = $CH_2 \cdot CH_2Cl$
f ; R = $CH_2 \cdot CH(OMe)_2$
g R = $CH_2 \cdot CO_2H$



(VI)



(VII)

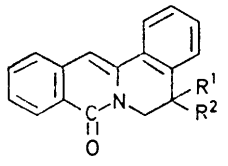
a ; X = $CH_2 \cdot CH_2$
b ; X = *o*-C_6H_4

with 2-aminoethanol. When the oxo-acid was condensed with ethane-1,2-diamine and with *o*-phenylenediamine, tricyclic products (VIIa and b) were obtained.[13]

3-Phenylisoquinolin-1(2*H*)-ones (V) are also useful intermediates for the synthesis of dibenzo[*a*,*g*]quinolizin-8-one derivatives.[4,14] Thus the isoquinolones (Vc and d) were prepared in good yields from *o*-phenacylbenzoic acid and the appropriate amine. Sodium aluminium chloride [15] cyclised compounds (Vc and d) to give the dibenzoquinolizinones (VIIIa and b) in high yields. When polyphosphoric acid was used for these cyclisations, however, yields of dibenzoquinolizinones were low and the main products were oxazoloisoquinolinylium compounds which were isolated as the perchlorates (IXa and b).[16] Similarly 2-(2-hydroxyethyl)-3-phenylisoquinolin-1(2*H*)-one (Vb) with polyphosphoric acid yielded the oxazoloisoquinolinylium salt (IXc). In contrast, treatment of the hydroxylalkyl derivative (Va) with polyphosphoric acid gave only the dibenzoquinolizinone (VIIIc), but the corresponding oxazoloisoquinolinylium salt (IXd) was obtained by the action of sulphuric acid and perchloric acid. When the hydroxyethyl compound (Vb) was converted into the chloroethyl

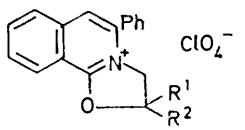
[11] *Cf.* D. E. Horning, G. Lacasse, and J. M. Muchowski, *Canad. J. Chem.*, 1971, **49**, 2797; T. Watanabe, F. Hamaguchi, and S. Ohki, *Chem. and Pharm. Bull.* (*Japan*), 1972, **20**, 2123.
[12] T. S. Sulkowski, U.S.P., 3 336 306/1967.
[13] *Cf.* T. Jen, B. Dienel, F. Dowalo, H. V. Hoeven, P. Bender, and B. Loev, *J. Medicin. Chem.*, 1973, **16**, 633.
[14] *Cf.* S. F. Dyke and E. P. Tiley, *Tetrahedron*, 1975, **31**, 561.
[15] L. F. Fieser and M. Fieser, 'Reagents for Organic Chemistry,' Wiley, New York, 1967, p. 1027.
[16] H. J. Roth and R. Rohrback, *Arch. Pharm.*, 1970, **303**, 585; *cf.* C. K. Bradsher and M. F. Zinn, *J. Heterocyclic Chem.*, 1967, **4**, 66.

derivative (Ve), by using thionyl chloride and pyridine, and the product was cyclised by the action of sodium aluminium chloride, 5,6-dihydrodibenzo[*a*,*g*]quinolizin-8-one [17] (VIIId) was obtained. The dimethoxyethylisoquinolinone (Vf) reacted with polyphosphoric acid to give dibenzo[*a*,*g*]quinolizin-8-one (X).



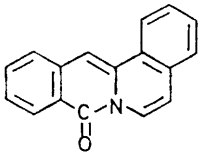
(VIII)

a ; R^1 = H, R^2 = Me
b ; R^1 = R^2 = Me
c ; R^1 = H, R^2 = Ph
d ; R^1 = R^2 = H



(IX)

a ; R^1 = H, R^2 = Me
b ; R^1 = R^2 = Me
c ; R^1 = R^2 = H
d ; R^1 = H, R^2 = Ph
e ; R^1R^2 = O



(X)

o-Phenacylbenzoic acid did not react with glycine in ethanol but the tetramethylammonium salt of glycine and 3-phenylisocoumarin in hexamethylphosphoric triamide gave 1,2-dihydro-1-oxo-3-phenylisoquinoline-2-acetic acid (Vg). Attempted cyclisation with sodium aluminium chloride or polyphosphoric acid yielded only the oxo-oxazoloisoquinolinylium salt (IXe).

Thus *o*-phenacylbenzoic acid is a useful intermediate for the synthesis of dibenzoquinolizinones (VIII), and it is of interest that no activation by alkoxy-groups is required to facilitate the final cyclisation step.[18]

EXPERIMENTAL

General procedures and instruments used were as given in ref. 1.

2-Acetylacetonyl-3-nitrobenzoic Acid.—Acetylacetone (6.4 g) in ethanol (20 ml) was added to a cooled solution of sodium ethoxide [from sodium (2.2 g) and ethanol (100 ml)]. The mixture was shaken and cooled for 2 min, and then 2-bromo-3-nitrobenzoic acid [7,8] (8 g) and copper(II) acetate (0.4 g) were added. The mixture was boiled under reflux for 4.5 h, poured into M-sodium hydroxide (900 ml), and washed repeatedly with ether. The combined washings were counter-extracted with M-sodium hydroxide and the alkaline solutions were acidified with concentrated hydrochloric acid (130 ml). Isolation with ethyl acetate gave the *acid* (4.9 g; 57%) as pale yellow prisms (from benzene–petroleum), m.p. 140—142° (Found: C, 54.3; H, 4.0; N, 5.2. $C_{12}H_{11}NO_6$ requires C, 54.3; H, 4.2; N, 5.3%), $\nu_{max.}$ 1 729 cm^{-1}, $\lambda_{max.}$ 278 nm (ε 7 500), δ($CDCl_3$) 1.86 (6 H, s, 2Me), 7.20—8.40 (4 H, m, ArH + CH), and 11.3br (1 H, s, CO_2H). Similarly prepared were *2-α-acetylphenacyl-3-nitrobenzoic acid* (45%), as a *solvate*, m.p. 101—102° (from benzene) (Found: C, 65.5; H, 4.5; N, 3.6. $C_{17}H_{13}NO_6$,0.5C_6H_6 requires C, 65.6; H, 4.5; N, 3.4%), $\nu_{max.}$ 3 350, 1 740, and 1 690 cm^{-1}, $\lambda_{max.}$ 304 nm (ε 7 600), δ($CDCl_3$) 1.99 (3 H, s, Me), 5.88 (1 H, s, CO_2H, exchanges with D_2O), 7.13—8.50 (12 H, m, ArH + CH); and ethyl α-(2-carboxy-6-nitrophenyl)acetoacetate (36%), m.p. 119—121° (from benzene) (lit.,[5] 123—124°).

Methyl α-(2-carboxy-6-nitrophenyl)acetoacetate (51%), prepared by the procedure of Bruggink and McKillop,[5] had m.p. 129—131° (from benzene) (Found: C, 51.6; H, 4.0; N, 4.9. $C_{12}H_{11}NO_7$ requires C, 51.3; H, 3.9; N, 5.0%), δ($CDCl_3$) 1.68 and 1.80 (3 H, two s, CO·CH_3), 3.63 and 3.73 (3 H, two s, CO_2·CH_3) (each corresponding to keto- and enol forms), 7.3—8.5 (3 H, m, ArH), and 12.8br (1 H, s, CO_2H). When this product was prepared by the previous procedure, using methanolic sodium methoxide, the yield was low and 2-methoxy-3-nitrobenzoic acid, m.p. 200—203° (from water), was also isolated (lit.,[19] m.p. 194—195°), δ[$CDCl_3$–$(CD_3)_2SO$] 4.03 (3 H, s, Me) and 7.2—8.3 (4 H, m, ArH + CO_2H).

3-Methyl-5-nitroisocoumarin.— 2-Acetylacetonyl-3-nitrobenzoic acid (1 g), sodium chloride (1 g), water (1 ml), and dimethyl sulphoxide (20 ml) were heated at 170 °C under reflux for 4 h, and poured into water. The precipitate was collected, dried, and crystallised from benzene–petroleum to give *3-methyl-5-nitroisocoumarin* (0.52 g, 67%), as pale yellow crystals, m.p. 196—197° (Found: C, 56.2; H, 3.5; N, 6.2. $C_{10}H_7NO_4$,0.5H_2O requires C, 56.1; H, 3.8; N, 6.5%). Sublimation at 160° and 0.5 mmHg gave the anhydrous compound, m.p. 195—196° (Found: C, 58.7; H, 3.6; N, 6.7. $C_{10}H_7NO_4$ requires C, 58.5; H, 3.4; N, 6.8%), $\nu_{max.}$ 1 749 cm^{-1} (C:O), $\lambda_{infl.}$ 233 nm (ε 13 600), $\lambda_{max.}$ 298 and 353 nm (ε 5 400 and 3 500), δ($CDCl_3$) 2.37 (3 H, s, Me) and 7.1—8.6 (4 H, m, ArH + 4-H). The same product was obtained when the sodium chloride was omitted (yield 78%) and when sodium chloride and water were both omitted (35%). The product (58%) was also obtained from ethyl α-(2-carboxy-6-nitrophenyl)acetoacetate, water, and dimethyl sulphoxide.

Similarly 2-acetylphenacyl-3-nitrobenzoic acid with water–dimethyl sulphoxide gave *3-phenyl-5-nitroisocoumarin* (57%) as the *hemihydrate*, m.p. 129—130° (from benzene–petroleum) (Found: C, 65.2; H, 3.5; N, 5.3. $C_{15}H_9NO_4$,0.5H_2O requires C, 65.2; H, 3.7; N, 5.1%), $\nu_{max.}$ 1 740 cm^{-1}, $\lambda_{max.}$ 251 and 329 nm (ε 13 200 and 12 000).

Other Experiments with 1,3-Diketones (with Miss L. L. Sarkissian and A. R. Benn).—No cleavage of dibenzoylmethane was detected when it was heated for 4 h at 160—170 °C with dimethyl sulphoxide and water in the presence or absence of sodium chloride. Water–hexamethylphosphoric triamide under the same conditions also effected no cleavage. *o*-Acetylacetonylbenzoic acid [2] with water–dimethyl sulphoxide (or dry solvent) at 170 °C for 4 h gave 4-acetyl-3-methylisocoumarin (49 and 57%, respectively), m.p. and mixed m.p. 100—102° (lit.,[20] 99°).

5-Amino-3-methylisocoumarin.—The nitroisocoumarin (250 mg) in ethanol (50 ml) was hydrogenated over palladium–charcoal (400 mg; 10%). Filtration, evaporation, and crystallisation from benzene–petroleum gave

[17] N. C. Yang, A. Shani, and G. R. Lenz, *J. Amer. Chem. Soc.*, 1966, **88**, 5369.
[18] *E.g.* D. W. Brown and S. F. Dyke, *Tetrahedron*, 1966, **22**, 2437.
[19] J. L. Simonsen and M. G. Rao, *J. Chem. Soc.*, 1917, **111**, 220.
[20] G. G. Smith, C. W. Delong, W. H. Wetzel, and V. P. Muralidharan, *J. Heterocyclic Chem.*, 1967, **4**, 501.

the *amine* (130 mg), m.p. 146—148° (Found: C, 68.6; H, 5.3; N, 7.9. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.2; N, 8.0%), $\nu_{max.}$ 3 400, 3 340 (NH_2), and 1 725 cm^{-1} (C:O), $\lambda_{max.}$ 235, 243, 274, and 364 nm (ε 18 600, 19 300, 9 300, and 4 500), δ($CDCl_3$) 2.29 (3 H, s, 3-Me), 3.5—4.3br (2 H, NH_2), 6.22 (1 H, s, 4-H), and 6.9—7.8 (3 H, m, ArH). Similarly 5-nitro-3-phenylisocoumarin gave *5-amino-3-phenylisocoumarin*, m.p. 178—180° (from benzene) (Found: C, 76.0; H, 4.5; N, 6.0. $C_{15}H_{11}NO_2$ requires C, 75.9; H, 4.7; N, 5.9%), $\nu_{max.}$ 3 350, 3 440, and 1 692 cm^{-1}, $\lambda_{max.}$ 259, 303, 312infl, and 390 nm (ε 20 000, 11 500, 11 300, and 11 200).

2-Methylindole-4-carboxylic Acid.—3-Methyl-5-nitroisocoumarin (1.3 g) in ethanol (75 ml) was hydrogenated over palladium–charcoal (0.5 g; 10%). The solution was filtered and the catalyst was washed with ethanol (50 ml) and then with 2M-sodium hydroxide (25 ml) and ethanol (25 ml). The filtrates were concentrated to 60 ml and boiled under reflux for 1 h. The solution was filtered [washing with water (10 ml)] and the filtrate was concentrated to 25 ml and acidified with acetic acid (6 ml). 2-Methylindole-4-carboxylic acid (0.69 g, 62%), m.p. 228—231°, crystallised out (lit.,[11] 230—232°). Esterification with diazomethane gave the methyl ester, m.p. 128—130° (lit.,[11] m.p. 131—132°), δ($CDCl_3$) 2.36 (3 H, s, CO_2Me), 3.94 (3 H, s, 2-Me), 6.85—7.9 (4 H, m, ArH + 3-H), and 8.5br (1 H, s, NH), similar to that reported.[11]

Similarly 5-amino-3-phenylisocoumarin gave 2-phenylindole-4-carboxylic acid (46%), m.p. 255—260° (decomp.) (from aqueous methanol) (lit.,[11] 265—267°); methyl ester, m.p. 122—124° (from petroleum) (lit.,[11] 124.5—126°).

3-Acetyl-2-methylindole-4-carboxylic Acid.—2-Acetylacetonyl-3-nitrobenzoic acid (1 g) in ethanol (50 ml) was added to pre-reduced palladium–charcoal (1 g, 5%) in ethanol (50 ml). The mixture was hydrogenated until absorption ceased (uptake *ca.* 2.5 mol. equiv.) and filtered at the b.p. Evaporation and crystallisations from ethanol gave the *acid* (260 mg), m.p. 225—227° (decomp.) (Found: C, 64.2; H, 4.9; N, 6.0. $C_{12}H_{11}NO_3,0.5H_2O$ requires C, 63.8; H, 5.3; N, 6.2%), $\nu_{max.}$ 1 670 cm^{-1}, $\lambda_{max.}$ 223, 278, and 303 nm (ε 22 000, 8 400, and 8 100), δ[$(CD_3)_2SO$] 2.60 and 2.37 (each 3 H, s, 2-Me and 3-COMe), 7.1—7.8 (3 H, m, ArH), and 11.85br (2 H, NH and CO_2H). Similarly ethyl α-(2-carboxy-6-nitrophenyl)acetoacetate gave *3-ethoxycarbonyl-2-methylindole-4-carboxylic acid* (as the hemihydrate), m.p. 170° (decomp.) [Found: C, 61.3; H, 5.4; N, 5.1 (after drying at 100 °C and 0.1 mmHg). $C_{13}H_{13}NO_4,0.5H_2O$ requires C, 60.9; H, 5.5; N, 5.5%], $\nu_{max.}$ 1 718 cm^{-1}, $\lambda_{max.}$ 219, 258, and 293 nm (ε 31 000, 8 400, and 7 400), δ[$(CD_3)_2SO$] 1.32 (3 H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 2.60 (3 H, s, 2-Me), 4.25 (2 H, q, *J* 7 Hz, $CH_2{\cdot}CH_3$), 7.05—7.53 (3 H, m, ArH), and 11.66br (1 H, CO_2H).

Methyl α-(2-Methoxycarbonyl-6-nitrophenyl)acetoacetate.—Methyl α-(2-carboxy-6-nitrophenyl)acetoacetate (5 g) in methanol (50 ml) was treated with an excess of ethereal diazomethane. After 5 min, acetic acid (15 ml) and then M-sulphuric acid (100 ml) were added and the mixture was left at room temperature for 30 min. Isolation with ether gave the *dimethyl ester* (3.89 g), m.p. 91—93° (from petroleum) (Found: C, 53.3; H, 4.6; N, 4.8. $C_{13}H_{13}NO_7$ requires C, 52.9; H, 4.4; N, 4.7%), δ($CDCl_3$) 1.69 (3 H, s, COMe), 3.66 (3 H, s, $CH{\cdot}CO_2Me$), 3.87 (3 H, s, 2-CO_2Me), and 7.3—8.3 (4 H, m, ArH + enolic OH).

Dimethyl 2-Methylindole-3,4-dicarboxylate.—The foregoing diester (1 g) in methanol (50 ml) was hydrogenated over palladium–charcoal (0.4 g, 5%). Filtration, evaporation, and trituration with ether gave the *dimethyl ester* (0.75 g), m.p. 96—98° (from ether) (Found: C, 63.2; H, 5.4; N, 5.4. $C_{13}H_{13}NO_4$ requires C, 63.2; H, 5.3; N, 5.7%), $\nu_{max.}$ 1 705 cm^{-1}, δ($CDCl_3$) 2.40 (3 H, s, 2-Me), 3.79 and 3.89 (each 3 H, s, 3- and 4-CO_2Me), 6.9—7.5 (3 H, m, ArH), and 9.62br (1 H, s, NH).

Condensation with o-Bromobenzoic Acid.—Benzoylacetanilide (4.8 g), the bromo-acid (2 g), and copper(II) acetate (0.1 g) were added successively to sodium ethoxide solution [from sodium (0.46 g) in ethanol (25 ml)] and the mixture was boiled under reflux for 3 h. Acidification, filtration, and crystallisations from aqueous ethanol gave *benzoyl-o-carboxyphenylacetanilide* (2.3 g), m.p. 150—151° (decomp.) (Found: C, 73.6; H, 4.8; N, 3.8. $C_{22}H_{17}NO_4$ requires C, 73.5; H, 4.8; N, 3.9%). Similarly (after 7 h heating) ethyl phenylsulphonylacetate gave *ethyl o-carboxyphenyl-(phenylsulphonyl)acetate* (45%), m.p. 135—136° (from benzene) (Found: C, 58.4; H, 4.6; S, 9.5. $C_{17}H_{16}O_6S$ requires C, 58.6; H, 4.6; S, 9.2%), δ($CDCl_3$) 1.22 (3 H, t, *J* 6 Hz, Me), 4.25 (2 H, q, *J* 6 Hz, CH_2), 7.0—8.25 (10 H, m, CH + ArH); also phenylsulphonylacetone gave (after 9 h heating) *ω-phenylsulphonyl-o-toluic acid* (59%), m.p. 154—155° (from aqueous ethanol) (Found: C, 61.0; H, 4.3; S, 11.6. $C_{14}H_{12}O_4S$ requires C, 60.9; H, 4.4; S, 11.6%), δ[$CDCl_3$–$(CD_3)_2SO$] 5.15 (2 H, s, CH_2), 6.60br (1 H, s, CO_2H), and 7.2—8.05 (9 H, m, ArH).

o-Bromobenzoylacetone.[21]—Acetone (34.8 g) in ether (35 ml) was added gradually to a stirred suspension of sodamide [from sodium (13.8 g)] in ether (200 ml). After 5 min, methyl *o*-bromobenzoate (64.5 g) in ether (50 ml) was added during 5 min. The mixture was stirred and boiled under reflux for 2 h and poured into ice–dilute hydrochloric acid. The separated ether layer was washed with sodium hydrogen carbonate solution and water and evaporated. The residue in methanol (100 ml) was added to a hot, filtered solution of copper(II) acetate (40 g) in water (350 ml) and left overnight. The copper complex was collected, washed with petroleum, and shaken with M-sulphuric acid (500 ml) and ether (200 ml). Separation and isolation with ether gave *o-bromobenzoylacetone* (40%), b.p. 120° at 1.5 mmHg (Found: C, 50.1; H, 3.8. $C_{10}H_9BrO_2$ requires C, 49.8; H, 3.8%), $\nu_{max.}$ 1 610 cm^{-1}, δ($CDCl_3$) 2.10 (3 H, s, Me), 5.90 (1 H, s, C=CH), 7.10—7.60 (5 H, m, ArH + enolic OH), corresponding to the enol form.

o-Ethoxybenzoylacetone.—The foregoing bromo-dione (1 g) and copper(II) acetate (0.1 g) were added to sodium ethoxide solution [from sodium (0.2 g) and ethanol (10 ml)]. The mixture was boiled under reflux for 1 h, cooled, and poured into 2M-hydrochloric acid. Isolation with ether gave the ethoxy-dione (60%), m.p. 54—56° (lit.,[22] 58°) (from petroleum) (Found: C, 69.8; H, 6.9. Calc. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8%), $\nu_{max.}$ 1 610 cm^{-1}, δ($CDCl_3$) 1.45 (3 H, t, *J* 6 Hz, $CH_2{\cdot}CH_3$), 2.12 (2.1 H, s, $HO{\cdot}C{=}CH{\cdot}CO{\cdot}CH_3$), 2.20 (0.9 H, s, $CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$), 4.11 (2.6 H, q, *J* 6 Hz, $CH_2{\cdot}CH_3$ with superimposed $CO{\cdot}CH_2{\cdot}CO$), 6.50 (0.7 H, s, C=CH), and 6.88—7.9 (4 H, m, ArH), corresponding to about 70% of enol form. Attempted condensation with *o*-bromobenzoic acid gave only a small yield of the same product.

2-(2-Hydroxy-2-phenylethyl)-3-phenylisoquinolin-1(2H)-one.—*o*-Phenacylbenzoic acid (1 g), 2-amino-1-phenylethanol (1.5 g), and acetic acid (0.7 g) in ethanol (25 ml)

[21] C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, 1954, **8**, 90.

[22] E. Besthorn, E. Banzhaf, and G. Jaegle, *Ber.*, 1894, **27**, 3035.

were boiled under reflux for 18 h, cooled, and poured into water (250 ml). Isolation with ethyl acetate and crystallisation from benzene–petroleum gave the *isoquinolinone* (75%), m.p. 158—159.5° (Found: C, 81.1; H, 5.6; N, 3.9. $C_{23}H_{19}NO_2$ requires C, 80.9; H, 5.6; N, 4.1%), $\nu_{max.}$ 3 400 and 1 590 cm^{-1}, δ($CDCl_3$) 3.6—4.5 (3 H, m, CH_2 and OH), 5.05 (1 H, q, CH), 6.41 (1 H, s, 4-H), 6.5—8.0 (13 H, m, ArH), and 8.40 (1 H, ABCX pattern, 8-H).

When 2-amino-1-phenylethanol (5 g), *o*-phenacylbenzoic acid (3 g), and acetic acid (2 g) in ethanol (30 ml) were treated similarly, the yield of isoquinolinone was 63%. Evaporation of the mother liquors and crystallisations from ethanol gave 2,3,10,10a-*tetrahydro*-2,10a-*diphenyloxazolo*-[3,2-b]*isoquinolin*-5-*one* (12%), m.p. 179—180° (Found: C, 81.1; H, 5.7; N, 4.0. $C_{23}H_{19}NO_2$ requires C, 80.9; H, 5.6; N, 4.1%), $\nu_{max.}$ 1 658 cm^{-1} (C:O), $\lambda_{max.}$ 235, 250, and 263 nm (ε 11 400, 9 500, and 6 100), δ($CDCl_3$) 3.1—4.1 (4 H, m, 3- and 10-H_2), 4.7—5.4 (1 H, m, 2-H), and 6.5—8.2 (14 H, m, ArH).

2,3,10,10a-*Tetrahydro*-10a-*phenylimidazo*[1,2-b]*isoquinolin*-5(1H)-*one*.—Ethane-1,2-diamine (3 ml), *o*-phenacylbenzoic acid (1 g), and acetic acid (2.9 ml) in ethanol (25 ml) were boiled under reflux for 18 h, cooled, and poured into water (150 ml). Filtration and crystallisations from aqueous ethanol gave the *product* (0.6 g), m.p. 193—194° (Found: C, 77.1; H, 6.2; N, 10.4. $C_{17}H_{16}N_2O$ requires C, 77.3; H, 6.1; N, 10.6%), $\nu_{max.}$ 3 300 (NH) and 1 648 cm^{-1} (C:O), $\lambda_{max.}$ 237, 252, and 263 nm (ε 12 000, 9 900, and 7 500), δ($CDCl_3$) 2.45—4.08 (6 H, m, $[CH_2]_2$ and CH_2) and 6.9—8.1 (9 H, m, ArH).

o-Phenylenediamine similarly gave 5a,6-*dihydro*-6a-*phenylbenzimidazo*[1,2-b]*isoquinolin*-11(5H)-*one* (31%), m.p. 227—230° (from ethanol) (Found: C, 80.9; H, 5.3; N, 8.9. $C_{21}H_{16}N_2O$ requires C, 80.8; H, 5.2; N, 9.0%), $\nu_{max.}$ 3 240 and 1 638 cm^{-1}, $\lambda_{max.}$ 240 and 350 nm (ε 21 300 and 7 100).

2-*Allyl*-3-*phenylisoquinolin*-1(2H)-*one*.—Allylamine (3 ml), acetic acid (1.5 ml), *o*-phenacylbenzoic acid (1 g), and ethanol (25 ml) were boiled under reflux for 18 h, cooled, and poured into ice–water. Filtration and crystallisation from hexane gave the *isoquinolinone* (95%), m.p. 94—95.5° (Found: C, 82.5; H, 5.7; N, 5.0. $C_{18}H_{15}NO$ requires C, 82.7; H, 5.8; N, 5.4%), $\nu_{max.}$ 1 655 cm^{-1} (C:O), δ($CDCl_3$) 4.51 (2 H, m, 1'-H_2), 4.91 (2 H, m, 3'-H_2), 5.60—6.03 (1 H, m, 2'-H), 6.32 (1 H, s, 4-H), 7.0—7.8 (8 H, m, ArH), and 8.3—8.5 (1 H, ABCX pattern, 8-H). Similarly prepared were: 2-(2-*hydroxyethyl*)-3-*phenylisoquinolin*-1(2H)-*one* (78%), m.p. 145—146° (from benzene–petroleum) (Found: C, 77.1; H, 5.5; N, 5.3. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%), $\nu_{max.}$ 3 360 and 1 642 cm^{-1}, δ($CDCl_3$) 3.8 (3 H, t, *J* 6 Hz, CH_2, with OH superimposed), 4.1 (2 H, t, *J* 6 Hz, CH_2), 6.37 (1 H, s, 4-H), 7.21—7.60 (8 H, m, ArH), and 8.36 (1 H, d, splitting 8 Hz, 8-H); 2-(2-*methylallyl*)-3-*phenylisoquinolin*-1(2H)-*one* (87%), m.p. 78—79° (from hexane) (Found: C, 83.2; H, 6.1; N, 5.1. $C_{19}H_{17}NO$ requires C, 82.9; H, 6.2; N, 5.1%), $\nu_{max.}$ 1 653 cm^{-1}, δ($CDCl_3$) 1.53 (3 H, s, Me), 4.37 (1 H, s, C=CH_2), 4.43 (2 H, s, N·CH_2), 4.75 (1 H, s, C=CH_2), 6.39 (1 H, s, 4-H), 7.3—7.6 (8 H, m, ArH), and 8.45 (1 H, d, splitting 8 Hz, 8-H); 2-*phenethyl*-3-*phenylisoquinolin*-1(2H)-*one* (88%), m.p. 125—126° (from petroleum) (Found: C, 85.0; H, 6.0; N, 4.1. $C_{23}H_{19}NO$ requires C, 48.9; H, 5.9; N, 4.3%), $\nu_{max.}$ 1 650 cm^{-1}, δ($CDCl_3$) 2.86 (2 H, t, *J* 7 Hz, CH_2Ph), 4.15 (2 H, t, *J* 7 Hz, CH_2·N), 6.38 (1 H, s, 4-H), 6.90—7.65 (13 H, m, ArH), and 8.50 (1 H, d, splitting 8 Hz, 8-H); 2-(2,2-dimethoxyethyl)-3-phenylisoquinolin-1(2*H*)-one (70%), m.p. 74—75.5° (from petroleum) (Found: C, 74.0; H, 6.2; N, 4.4. Calc. for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5%), reported as an oil,[4] δ($CDCl_3$) 3.24 (6 H, s, 2 Me), 4.10 (2 H, d, *J* 6 Hz, CH_2), 4.39 (1 H, t, *J* 6 Hz, CH), 6.39 (1 H, s, 4-H), 7.4—7.6 (8 H, m, ArH), 8.45 (1 H, d, splitting 8 Hz, 8-H).

1,2-*Dihydro*-1-*oxo*-3-*phenylisoquinoline*-2-*acetic Acid*.—Glycine (4.0 g) was dissolved in aqueous tetramethylammonium hydroxide (17.3 ml; 25%) and the solution was evaporated; the residue was dried at 100 °C and 1 mmHg for 2 h. The salt was dissolved in hexamethylphosphoric triamide (50 ml), 3-phenylisocoumarin (3.8 g) was added, and the mixture was heated at 100 °C for 1.5 h, cooled, and poured into ice–water. Acidification, filtration, and crystallisations from aqueous ethanol gave the *acid* (3.5 g), m.p. 233—234° (Found: C, 73.1; H, 4.7; N, 4.9. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%), $\nu_{max.}$ 1 770, 1 750, and 1 648 cm^{-1}.

Methyl 1,2-*Dihydro*-1-*oxo*-3-*phenylisoquinoline*-2-*acetate*.—The acid (1 g) and a methanolic solution of boron trifluoride–ether (100 ml; 5%) were boiled under reflux for 16 h. After most of the methanol had been removed by distillation, the solution was poured into M-sodium hydrogen carbonate (100 ml). Isolation with ether gave the *ester* (0.85 g), m.p. 140—142° (from petroleum) (Found: C, 73.7; H, 5.1; N, 4.7. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.2; N, 4.8%), $\nu_{max.}$ 1 750 (CO_2Me) and 1 660 cm^{-1} (C:O), δ($CDCl_3$) 3.70 (3 H, s, Me), 4.58 (2 H, s, CH_2), 6.46 (1 H, s, 4-H), 7.3—7.6 (8 H, m, ArH), and 8.40 (1 H, d, splitting 8 Hz, 8-H).

5,6-*Dihydro*-5-*methyldibenzo*[a,g]*quinolizin*-8-*one*.—A mixture of aluminium chloride (7.5 g) and sodium chloride (1.5 g) was heated until completely molten and cooled to 100 °C. 2-Allyl-3-phenylisoquinolin-1(2*H*)-one (1 g) was stirred into the mass, which was kept at 100 °C for 1 h and then poured into concentrated hydrochloric acid (100 ml) containing ice (100 g). Addition of water (200 ml), isolation with ether, and chromatography on silica (60 g) in benzene–petroleum gave the *quinolizinone* (70%), m.p. 128—130° (from petroleum) (Found: C, 82.4; H, 5.9; N, 5.2. $C_{18}H_{15}NO$ requires C, 82.7; H, 5.8; N, 5.4%), $\nu_{max.}$ 1 646 cm^{-1}, δ($CDCl_3$) 1.29 (3 H, d, *J* 6 Hz, Me), 3.15 (1 H, m, 5-H), 4.05—4.52 (2 H, m, CH_2), 7.02 (1 H, s, 13-H), 7.3—7.9 (7 H, m, ArH), 8.45 (1 H, d, splitting 8 Hz, 9-H).

5,6-*Dihydro*-5,5-*dimethyldibenzo*[a,g]*quinolizin*-8-*one*.—This *compound* (87%), prepared similarly, had m.p. 141—142° (from benzene–petroleum) (Found: C, 82.7; H, 6.1; N, 5.0. $C_{19}H_{17}NO$ requires C, 82.9; H, 6.2; N, 5.1%), $\nu_{max.}$ 1 663 cm^{-1}, δ($CDCl_3$) 1.31 (6 H, s, 2Me), 4.15 (2 H, s, CH_2), 7.02 (1 H, s, 13-H), 7.3—7.8 (7 H, m, ArH), and 8.45 (1 H, d, splitting 7 Hz, 9-H).

5,6-*Dihydrodibenzo*[a,g]*quinolizin*-8-*one*.— 2-(2-Hydroxyethyl)-3-phenylisoquinolin-1(2*H*)-one (2 g), thionyl chloride (1.78 g), and pyridine (1.25 g) in chloroform (50 ml) were heated at 50 °C for 3 h, cooled, washed with water and evaporated to give 2-(2-*chloroethyl*)-3-*phenylisoquinolin*-1(2H)-*one* (1.84 g), m.p. 107—108° (from petroleum) (Found: C, 71.8; H, 5.1; N, 4.8. $C_{17}H_{14}ClNO$ requires C, 71.9; H, 5.0; N, 5.0%), $\nu_{max.}$ 1 655 cm^{-1}, δ($CDCl_3$) 3.70 (2 H, t, *J* 7 Hz, $ClCH_2$), 4.29 (2 H, t, *J* 7 Hz, N·CH_2), 6.42 (1 H, s, 4-H), 7.3—7.8 (8 H, m, ArH), and 8.45 (1 H, d, splitting 7 Hz, 8-H). Treatment with sodium chloride–aluminium chloride as described gave 5,6-dihydrodibenzo-[*a*,*g*]quinolizin-8-one (68%), m.p. 96—97° (from petroleum) (lit.,[17] 94—96°).

Dibenzo[a,g]*quinolizin-8-one*.— 2-(2,2-Dimethoxyethyl)-3-phenylisoquinolin-1(2*H*)-one (1 g) was added to polyphosphoric acid (25 g) at 150 °C with stirring. The mixture was stirred and heated at 150 °C for 1 h, cooled, and poured into water (200 ml). Filtration and crystallisations from aqueous ethanol gave the *dibenzoquinolizinone* (70%), m.p. 149—150° (Found: C, 83.5; H, 4.8; N, 5.7. $C_{17}H_{11}NO$ requires C, 83.2; H, 4.5; N, 5.7%), $\nu_{max.}$ 1 660 cm^{-1}. Similarly 2-(2-hydroxy-2-phenylethyl)-3-phenylisoquinolin-1(2*H*)-one gave (after 1.5 h reaction time) 5,6-*dihydro*-5-*phenyldibenzo*[a,g]*quinolizin*-8-*one*, m.p. 166—167° (from aqueous ethanol) (Found: C, 85.5; H, 5.5; N, 4.3. $C_{23}H_{17}NO$ requires C, 85.5; H, 5.3; N, 4.3%), $\nu_{max.}$ 1 655 cm^{-1}, $\delta(CDCl_3)$ 4.25—4.90 (3 H, m, CH_2·CH), 7.03 (1 H, s, 13-H), 7.1—7.9 (12 H, m, ArH), and 8.4 (1 H, d, splitting 8 Hz, 9-H).

2,3-*Dihydro*-2-*methyl*-5-*phenyloxazolo*[2,3-a]*isoquinolinylium Perchlorate*.—2-Allyl-3-phenylisoquinolin-1(2*H*)-one (1 g) was heated with polyphosphoric acid as described and the mixture was poured into ice–water (100 ml) and left overnight. Extraction with ether gave 5,6-dihydro-5-methyldibenzo[*a*,*g*]quinolizin-8-one (25%). Addition of perchloric acid (70%; 1 ml) to the aqueous layer gave a precipitate which was collected, washed with water, and crystallised from acetonitrile–ether to furnish the *oxazoloisoquinolinylium salt* (49%), m.p. 174—176° (Found: C, 59.6; H, 4.4; N, 3.8. $C_{18}H_{16}ClNO_5$ requires C, 59.8; H, 4.5; N, 3.9%), $\nu_{max.}$ 1 650 and 1 090 cm^{-1}, $\delta(CF_3{\cdot}CO_2H)$ 1.84 (3 H, d, J 7 Hz, Me), 4.42 and 5.02 (2 H, m, CH_2), 5.60—5.95 (1 H, m, 2-H), and 7.55—8.47 (10 H, m, ArH). Similarly 2-(2-methylallyl)-3-phenylisoquinolin-1(2*H*)-one gave a trace of the quinolizinone and 2,3-*dihydro*-2,2-*dimethyl*-5-*phenyloxazolo*[2,3-a]*isoquinolinylium perchlorate* (75%), m.p. 212—213° (from methanol) (Found: C, 60.6; H, 5.0; N, 3.9. $C_{19}H_{18}ClNO_5$ requires C, 60.7; H, 4.8; N, 3.7%), $\nu_{max.}$ 1 650 cm^{-1}, $\delta(CF_3{\cdot}CO_2H)$ 1.90 (6 H, s, 2 Me), 4.63 (2 H, s, CH_2), 7.57—8.47 (10 H, m, ArH); also 2-(2-hydroxyethyl)-3-phenylisoquinolin-1(2*H*)-one gave only 2,3-*dihydro*-5-*phenyloxazolo*[2,3-a]*isoquinolinylium perchlorate* (70%), m.p. 243—245° (from ethanol) (Found: C, 58.4; H, 4.1; N, 4.2. $C_{17}H_{14}ClNO_5$ requires C, 58.7; H, 4.1; N, 4.0%), $\nu_{max.}$ 1 650 cm^{-1}, $\delta(CF_3{\cdot}CO_2H)$ 4.94 (2 H, t, separation 9 Hz, CH_2), 5.32 (2 H, t, separation 9 Hz, CH_2), and 7.5—8.5 (10 H, m, ArH).

2,3-*Dihydro*-2,5-*diphenyloxazolo*[2,3-a]*isoquinolinylium Perchlorate*.—A mixture of 2-(2-hydroxy-2-phenylethyl)-3-phenylisoquinoline-1(2*H*)-one (0.3 g), water (7.5 ml), and concentrated sulphuric acid (7.5 ml) was boiled under reflux for 2 h, cooled, and filtered. Addition of perchloric acid (70%; 1 ml) precipitated the *salt* (45%), m.p. 223—224° (from methanol) (Found: C, 65.1; H, 4.3; N, 3.2. $C_{23}H_{18}ClNO_5$ requires C, 65.2; H, 4.3; N, 3.3%), $\nu_{max.}$ 1 650 cm^{-1}, $\delta(CF_3{\cdot}CO_2H)$, 4.72 and 5.29 (2 H, part of ABX, J_{AB} 13 Hz, CH_2), 6.62 (1 H, t, $J_{AX} + J_{BX}$ 19 Hz, 2-H), and 7.40—8.45 (15 H, m, ArH).

2,3-*Dihydro*-2-*oxo*-5-*phenyloxazolo*[2,3-a]*isoquinolinylium Perchlorate*.—Perchloric acid (70%; 1 ml) was added to a suspension of 1,2-dihydro-1-oxo-3-phenylisoquinoline-2-acetic acid (0.5 g) in acetic anhydride (15 ml). After 15 min, the solution was poured into ether (100 ml) and filtered; recrystallisation from acetonitrile gave the *salt* (0.4 g), m.p. 237° (decomp.) (Found: C, 56.6; H, 3.5; N, 4.0. $C_{17}H_{12}ClNO_6$ requires C, 56.4; H, 3.3; N, 3.9%), $\nu_{max.}$ 1 875 and 1 650 cm^{-1}, $\delta(CF_3{\cdot}CO_2H)$ 5.42 (2 H, s, CH_2) and 7.6—8.5 (10 H, m, ArH).

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