Reissert Compound Chemistry. Part III.[1] Some Rearrangement and Substitution Reactions

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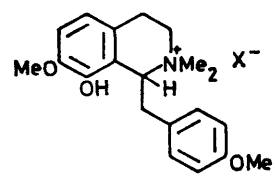
Reissert anion alkylation has led to a new synthesis of petaline, and a 1-benzoyl-8-hydroxyisoquinoline derivative has been obtained by rearrangement of the corresponding 8-benzoyloxy Reissert compound. Competitive reactions of the anion of 3-methylisoquinoline Reissert compound are described.

We have reported [1] the synthesis of 1-benzylisoquinolines by alkylation of the Reissert anion [2] utilising the improved procedure of carbanion generation with sodium hydride in dimethylformamide.[3] In continuing studies on the rearrangement and substitution reactions of the anion we report a new synthesis of the alkaloid petaline, demonstrating further the value of this approach [1,3] to 1-benzylisoquinoline alkaloids,[4] and in relation to this we have studied the formation of a 1-benzoyl-8-hydroxyisoquinoline derivative from competitive C-1 carbanion rearrangement of the corresponding 8-benzoyloxy Reissert compound. We also report the anomalous behaviour of the anion of 2-benzoyl-1,2-dihydro-3-methylisoquinoline-1-carbonitrile.



(I)

The quaternary benzylisoquinoline alkaloid petaline (I), isolated from *Leontice leontopetalum* L., contains

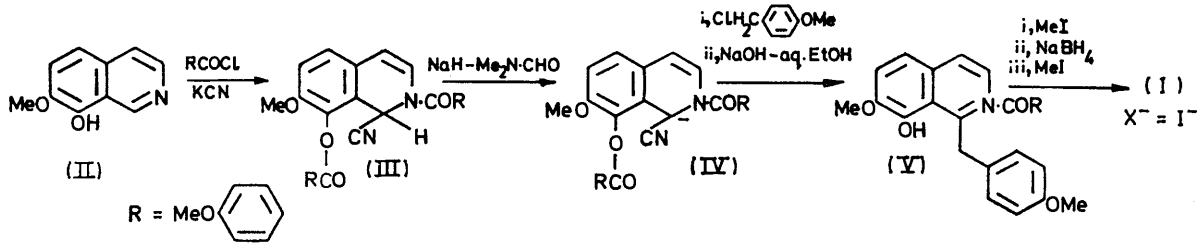
[1] Part II, B. C. Uff, and J. R. Kershaw, *J. Chem. Soc.* (*C*), 1969, 666.

[2] V. Boekelheide and C. Ainsworth, *J. Amer. Chem. Soc.*, 1950, **72**, 2134.

[3] F. D. Popp and J. M. Wefer, *Chem. Comm.*, 1966, 207; J. R. Kershaw and B. C. Uff, *ibid.*, p. 331; F. D. Popp and J. M. Wefer, *J. Heterocyclic Chem.*, 1967, **4**, 183.

[4] *Cf.* J. L. Neumeyer, K. H. Oh, K. K. Weinhardt, and B. R. Neustadt, *J. Org. Chem.*, 1969, **34**, 3786; J. L. Neumeyer, B. R. Neustadt, and K. K. Weinhardt, *J. Pharm. Sci.*, 1970, **59**, 1850; A. H. Jackson and G. W. Stewart, *Chem. Comm.*, 1971, 149.

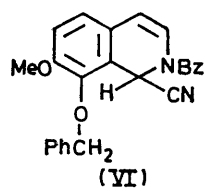
the unique 7,8-dioxygenation pattern; [5,6] only the small group of tetracyclic cularine alkaloids is similarly substituted.[7] While our synthesis of the alkaloid was in progress two other groups reported syntheses [8,9] by routes different from our own, which is shown in the Scheme. We required 8-hydroxy-7-methoxyisoquinoline (II); this was prepared by the reductive



SCHEME

Pomeranz–Fritsch method of Bobbitt *et al.*[10] from *o*-vanillin, aromatisation of the intermediate 1,2,3,4-tetrahydro-8-hydroxy-7-methoxyisoquinoline being effected in variable yield (2—49%) by heating with palladium–charcoal in *p*-cymene. Dehydrogenation with iodine [11] or with chloranil [12] failed to yield any of the required isoquinoline. Additional material was, however, obtained by the modified Pomeranz–Fritsch procedure of Bevis *et al.*,[13] in which boron trifluoride in trifluoroacetic anhydride is used as cyclisation reagent, though again variable yields were experienced.

Protection of the 8-hydroxy-group of compound (II) with a benzyl substituent gave a product which was contaminated by a deep red material and which could only be converted into the Reissert compound (VI)



(VI)

after repeated chromatography. In relation to this it was noted that addition of chloromethyl methyl ether to the potassium salt of (II) and to the salt of 8-hydroxyquinoline also gave an immediate deep red colouration, possibly indicating the presence of charge-transfer intermediates. In view of these difficulties the 8-hydroxy-7-methoxyisoquinoline was converted into the Reissert compound (III) by use of 4-methoxybenzoyl chloride. This chloride was employed in preference to benzoyl chloride so that if a migration of the anisoyl group from the 2-position [14] or 8-position (see later) took place in the subsequent reaction instead of (or in conjunction with) substitution by the anisyl chloride, the required methoxy-group would appear in the 4′-position. Acyl rearrangements of Reissert carbanions can usually be suppressed by use of lower temperatures (0° or less), in favour of alkyl substitution at C-1. Generation of the carbanion (IV) and addition of anisyl chloride resulted in a preponderance of the required substitution product (V) after base hydrolysis. The only by-product was a small amount of red crystalline material, considered to be 8-anisyloxy-7-methoxyisoquinoline in the light of spectroscopic data.

The possibility, already mentioned, of migration of an acyl group from the 8-position to the 1-position during the C-1 carbanion reaction could provide an attractive alternative route to an 8-hydroxybenzylisoquinoline, since, in the one rearrangement step the protected 8-position is regenerated and the 1-benzyl skeleton formed. We investigated this by use of 8-benzoyloxy-1,2-dihydro-2-*p*-toluoylisoquinoline-1-carbonitrile (VII) as a model compound, prepared from 8-hydroxyisoquinoline. The amide phenyl group of (VII) was ' labelled ' with a methyl group to assist n.m.r. interpretation and to discourage the alternative possible rearrangement *via* carbanion attack at the amide carbonyl group.[14]

We employed the sodium hydride–dimethylformamide system for carbanion generation since analogous studies had shown earlier that rearrangements of this type could not be achieved with phenyl-lithium in tetrahydrofuran.[15] Work-up gave the required phenol (IX), whose identification was supported by spectroscopic and analytical data. A small amount of what appeared to be 8-hydroxyisoquinoline-1-carbonitrile was also obtained and could have resulted from reaction of the

[5] N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Letters*, 1964, 3841; J. C. Craig, M. Martin-Smith, S. J. Roy, and J. B. Stenlake, *Tetrahedron*, 1966, **22**, 1335.

[6] N. J. McCorkindale, A. W. McCulloch, D. S. Magrill, B. Caddy, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron*, 1969, **25**, 5475.

[7] K. W. Bentley, ' The Isoquinoline Alkaloids,' Pergamon, London, 1965, p. 60.

[8] (*a*) G. Grethe, M. Uskoković, and A. Brossi, *J. Org. Chem.*, 1968, **33**, 2500; (*b*) G. Grethe, H. L. Lee, M. R. Uskoković, and A. Brossi, *Helv. Chim. Acta*, 1970, **53**, 874.

[9] T. Kametani, T. Kobari, K. Fukumoto, and M. Fujihara, *J. Chem. Soc.* (*C*), 1971, 1796.

[10] (*a*) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Eberman, *J. Org. Chem.*, 1965, **30**, 2247; (*b*) J. M. Bobbitt and J. C. Sih, *ibid.*, 1968, **33**, 856.

[11] *Cf.* D. W. Brown and S. F. Dyke, *Tetrahedron*, 1966, **22**, 2429.

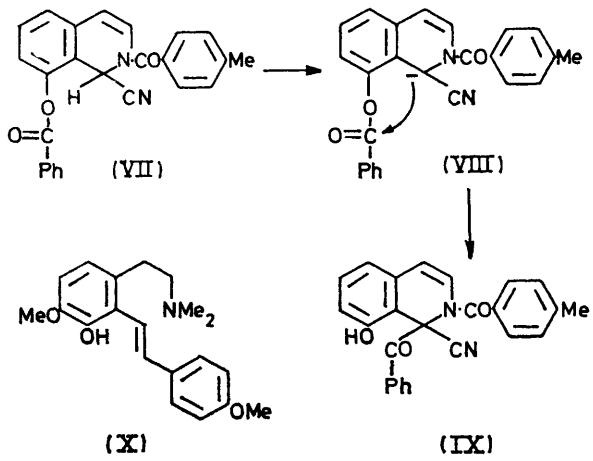
[12] *Cf.* L. M. Jackman, *Adv. Org. Chem.*, 1960, **2**, 329.

[13] M. J. Bevis, E. J. Forbes, N. N. Naik, and B. C. Uff, *Tetrahedron*, 1971, **27**, 1253.

[14] V. Boekelheide and J. Weinstock, *J. Amer. Chem. Soc.*, 1952, **74**, 660.

[15] E. J. Forbes and B. C. Uff, unpublished work.

anion (VIII) with a little extraneous oxygen.[16] The rearrangement product (IX) was only formed in relatively low yield (15%) and thus we were not encouraged to use



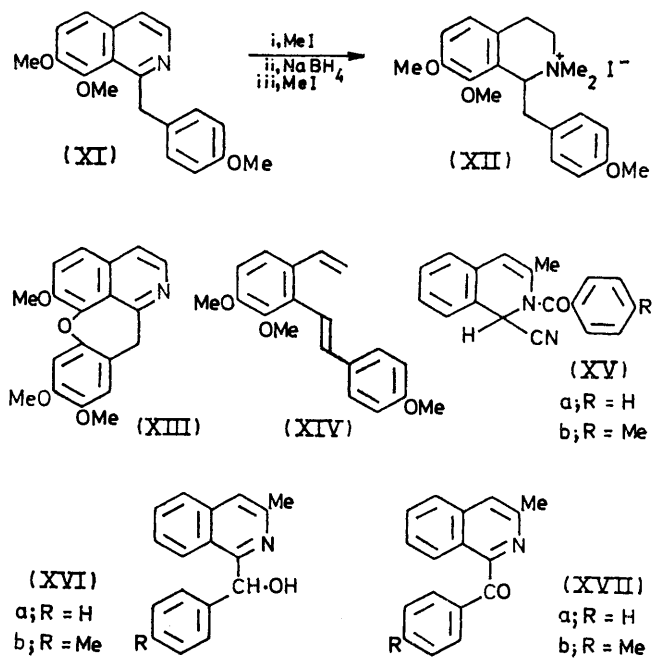
the route for the petaline synthesis. The substitution route employed instead gave a 40% yield of (V) from (III).

Conversion of the benzylisoquinoline (V) into its methiodide, reduction with borohydride, and further treatment with methyl iodide gave, after purification and crystallisation from acetone, racemic petaline iodide, m.p. 133—137° (lit.,[8a] 134—138°). The i.r. spectrum of the product and its R_F value on silica gel were identical with those of natural petaline iodide prepared from the reineckate.[17] Further proof of structure was provided by Hofmann degradation of the racemic petaline iodide to petaline methine (X) on an anion-exchange column,[6,8a] the product proving identical with authentic petaline methine.[17]

In an analogous sequence of reactions we also prepared (±)-*O*-methylpetaline iodide (XII) from 1-anisyl-7,8-dimethoxyisoquinoline (XI).[1] The methiodide (XII) was obtained initially as an oil and repeated chromatography was required to give crystalline material. Similar difficulties were reported by Kametani and Fukumoto in the formation of the methiodide of cularine precursor (XIII).[18] The structure of the synthetic *O*-methylpetaline iodide was confirmed by spectral comparison with a sample prepared from natural petaline by treatment of petaline reineckate[17] with methyl iodide in the presence of a trace of sodium hydroxide and conversion into the quaternary iodide. Further support was provided by exhaustive Hofmann degradation of racemic (XII) to give trimethylamine and the styrene (XIV), m.p. 166—169° (lit.,[6] 168—170°), whose i.r. spectrum was identical with that[17] of material prepared from natural petaline.[6]

During examination of the general applicability of the sodium hydride–dimethylformamide reagent in facilitating substitution reactions of the Reissert system we attempted to prepare 1-benzyl-3-methylisoquinoline from 2-benzoyl-1,2-dihydro-3-methylisoquinoline-1-carbonitrile (XVa) and benzyl chloride as in the preparation of (V) from (III). However, the product showed spectroscopic and analytical data in accord with the carbinol structure (XVIa).[19] It was not apparent whether the carbinol had arisen by oxidation of the methylene group of the expected product, 1-benzyl-3-methylisoquinoline, or by intramolecular rearrangement of the *N*-benzoyl group of (XVa).[14] With respect to the former possibility, ready oxidation of a methylene group in benzylisoquinolines has been observed;[20,21] such a reaction, however, usually generates the ketone. For example, purification of 3,4-dihydropapaverine on an alumina column is sufficient to give some 3,4-dihydropapaveraldine.[22] The rearrangement route[14] would also give a ketone (XVIIa), which would require reduction.

To establish whether the reaction involved substitution or rearrangement the experiment was repeated



but with Reissert compound (XVb) and benzyl chloride. The product was the carbinol (XVIb), thus indicating that no substitution by benzyl chloride had occurred. Examination of the products obtained prior to the alkaline hydrolysis stage revealed the presence of ketones (XVIIa and b) in each sequence. Borohydride reduction of (XVIIa) gave (XVIa) and, correspondingly, dichromate oxidation of the original carbinol provided

[16] G. W. Kirby, S. L. Tan, and B. C. Uff, International Congress of Pure and Applied Chemistry, Boston, 1971, Abstract 270, p. 113.
[17] Provided by Dr. N. J. McCorkindale, Glasgow University.
[18] T. Kametani and K. Fukumoto, *J. Chem. Soc.*, 1963, 4289.
[19] Preliminary communication, B. C. Uff, J. R. Kershaw, and S. R. Chhabra, Chemical Society Meeting, Keele, 1968, Abstract F9.
[20] T. H. Yang, *J. Pharm. Soc. Japan*, 1962, **82**, 811.
[21] T. Kametani, K. Fukumoto, and K. Ogasawara, *J. Pharm. Soc. Japan*, 1963, **83**, 180.
[22] T. Kametani and K. Fukumoto, *J. Pharm. Soc. Japan*, 1963, **83**, 1031.

the ketone (XVIIa). The products (XVI) were also obtained if the Reissert compounds (XV) were subjected to the rearrangement sequence in the absence of benzyl chloride.

Although there are a few examples in the literature of sodium hydride effecting reduction of carbonyl compounds,[23] no reduction took place when ketone (XVIIa) was stirred with sodium hydride in dimethylformamide for several hours at room temperature. It thus appeared that the reduction we observed had taken place during the treatment of the reaction mixture with sodium hydroxide in aqueous ethanol. It was likely that the ethoxide present had effected reduction by a hydride-transfer process of the Meerwein–Ponndorf–Verley type, and this was confirmed by the isolation of acetaldehyde, carried through in the nitrogen stream, as its 2,4-dinitrophenylhydrazone.

The literature reveals only infrequent use of sodium (or potassium) ethoxide or of the hydroxide in aqueous ethanol as reducing agents,[24] despite the application by Fischer [24a] in his classical synthesis of haemin; presumably the tendency for condensation reactions to result has caused the milder aluminium alkoxides to be preferred. However, we have shown for a range of non-enolisable ketones (see Table) that sodium hydroxide

Reduction of ketones with NaOH–aq.EtOH

Ketone	Period of reflux (h)	Yield (%)
1-Benzoylisoquinoline	7	85
1-Benzoyl-3-methylisoquinoline	7	85
Benzophenone	3·5	86
1-Benzoylnaphthalene	4	78
Benzoin	3·5	79
Chalcone	8	89
Fluorenone	5	79
Xanthone	4	0

in aqueous ethanol effects reductions very efficiently. The failure in the case of xanthone is likely to be due to electronic factors.

Since the preliminary report of this work,[19] the propensity of 3-methylisoquinoline Reissert compounds for rearrangement relative to condensation with an alkyl halide has also been reported by Gibson,[25] substitution being observed, however, if large excesses of the alkyl halides were used. We found that substitution also became competitive with rearrangement if a more electrophilic substrate were employed. Thus, in the reaction of *p*-tolualdehyde with the anion of (XVa) examination of the products revealed rearrangement and addition to have taken place in the approximate ratio 2 : 1.

It was observed during this work that the 1-aroylisoquinolines were not readily extracted into dilute acid. Their weak basicity was confirmed by pK_a measurements, 1-benzoylisoquinoline showing a pK_a value of 2·22 (spectroscopic method [26]) as compared with 5·40 for isoquinoline.[26]

EXPERIMENTAL

1,2,3,4-Tetrahydro-8-hydroxy-7-methoxyisoquinoline Hydrochloride.—A mixture of *o*-vanillin (5·0 g, 0·03 mol) and aminoacetaldehyde diethyl acetal (4·0 g, 0·03 mol) in ethanol (80 ml) was added to platinum oxide (0·3 g) in ethanol (20 ml) which had been pre-reduced. The mixture was hydrogenated at room temperature and pressure until uptake ceased (*ca.* 9 h). The catalyst was filtered off and the solvent evaporated. The residue was taken up in hydrochloric acid (6N; 150 ml), washed with ether (50 ml), and set aside overnight. Palladium–carbon (5%; 3 g) was added, and the solution was hydrogenated at room temperature and pressure until uptake ceased (*ca.* 18 h). The catalyst was filtered off and the solvent removed by evaporation to give the tetrahydroisoquinoline hydrochloride. Recrystallisation from ethanol gave cream needles, m.p. 277—280° (lit.,[10b] 282—283°) (3·8 g, 62%). The picrate crystallised as yellow needles from ethanol, m.p. 204—206° (lit.,[10b] 204—206°).

8-Hydroxy-7-methoxyisoquinoline.—1,2,3,4-Tetrahydro-8-hydroxy-7-methoxyisoquinoline hydrochloride (1·3 g) was dissolved in water, neutralised, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give the free base. This was immediately dissolved in *p*-cymene (200 ml) and heated under reflux with palladium–carbon (10%; 0·75 g) for 2 h. The solvent was evaporated and the crude material sublimed and recrystallised from ethanol to give 8-hydroxy-7-methoxyisoquinoline (0·52 g, 49%) as straw-coloured needles, m.p. 181—183° (lit.,[13] 183—184°) (Found: C, 68·2; H, 5·5; N, 7·8. Calc. for $C_{10}H_9NO_2$: C, 68·6; H, 5·5; N, 8·0%); τ ($CD_3{\cdot}CO_2D$) 0·34 [1H, s, C(1)H], 2·50 (4H, m, aromatic), and 5·95 (s, 7-O·CH_3). The picrate crystallised from ethanol as yellow needles, m.p. 218—220°.

8-Benzyloxy-7-methoxyisoquinoline.— 8-Hydroxy-7-methoxyisoquinoline (1 g) was dissolved in a solution of potassium hydroxide (0·4 g) in water (1 ml) and diluted with ethanol (25 ml). The mixture was heated under reflux under nitrogen with benzyl chloride (1 ml) for 5 h. The colour became red immediately on addition of benzyl chloride. The deep red solution was evaporated; the residue was dissolved in chloroform, washed with dilute sodium hydroxide (×3) and with water (×3) and evaporated to give a red solid. Column chromatography gave red needles (0·7 g), m.p. 185—188° (from benzene), τ 0·63 [1H, s, C(1)H], 2·56—3·00 (8H, m), 3·57 (1H, d, aromatic protons), 4·72 (2H, s, CH_2), and 6·13 (3H, s, O·CH_3). The *picrate* crystallised from ethanol as yellow needles, m.p. 189—191° (Found: C, 55·3; H, 3·9. $C_{23}H_{18}N_4O_9$ requires C, 55·8; H, 3·7%). The *methiodide* crystallised from methanol; m.p. 182·5—184° (Found: C, 53·2; H, 4·9. $C_{18}H_{18}INO_2$ requires C, 53·1; H, 4·5%).

N-Benzoyl-8-benzyloxy-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (VI).—To a solution of 8-benzyloxy-7-methoxyisoquinoline (1·17 g) in dichloromethane (10 ml)

[23] F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 2647; J. S. McConaghy and J. J. Bloomfield, *J. Org. Chem.*, 1968, **33**, 3425.

[24] (*a*) H. Fischer and K. Zeile, *Annalen*, 1929, **468**, 98; (*b*) A. Zagoumenny, *Annalen*, 1877, **184**, 174; P. J. Montagne, *Rec. Trav. chim.*, 1908, **27**, 327; C. F. H. Allen, J. E. Jones, and J. A. VanAllen, *J. Org. Chem.*, 1946, **11**, 268; G. H. Hargraves and L. N. Owen, *J. Chem. Soc.*, 1947, 750; N. Campbell and E. B. McCall, *ibid.*, 1951, 2411.

[25] H. W. Gibson, *J. Heterocyclic Chem.*, 1970, **7**, 1169.

[26] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962, p. 69 ff.

was added a solution of potassium cyanide (0·86 g) in water (6 ml). The mixture was cooled in ice–water and stirred vigorously as benzoyl chloride (1·02 ml) in dichloromethane (2 ml) was added dropwise over 45 min, and stirring was continued for a further 45 min. The organic layer was washed with water, 10% hydrochloric acid, water, 5% sodium hydroxide, and water. Concentration, followed by trituration of the residue with ether and filtration gave the *nitrile* (VI) (0·78 g, 44·8%), which crystallised from ethyl acetate as broad daggers, m.p. 135° (Found: C, 75·4; H, 4·9; N, 7·0; OMe, 7·5. $C_{25}H_{20}N_2O_3$ requires C, 75·7; H, 5·1; N, 7·1; OMe, 7·8%).

1,2-*Dihydro*-7-*methoxy*-2-(4-*methoxybenzoyl*)-8-(4-*methoxybenzoyloxy*)*isoquinoline*-1-*carbonitrile* (III).—*p*-Methoxybenzoic acid (20 g) on treatment with thionyl chloride in dry benzene [27] gave *p*-methoxybenzoyl chloride as a glass, b.p. 96—98° at 2 mmHg, m.p. 23°.

8-Hydroxy-7-methoxyisoquinoline (0·7 g) was treated with potassium cyanide (1·0 g) and *p*-methoxybenzoyl chloride (1·5 ml) in methylene chloride–water by the method already described. Work-up gave an oily product which on addition of ethyl acetate precipitated a cream solid. Recrystallisation from ethanol–ether gave 7-*methoxy*-8-(4-*methoxybenzoyloxy*)*isoquinoline* (0·2 g) as cream needles, m.p. 204—206° (Found: C, 69·9; H, 5·1; N, 5·1. $C_{18}H_{15}NO_4$ requires C, 69·9; H, 4·9; N, 4·5%), τ ($CD_3{\cdot}CO_2$-D–$CDCl_3$) 0·25 [1H, s, C(1)H], 1·35 [1H, d, C(3)H], 1·60—3·0 (7H, m, aromatic protons), 5·93 (3H, s, 7-O·CH_3), and 6·05 (3H, s, anisoyl O·CH_3), $\nu_{max.}$ 1730 cm^{-1} (CO of aryl ester).

The product (0·15 g) was further treated with potassium cyanide (0·2 g) and *p*-methoxybenzoyl chloride (0·25 ml) in methylene chloride–water by the foregoing procedure; work-up of this reaction and of the mother liquors of the previous reaction gave 1,2-*dihydro*-7-*methoxy*-2-(4-*methoxybenzoyl*)-8-(4-*methoxybenzoyloxy*)*isoquinoline*-1-*carbonitrile* (III) (0·50 g, 23%) [from ethyl acetate as the monoethyl acetate (cream needles)], m.p. 86—88° (Found: C, 66·1; H, 5·8; N, 5·4. $C_{27}H_{22}N_2O_6,C_4H_8O_2$ requires C, 66·6; H, 5·4; N, 5·0%), τ 1·63—3·13 (10H, m, aromatic protons), 3·34 [1H, q, C(3)H, $J_{3,4}$ 8·0 Hz], 3·40 [1H, d, C(1)H, $J_{1.3}$ 0·8 Hz], 3·94 [1H, d, C(4)H], 5·87 (1H, q, CH_2 of ethyl acetate), 6·06 (3H, s, 7-O·CH_3), 6·16 (6H, s, two O·CH_3), 7·97 (3H, s, CH_3 of acetate), and 8·75 (3H, t, CH_3 of ethyl), $\nu_{max.}$ 1745 (CO of saturated ester), 1730 (CO of aryl ester), and 1665 cm^{-1} (CO of amide).

8-*Hydroxy*-7-*methoxy*-1-(4-*methoxybenzoyl*)*isoquinoline* (V).—The nitrile (III) (0·44 g) was treated with sodium hydride [50% in oil; washed with dry petroleum (b.p. 60—80°); 0·15 g] and *p*-methoxybenzyl chloride (0·2 g) in dry dimethylformamide (30 ml). After 2 h at 0° the red colour had faded to pale pink. Ethanol was added to destroy the excess of sodium hydride, most of the solvent was removed, and the product was taken up in benzene.

The benzene solution was evaporated to give the substituted Reissert compound as an oil, to which ethanol (150 ml) and a solution of sodium hydroxide (50 g) in water (50 ml) were added. The mixture was heated under reflux for 2·5 h, the ethanol was distilled off, and the product was extracted with benzene. The benzene solution was extracted with acid, the acid extract was basified and extracted with chloroform, and the chloroform solution was dried (K_2CO_3) and evaporated. The residue was purified by column chromatography to give 7-methoxy-8-(4-methoxybenzoyloxy)-1-(4-methoxybenzyl)isoquinoline (0·15 g, 45%) as cream needles (from benzene), m.p. 134—138°, τ 2·18—3·40 (12H, m, aromatic protons), 5·54 (2H, s, CH_2), 6·25 (6H, s, anisyl and anisoyl O·CH_3), and 6·28 (3H, s, 7-OCH_3); and 8-anisyloxy-7-methoxyisoquinoline (*ca.* 30 mg) as red needles, m.p. 165—170° (from benzene) τ 0·27 [1H, s, C(1)H], 1·63—3·40 (8H, m, aromatic protons), 4·64 (2H, s, CH_2), and 6·20 (6H, s, two O·CH_3).

The 7-methoxy-8-(4-methoxybenzoyloxy)-1-(4-methoxybenzyl)isoquinoline (0·15 g) in ethanol (35 ml) was further heated under reflux for 2 h with sodium hydroxide (10 g) in water (20 ml). Removal of the ethanol, neutralisation, and extraction with chloroform gave 8-*hydroxy*-7-*methoxy*-1-(4-*methoxybenzyl*)*isoquinoline* (V) (90 mg, 88%) as cream needles, m.p. 195—197° (from ethanol) (Found: C, 72·8; H, 6·4; N, 5·0. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·8; N, 4·7%), τ ($CD_3{\cdot}CO_2D$–$CDCl_3$) 1·80—3·14 (8H, m, aromatic protons), 5·34 (2H, s, CH_2), 6·10 (3H, s, 7-O·CH_3), and 6·17 (3H, s, anisyl O·CH_3).

8-*Hydroxyisoquinoline*.[28]—This crystallised from ethanol as buff needles, m.p. 215° (lit.,[28] 213°) (Found: C, 74·3; H, 4·9; N, 9·7. Calc. for C_9H_7NO: C, 74·5; H, 4·9; N, 9·7%), $\nu_{max.}$ 3440 cm^{-1} (OH), τ ($CD_3{\cdot}CO_2D$) 0·28 [1H, s, C(1)H], 1·50 [1H, d, C(3)H, $J_{3,4}$ 6·0 Hz], 1·85 [1H, d, C(4)H, $J_{4,3}$ 6·0 Hz], 2·06 [1H, t, C(6)H, *J* 8·0 Hz], 2·46 [1H, q, C(5) or C(7)-H, $J_{5,7}$ 2·5 Hz, $J_{5,6} = J_{6,7}$ = 8·0 Hz], and 2·70 [1H, q, C(7) or C(5)H].

8-*Benzoyloxyisoquinoline*.—8-Hydroxyisoquinoline (2·0 g) was converted into 8-*benzoyloxyisoquinoline* by use of the usual Schotten–Baumann conditions. The semi-solid obtained was chromatographed on neutral alumina. Recrystallisation from ether–light petroleum (b.p. 40—60°) gave pale pink needles, m.p. 76—77° (2·0 g, 59%) (Found: C, 76·9; H, 4·5; N, 5·6. $C_{16}H_{11}NO_2$ requires C, 77·1; H, 4·5; N, 5·6%), $\nu_{max.}$ 1740 cm^{-1} (ester C=O), τ 0·47 [1H, s, C(1)H], 1·36 [1H, d, C(3)H, $J_{3,4}$ 6·0 Hz], *ca.* 1·64 (2H, m, *ortho*-hydrogens of benzoyloxy-group), and 2·1—2·6 (7H, m, other aromatic protons).

8-*Benzoyloxy*-1,2-*dihydro*-2-p-*toluoylisoquinoline*-1-*carbonitrile* (VII).—Use of 8-benzoyloxyisoquinoline (1·65 g, 6·5 mmol), *p*-toluoyl chloride (2·04 g, 13 mmol), and potassium cyanide (1·3 g, 19·5 mmol) in the foregoing method gave the *nitrile* (VII) (1·3 g, 50%). Recrystallisation from ethyl acetate gave needles, m.p. 207—207·5° (Found: C, 76·0; H, 4·6; N, 6·9. $C_{25}H_{18}N_2O_3$ requires C, 76·1; H, 4·6; N, 7·1%), $\nu_{max.}$ 2260w (CN), 1735 (ester C=O), and 1660 cm^{-1} (N–C=O), τ *ca.* 1·72 (2H, m, benzoyloxy *ortho*-hydrogens), 2·2—3·1 (10H, m, aromatic), 3·27 [1H, q, C(3)H, $J_{3,4}$ 8, $J_{1.3}$ 0·8 Hz], 3·33 [1H, d, C(1)H, $J_{1.3}$ 0·8 Hz], 3·95 [1H, d, C(4)H, $J_{4.3}$ 8·0 Hz], and 7·62 (3H, s, CH_3).

Rearrangement of 8-*Benzoyloxy*-1,2-*dihydro*-2-p-*toluoylisoquinoline*-1-*carbonitrile*.—A suspension of sodium hydride (0·03 g, 1·15 mmol) in dimethylformamide was added slowly to a stirred solution of the nitrile (VIII) (0·45 g, 1·15 mmol) in dimethylformamide (20 mmol). After 40 min, a red colour started appearing with evolution of hydrogen. Stirring was continued for 30 min at 0° and for the next 6 h at room temperature, during which time the colour faded slightly. The mixture was then poured on ice to give a yellow solution which was neutralised with dilute hydrochloric acid. The solution was extracted with chloroform several times; the extracts were dried (Na_2SO_4) and evaporation of chloroform and dimethylformamide left a yellow oil. The yellow oil was taken

[27] R. Grice and L. N. Owen, *J. Chem. Soc.*, 1963, 1947.
[28] R. A. Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1944.

into chloroform and extracted several times with *ca.* 50% hydrochloric acid. The chloroform layer and the acid extract were worked up separately.

The acid extract was basified with ammonium hydroxide and extracted with chloroform (liquid–liquid continuous extractor). The chloroform extract was dried (K_2CO_3) and evaporated to give light brown crystalline material (14 mg, 3%), m.p. 214—218°. Recrystallisation from methanol gave a compound considered to be 8-hydroxyisoquinoline-1-carbonitrile, m.p. 216—218°, $\nu_{max.}$ 3400 (OH) and 2160 cm^{-1} (CN), τ ($CD_3{\cdot}CO_2D$) 1·30 [1H, d, C(3)H, $J_{3,4}$ 6 Hz], 1·97 [1H, d, C(4)H, $J_{4,3}$ 6 Hz], and 2·05—3·0 (3H, m, other aromatic protons), *m/e* 170.

The chloroform layer was dried (Na_2SO_4) and evaporated to give a yellow syrup (0·2 g) which could not be induced to crystallise. Preparative layer chromatography in 19 : 1 benzene–ethyl acetate gave four products: (i) R_F 0·744, corresponding to the starting compound, (ii) and (iii) minor fractions, R_F 0·457 and 0·628, which were not investigated further, and (iv) a light yellow amorphous solid (68 mg, 15%), which gave *1-benzoyl-1,2-dihydro-8-hydroxy-2-p-toluoylisoquinoline-1-carbonitrile* (IX) as pale brown rhombs, m.p. 231—232° (from methanol) (Found: N, 6·7. $C_{25}H_{18}N_2O_3$ requires N, 7·1%), $\nu_{max.}$ 3200 (OH), 2220 (CN), 1695 (aryl ketone), 1665 (N–C=O), and 1630 cm^{-1} ($\Delta^{3,4}$), τ [$(CD_3)_2SO$] 0·55br (1H, s, exchangeable, OH), 2·2—3·8 [13H, m, aromatic and C(3)H], 4·02 [1H, d, C(4)H, $J_{4,3}$ 8·0 Hz], and 7·60 (3H, s, CH_3).

(±)-*Petaline Iodide*.—8-Hydroxy-7-methoxy-1-(4-methoxybenzyl)isoquinoline (V) (70 mg) was converted into its methiodide (0·11 g) by heating under reflux with methyl iodide in methanol.[18] Reduction of the methiodide (0·11 g) in methanol with sodium borohydride[18] gave 1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (50 mg) as an oil which could not be induced to crystallise. The tetrahydroisoquinoline was treated with methyl iodide in methanol to give an oil. Column chromatography on neutral alumina gave (±)-petaline iodide (15 mg) as a pale yellow solid which crystallised from acetone as the hemiacetonate, m.p. 133—137° (lit.,[8a] 134—138°) (Found: N, 2·7. Calc. for $C_{20}H_{26}INO_3$: N, 3·1%). Its i.r. spectrum (Nujol) was identical with that of a sample prepared from natural petaline (see following experiment), R_F(EtOH) 0·64 on silica gel t.l.c.

Petaline Iodide from Natural Petaline Reineckate.—Petaline reineckate[17] (15 mg) in acetone was titrated with silver sulphate solution and then with barium iodide solution to give natural petaline iodide (10 mg), m.p. 140—143° (lit.,[8a] 127—131°), identical (i.r. and t.l.c.) with the foregoing product.

Hofmann Degradation of Racemic Petaline Iodide.—The racemic petaline iodide (10 mg) in methanol was eluted through a Permutit De-Acidite FF anion-exchange column (OH^- form) to give the methine, β-[3-hydroxy-4-methoxy-2-(*p*-methoxystyryl)phenyl]-*NN*-dimethylethylamine (X), m.p. and mixed m.p.[17] 119—121° (lit.,[29] 118·5—119·5°) (Found: N, 4·2. Calc. for $C_{20}H_{25}NO_3$: N, 4·3%).

(±)-O-*Methylpetaline Iodide*.—7,8-Dimethoxy-1-(4-methoxybenzyl)isoquinoline (1·0 g) was warmed with methyl iodide in dry ether (or refluxed with methyl iodide in methanol) to give the methiodide as an oil (1·4 g). Chromatography on neutral alumina gave material which formed yellow prisms from ethanol–ether, m.p. 139—140° (decomp.)

The methiodide (35 mg) was reduced with sodium borohydride in methanol to give 1,2,3,4-tetrahydro-7,8-dimethoxy-1-(4-methoxybenzyl)-2-methylisoquinoline as an oil (20 mg) which could not be induced to crystallise. It was converted into its methiodide, (±)-O-*methylpetaline iodide* (10 mg), which after alumina column chromatography crystallised as cream needles from ethanol–ether, m.p. 73—76° (Found: C, 53·6; H, 5·9. $C_{21}H_{28}INO_3$ requires C, 53·7; H, 6·0%). Its i.r. spectrum was identical with that of a sample prepared from natural petaline (see following experiment), R_F (1 : 1 $CHCl_3$–EtOH) 0·725 on silica gel t.l.c.

O-*Methylpetaline Iodide from Natural Petaline Reineckate*.—Petaline reineckate[17] (15 mg) was heated under reflux in methanol (10 ml) with methyl iodide (5 ml) and sodium hydroxide (1 drop) for 3 h. The solution was neutralised with dilute hydrochloric acid, and evaporated under reduced pressure. Water was added and the aqueous layer was extracted with chloroform. The extract was dried (K_2CO_3) and evaporated to give *O*-methylpetaline reineckate. This was then dissolved in acetone and titrated with silver sulphate solution until no further precipitate of silver reineckate was formed. Sulphate ions were displaced by quantitative precipitation with barium iodide solution, the solution was filtered, the precipitate was washed with acetone, and the combined filtrate and washings were evaporated to give *O*-methylpetaline iodide (*ca.* 8 mg) as cream needles (from ethanol–ether), m.p. 75—77°, identical (i.r. and t.l.c.) with the foregoing product.

Hofmann Exhaustive Methylation and Degradation of Racemic O-Methylpetaline Iodide.—The racemic *O*-methylpetaline iodide (50 mg) in methanol was eluted through a Permutit De-Acidite FF anion-exchange column (OH^- form). The brown eluate was evaporated to dryness; the residue was dissolved in methanol (20 ml) and heated under reflux with sodium methoxide (1 g) for 3 h under nitrogen. Water (10 ml) was added and the mixture was then neutralised with acetic acid and extracted several times with chloroform. The extracts were dried (K_2CO_3) and evaporated. The residue was then heated under reflux with methyl iodide (3 ml) in dry acetone (10 ml) for 2 h and evaporated to give the methiodide. This was treated as before by elution through the anion-exchange column and heated under reflux with sodium methoxide in methanol under nitrogen. The nitrogen stream was passed through saturated ethanolic picric acid, from which trimethylamine picrate precipitated, m.p. and mixed m.p. 210—212° (lit.,[6] 209—211°).

The main reaction mixture was worked up to give the nitrogen-free product, 2,3,4′-trimethoxy-6-vinylstilbene (*ca.* 6 mg) [from benzene–light petroleum (b.p. 40—60°)] as cream needles, m.p. 166—169° (lit.,[6] 168—170°), identical [i.r. spectrum[17] (KBr)] with an authentic sample.

Reaction of N-Benzoyl-1,2-dihydro-3-methylisoquinoline-1-carbonitrile with Benzyl Chloride.—The nitrile[30] (5·0 g) was treated with sodium hydride (0·88 g) and benzyl chloride (2·32 g) by the method already described. After hydrolysis in ethanol (100 ml) with sodium hydroxide (50 g) in water (50 ml) followed by extraction with acid, work-up gave *α-(3-methylisoquinolin-1-yl)benzyl alcohol* (XVIa) (2·3 g, 51%), which formed stars, m.p. 104—104·5° (from ether) (Found: C, 81·6; H, 6·7; N, 5·2. $C_{17}H_{15}NO$ requires C, 81·9; H, 6·1; N, 5·6%), τ 2·04—2·86 (10H, m,

[29] J. McShefferty, P. F. Nelson, J. L. Paterson, J. B. Stenlake, and J. P. Todd, *J. Pharm. Pharmacol.*, 1956, **8**, 1117.
[30] I. W. Elliott, *J. Amer. Chem. Soc.*, 1955, **77**, 4408.

aromatic), 3·70 [2H, s, CH·OH group; on addition of $CD_3{\cdot}CO_2D$–D_2O contracts to 3·62 (1H, s, CH)], and 7·27 (3H, s, CH_3), $\nu_{max.}$ 3190 cm^{-1} (OH). The *picrate* crystallised from ethanol as yellow needles, m.p. 180—181° (Found: C, 57·7; H, 4·0; N, 11·7. $C_{23}H_{18}N_4O_8$ requires C, 57·7; H, 3·8; N, 11·7%).

The foregoing carbinol (200 mg) was oxidised in glacial acetic acid (15 ml) with sodium dichromate (0·24 g). Recrystallisation from ether gave 1-benzoyl-3-methylisoquinoline (108 mg, 55%) as rhombs, m.p. 99·0—99·5° (lit.,[25] 102·5—103·0°), identical with samples obtained (*a*) by extraction with 60% hydrochloric acid of the products obtained prior to the alkaline hydrolysis stage in the foregoing reaction or (*b*) by omission of benzyl chloride (and the alkaline hydrolysis stage) from the foregoing reaction. Reduction of this latter sample with sodium borohydride in methanol correspondingly gave the carbinol (XVIa), m.p. 102—104°.

Reaction of 1,2-*Dihydro*-3-*methyl*-2-p-*toluoylisoquinoline*-1-*carbonitrile with Benzyl Chloride.*—The nitrile [25] (3 g) was treated with sodium hydride (0·53 g) and benzyl chloride (1·4 g) as already described. From the hydrolysed fraction was obtained p-*methyl*-α-(3-*methylisoquinolin*-1-*yl*)*benzyl alcohol* (XVIb) (1·3 g, 53%), which formed needles, m.p. 102—103° (from ether) (Found: C, 81·7; H, 6·4; N, 5·3. $C_{18}H_{17}NO$ requires C, 82·1; H, 6·5; N, 5·3%), τ 2·03—3·03 (9H, m, aromatic), 3·71 (1H, s, C*H*·OH), 3·92br (1H, s, OH, disappears on addition of $CD_3{\cdot}CO_2D$–D_2O), 7·26 (3H, s, 3-CH_3), and 7·76 (3H, s, *p*-Me), $\nu_{max.}$ 3320 cm^{-1} (OH).

Extraction of the products prior to the alkaline hydrolysis with 60% hydrochloric acid gave an oil (0·5 g). The n.m.r. spectrum showed that this was a mixture of 3-methylisoquinoline (30%) and 3-methyl-1-(*p*-toluoyl)-isoquinoline (70%), $\nu_{max.}$ 1680 cm^{-1} (CO).

Reduction of Ketones with Sodium Hydroxide–Ethanol–Water. General Method.—The ketone (1 g) in ethanol (200 ml) was heated under reflux with sodium hydroxide (50 g) in water (50 ml). The ethanol was removed and the product was partitioned between water and chloroform. The chloroform extract was dried (K_2CO_3) and evaporated to give the carbinol. This was purified by column chromatography and recrystallisation. The results are shown in the Table. On passing nitrogen over the refluxing mixture into 2,4-dinitrophenylhydrazine reagent, acetaldehyde 2,4-dinitrophenylhydrazone was precipitated, m.p. 144—146°.

Reaction of 2-*Benzoyl*-1,2-*dihydro*-3-*methylisoquinoline*-1-*carbonitrile with* p-*Tolualdehyde.*—The nitrile (1 g) was treated with sodium hydride (0·18 g) and *p*-tolualdehyde (1·0 g) by the method already described. Work-up gave 1-benzoyl-3-methylisoquinoline (2%), α-(3-methylisoquinolin-1-yl)benzyl alcohol (51%), and *p*-methyl-α-(3-methylisoquinolin-1-yl)benzyl alcohol (25%).

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