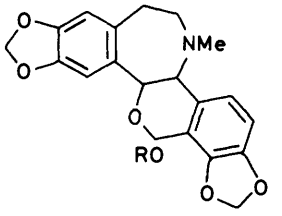
Rearrangement of 1-(α-Hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines to 1-Phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines

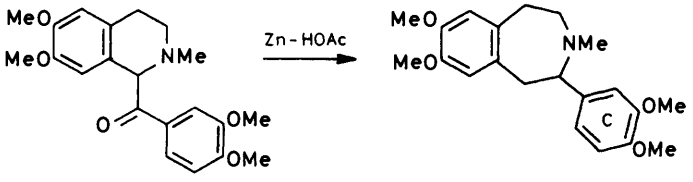
By **Robert M. McMahon** and **Craig W. Thornber,*** Imperial Chemical Industries PLC, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire,
Somsak Ruchirawat, Robert Robinson Laboratories, University of Liverpool, L69 3BX

When methoxy-substituted 1-(α-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines are heated in formic acid they rearrange initially to give 5-phenyl-2,3-dihydro-1*H*-3-benzazepines which, on further heating in formic acid, are reduced to 1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines.

PHENYL-SUBSTITUTED benzazepines are of interest because of their relationship to the Rhoeadine alkaloids (1).[1] By analogy with the work of Schöpf and Schweickert [2] the 1-benzoyltetrahydroisoquinoline (2) has been shown [3] to rearrange to the 3-methyl-2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (3) with zinc and acetic acid. It has also been reported [4] that the alcohol (4) rearranges with mesyl chloride and triethylamine to give the benzazepines (5) and (6). The only example of a rearrangement to give a 1-phenyl-1*H*-3-benzazepine comes from the work of Kametani *et al.*[5] The alcohol (7) on treatment with toluene-*p*-sulphonyl chloride and triethylamine gave the dihydrobenzazepine (11) in 3% yield, which was reduced catalytically to the tetrahydrobenzazepine (13). Ruchirawat [6] has reported some preliminary work on the acid-catalyzed rearrangement of the alcohol (7) to give the enamine (11) and its subsequent reduction to the benzazepine (13). We report now further studies on the scope of this reaction and the characterization of the products.



(1)

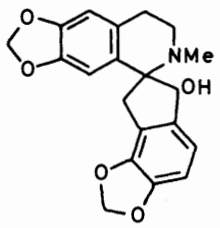


(2) (3)

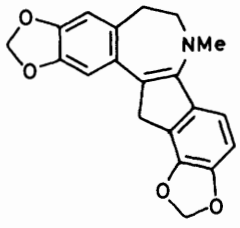
RESULTS AND DISCUSSION

The synthesis of 1-(α-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines has been reported by several groups.[3,7,8] Condensation of phenethylamines with phenylacetyl chlorides gives the known [7,8] amides (15)—(17), which are cyclized under Bischler–Napieralski conditions to give the 3,4-dihydroisoquinolines (18)—(20) as their hydrochlorides. These were used without further purification for the preparation of the 1-benzoyl-3,4-dihydroisoquinolines (21) and (22). Weisbach *et al.*[7] have described the preparative oxidation of several 3,4-dihydroisoquinolines with atmospheric oxygen. We have used similar conditions with the addition of platinum catalysts or with an excess of aqueous base present. Thus, when compound (18) was exposed to air in a two phase system of chloroform and aqueous sodium hydroxide, a mixture of the 1-benzoyl-3,4-dihydroisoquinoline (21) and the 1-benzoylisoquinoline (24) resulted. The mixture was converted into pure (24) by treatment with hot alcoholic potassium hydroxide.[9] However, treatment of compound (18) with air in chloroform–toluene in the presence of 5% platinum-on-charcoal gave pure (21) in 4 d.

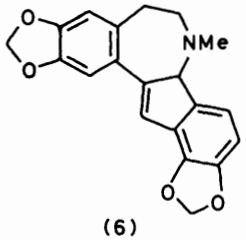
Whereas compound (19) was oxidized completely to compound (22) in 1 h, no air oxidation was observed with the isoquinoline (20), even after several days. Sodium dichromate in glacial acetic acid was used to oxidize compound (20) directly through to the 1-benzoylisoquinoline (25). The 1-benzoylisoquinoline (23) (papaveraldine) was prepared by selenium dioxide oxidation of papaverine.[10] The quaternary ammonium salts (26)—(29) were reduced by sodium borohydride to the alcohols (7)—(10). Whereas the alcohols (7) and (8)



(4)

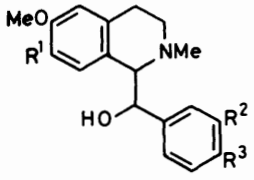


(5)

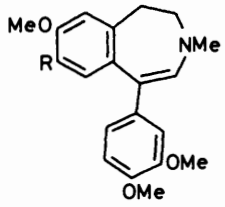


(6)

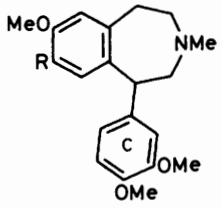
were obtained as mixed diastereoisomers, the alcohols (9) and (10) were obtained as single diastereoisomers. These alcohols show unusual signals in the ^{1}H n.m.r. spectrum. In compounds (9) and (10) signals for the C-8 protons at τ 4.35 and 4.36, respectively, are observed, compared with the C-5 proton singlets at τ 3.45 and 3.50.



(7) $R^1 = R^2 = R^3 = OMe$
(8) $R^1 = H, R^2 = R^3 = OMe$
(9) $R^1 = OMe, R^2 = R^3 = H$
(10) $R^1 = OMe, R^2 = H, R^3 = Cl$



(11) R = OMe
(12) R = H



(13) R = OMe
(14) R = H

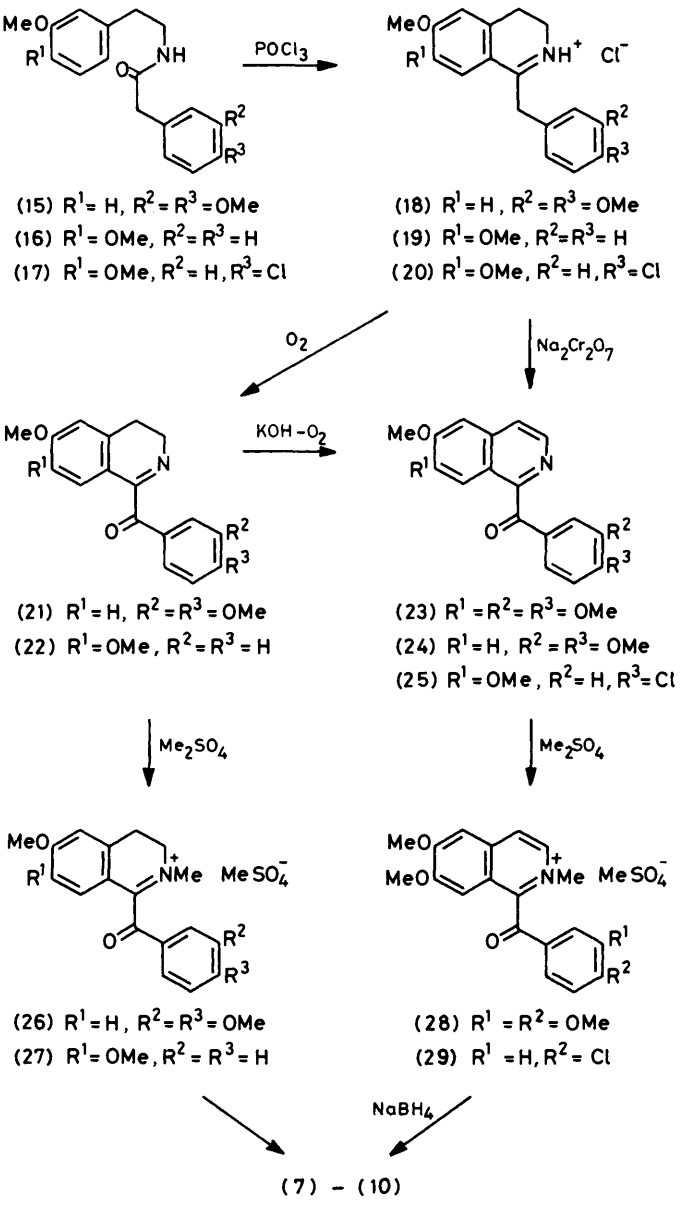
These two compounds are shown to be the same diastereoisomer by the fact that they have similar chemical shifts for the C-α protons at τ 4.86 and 5.00 with coupling constants of 4 Hz. They also show high field signals for the C-7 methoxy-protons at τ 6.7 and 6.65, respectively. In the alcohol (7) the two diastereoisomers show signals for the C-α protons at τ 4.95 with a coupling constant of 4 Hz and at τ 5.68 with a coupling constant of 9 Hz. The C-8 protons for the two diastereoisomers give signals at τ 4.22 and 4.62.

The alcohols (7) and (8), when subjected to prolonged reflux in formic acid, gave the benzazepines (13) and (14) as the major products in 58 and 74% yields, respectively, with small quantities of the intermediate enamines (11) and (12). In the case of the alcohols (9) and (10), where there are no methoxy-groups in the phenyl ring, no reaction was found even after the several days heating in formic acid. The rearrangement is envisaged to proceed by the acid catalyzed loss of water, assisted by the electron-donating groups at the 4′- and 6-positions of the 1-benzyltetrahydroisoquinoline ring system, to give the ions (30) and (31). These ions collapse, with assistance from the nitrogen lone pair electrons, to give the iminium cations which are the conjugate acids of the enamines (11) and (12). Reduction of the iminium system by formic acid then gives the 1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines (13) and (14).

The structures of the benzazepines (13) and (14) have been confirmed by comparison with the isomeric 1-benzyl-1,2,3,4-tetrahydroisoquinolines and 2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines and with the known compound (13) prepared by Kametani *et al.*[5] by two routes. In the mass spectrometer compound (13) gives, as the major ions, *m/e* 357 (M^+), 300 ($M^+ - 57$), 283 ($M^+ - 74$), 269 ($M^+ - 88$), 206 ($M^+ - 51$), 193 ($M^+ - 164$), and 165 ($M^+ - 192$). The parent ion is at 73% of the intensity of the base peak at *m/e* 269. This is in sharp contrast to the pattern observed [11] with the isomeric 1-benzyltetrahydroisoquinoline, laudanosine (32). Like all such compounds, laudanosine gives a base peak at *m/e* 206 ($M^+ - 151$) by loss of the 3,4-dimethoxybenzyl group. All other ions, including the parent at *m/e* 357, are small.

The benzazepine (14) was compared with the 1-benzyltetrahydroisoquinoline (33), prepared by methylation of the dihydroisoquinoline (18) and sodium borohydride reduction. It gave a mass spectral fragmentation pattern similar to compound (13), with the parent ion as the base peak and significant ions at *m/e* 283 ($M^+ - 44$) 270 ($M^+ - 57$), 269 ($M^+ - 58$), 253 ($M^+ - 74$), 239 ($M^+ - 88$), 176 ($M^+ - 151$), and 163 ($M^+ - 164$), whereas the tetrahydroisoquinoline (33) has the typical loss of 3,4-dimethoxybenzyl as the major fragmentation to give an ion at *m/e* 176 ($M^+ - 151$).

^{1}H N.m.r. spectroscopy allows characterization of the three isomeric structures (32), (13), and (3). The *N*-substituted 1-benzyltetrahydroisoquinolines have been shown [12] to give signals for the protons at C-8 and in the methoxy-group at C-7 at about τ 4.0 and 6.45, respectively, due to the shielding effect of ring C. The corresponding signals for the 2-phenyltetrahydrobenzazepine (3) are reported [3] to be at τ 3.35 (9-H) and 6.10 (8-OMe). In addition the *N*-methyl group resonance is seen at τ 6.95. We have observed in the case of the 1-phenyltetrahydrobenzazepine (13) that the corresponding signals are at τ 3.74 (9-H), 6.44 (8-OMe), and 7.66 (NMe). Thus, the shielding effects of ring C in the phenylbenzazepines are diagnostic. A further feature in the spectra of 1-phenyltetrahydrobenzazepines is the

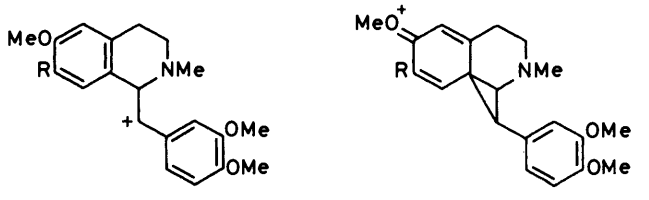


occurrence of a double doublet in the region of τ 5.8 for the proton at C-1. In 1-benzyltetrahydroisoquinolines the C-1 proton is seen at much higher field in the region of τ 6.3.

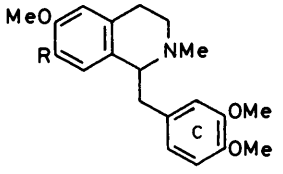
EXPERIMENTAL

I.r. spectra were recorded with solutions in chloroform on a Perkin-Elmer 157 instrument and ^{1}H n.m.r. spectra were recorded on a Varian A60 or HA 100 instrument. Mass spectra were recorded on either an A.E.I. MS9 or Hitachi-Perkin-Elmer RMU.6E instrument. The u.v. spectra were recorded in ethanol solution on a Pye-Unicam SP 8000 instrument. Kieselgel GF_{254} (Merck) was used for t.l.c. and silica M.F.C. (Hopkin and Williams) for column chromatography. Solvents were removed under reduced pressure below 50 °C.

1-(3,4-Dimethoxybenzoyl)-6-methoxy-3,4-dihydroisoquinoline (21).—To the amide (15) [8] (14 g, 42.5 mmol) in dry toluene (250 ml) was added phosphorus oxychloride (7.5 g, 49 mmol). The mixture was heated under reflux in an atmosphere of nitrogen for 1 h, then cooled and repeatedly evaporated to dryness from toluene to remove an excess of phosphorus oxychloride. The residue was crystallized once from isopropyl alcohol to give the crude imine hydrochloride (18) (12.9 g, 87%), m.p. 188—189 °C. This was used without further purification. The free base generated from compound (18) (8.4 g) was dissolved in chloroform–toluene and 5% platinum-on-charcoal catalyst (120 mg) was added. Air was bubbled through the mixture for 4 days, after which it was filtered and evaporated to dryness. The residue was crystallized from methanol to give the isoquinoline (21) (5.65 g, 64%), m.p. 99 °C (lit.,[7] m.p. 101—103 °C); $\nu_{max.}$ 1 660, 1 610, and 1 605 cm^{-1}; τ ($CDCl_3$) 6.04 (6 H, s, OMe), 6.16 (3 H, s, OMe), 6.10 (2 H, m, CH_2N), and 7.15 (2 H, m, Ar-CH_2); *m/e* 325 (M^+).



(30) (31)



(32) R = OMe

(33) R = H

1-*Benzoyl*-6,7-*dimethoxy*-3,4-*dihydroisoquinoline* (22).—Similarly to the foregoing example the amide (16) [7] (16 g) was converted into the imine hydrochloride (19) which was dissolved in a two phase mixture of diethyl ether (200 ml) and 10% sodium hydroxide (400 ml). Oxygen was bubbled through the mixture for 1 h. The phases were separated and the aqueous phase was washed once with chloroform. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on silica (90 g), with benzene and chloroform used as eluants to remove polar impurities, to give the benzoylisoquinoline (22) (12.3 g, 77%); $\nu_{max.}$ 1 675 and 1 610 cm^{-1}; τ ($CDCl_3$) 2.04 (2 H, dd, *J* 2 and 8 Hz, 2'- and 6'-H), 2.2—2.5 (3 H, m, 3'-, 4'-, and 5'-H), 2.93 (1 H, s, 8-H), 3.2 (1 H, s, 5-H), 5.86 (2 H, t, *J* 9 Hz, CH_2N), 5.97 (3 H, s, 7-OMe), 6.29 (3 H, s, 6-OMe), and 5.97 (2 H, t, *J* 9 Hz, Ar-CH_2). The compound formed a hydrochloride (which crystallized from ethanol–isopropyl alcohol), m.p. 168—170 °C (lit.,[9] m.p.168—170 °C) (Found: C, 65.5; H, 5.6; N, 4.1. Calc. for $C_{18}H_{17}NO_3$: C, 65.15; H, 5.4; N, 4.2%).

1-(3,4-*Dimethoxybenzoyl*)-6-*methoxyisoquinoline* (24).—The imine hydrochloride (18) (2.35 g), prepared as described above in the preparation of compound (21), was taken up in a two phase mixture of chloroform and 2M sodium hydroxide. The mixture was stirred vigorously for 3 d while air was bubbled through. T.l.c. (5% methanol in ethyl acetate on silica) showed the presence of the isoquinoline (21) and an additional component. The two phase mixture was separated and the organic phase evaporated to dryness and heated for 45 min with 10% ethanolic potassium hydroxide. When cold, the mixture was evaporated to low bulk, diluted with water, and the product was extracted with chloroform. The extract was washed with water and brine, and the chloroform layer was dried (Na_2SO_4) and evaporated. The residue was crystallized twice from isopropyl alcohol to give the *isoquinoline* (24) (950 mg, 44%), m.p. 132—134 °C; $\nu_{max.}$ 1 665, 1 630, and 1 603 cm^{-1}; τ ($CDCl_3$) 1.56 (1 H, d, *J* 5.5 Hz, 3-H), 2.0 (1 H, d, *J* 9 Hz, 8-H), 2.35 (1 H, d, *J* 2 Hz, 2'-H), 2.40 (1 H, d, *J* 5.5 Hz, 4-H), 2.69 (1 H, dd, *J* 2 and 9 Hz, 6'-H), 2.86 (1 H, dd, *J* 2 and 9 Hz, 7-H), 2.96 (1 H, d, *J* 2 Hz, 5-H), 3.23 (1 H, d, *J* 9 Hz, 5'-H), and 6.15 (9 H, s, OMe); *m/e* 323 (M^+) (Found: C, 70.4; H, 5.3; N, 4.2. $C_{19}H_{17}NO_4$ requires C, 70.6; H, 5.3; N, 4.3%).

1-(4-*Chlorobenzoyl*)-6,7-*dimethoxyisoquinoline* (25).—2-(4-chlorophenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide (17) (2.2 g, 6.6 mmol), toluene (80 ml), and phosphorus oxychloride (0.63 ml, 6.6 mmol) were heated at reflux under nitrogen for 45 min, cooled, and evaporated to dryness. The residue was crystallized from isopropyl alcohol–diethyl ether to give the crude imine hydrochloride (20) (1.6 g, 96%), m.p. 200—201 °C, which was used directly. The imine hydrochloride (3.0 g, 8.5 mmol) was converted into the free base by partitioning between chloroform and aqueous ammonia. The base was dissolved in glacial acetic acid (30 ml) and sodium dichromate (2.3 g, 8.5 mmol) in glacial acetic acid (30 ml) was added as drops. The mixture was stirred for 2 h at room temperature and then heated overnight on a steam-bath. When cold, it was diluted with water and neutralized, and the product was extracted with chloroform. The combined organic extracts were washed with water and dried (Na_2SO_4), and evaporated to yield a gum. Crystallization from methanol gave the *isoquinoline* (25) (0.45 g, 16%), m.p. 164—165 °C; $\nu_{max.}$ 1 665, 1 630, and 1 590 cm^{-1}; τ ($CDCl_3$) 1.48 (1 H, d, *J* 5.5 Hz, 3-H), 2.0 (2 H, d, *J* 8 Hz, 2'- and 6'-H), 2.23 (1 H, s, 8-H), 2.36 (1 H, d, *J* 3.5 Hz, 4-H), 2.50 (2 H, d, *J* 9 Hz, 3'- and 5'-H), 2.68 (1 H, s, 5-H), 5.90 (3 H, s, 7-OMe), and 5.96 (3 H, s, 6-OMe) (Found: C, 66.2; H, 4.4; Cl, 10.8; N, 3.8. $C_{18}H_{14}ClNO_3$ requires C, 65.9; H, 4.4; Cl, 10.8; N, 4.3%).

1-(3,4-*Dimethoxybenzoyl*)-6-*methoxy*-2-*methyl*-3,4-*dihydroisoquinolinium Methylsulphate* (26).—The foregoing isoquinoline (21) (5 g) was converted into the isoquinolinium methylsulphate (26) by heating with an excess of dimethyl sulphate on a steam-bath for 2 h. The mixture was then cooled and poured into diethyl ether. The crude isoquinolinium methylsulphate (26) was then crystallized from ethanol to give *material* (4.0 g, 57%) with m.p. 182—183 °C (Found: C, 55.8; H, 5.4; N, 3.0. $C_{20}H_{22}NO_4^+MeSO_4^-$ requires C, 55.8; H, 5.55; N, 3.1%).

Similarly, 1-benzoyl-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium methylsulphate (27) was obtained, but not in a pure form, and it was used directly in the next stage. Also obtained 1-(4-*chlorobenzoyl*)-6,7-*dimethoxy*-2-*methylisoquinolinium methylsulphate* (29), m.p. 218—219 °C (isopropyl alcohol) (Found: C, 52.5; H, 4.5; N, 3.1; S, 7.3. $C_{19}H_{17}NO_2Cl^+MeSO_4^-$ requires C, 52.9; H, 4.4; N, 3.1; S, 7.1%) and 1-(3,4-dimethoxybenzoyl)-6,7-dimethoxy-2-methylisoquinolinium methylsulphate (28), m.p. 125—126 °C (ethanol) (lit.,[10] m.p. 129—130 °C).

1-(α-*Hydroxy*-3,4-*dimethoxybenzyl*)-6-*methoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (8).—The foregoing isoquinolinium methylsulphate (26) (5 g) in ethanol (150 ml) was reduced with an excess of sodium borohydride under reflux for 1 h. The mixture was then evaporated to low bulk, diluted with water, and acidified. The mixture was stirred for 10 min, then basified, and the product extracted with chloroform. The chloroform extract was washed with water and dried (Na_2SO_4) to give a quantitative yield of two diastereoisomers of the alcohol (8) [which melted over a wide range (104—125 °C)]; $\nu_{max.}$ 3 600, 3 400br, and 1 605 cm^{-1}; *m/e* 343 (M^+) and 325 ($M^+ - H_2O$) (Found: 325.1678. $C_{20}H_{25}NO_4$ requires 325.1681). The two diastereoisomers had τ ($CDCl_3$) 5.05 (1 H, d, *J* 4 Hz, C*H*OH), 6.25 (1 H, d, *J* 4 Hz, Ar-C*H*NMe), and 7.43 (3 H, s, NMe); and 4.13 (1 H, d, *J* 9 Hz, 8-H), 5.71 (1 H, d, *J* 9 Hz C*H*OH), 6.64 (1 H, d, *J* 9 Hz C*H*NMe), and 7.49 (3 H, s, NMe) with intensities in the ratio 5 : 3.

The following compounds were obtained similarly. 1-(α-Hydroxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (9) was obtained as a single diastereoiso-

mer, m.p. 119—121 °C; $\nu_{max.}$ 3 600, 3 400 and 1 610 cm^{-1}; τ ($CDCl_3$) 2.7—2.85 (5 H, m, Ar-H), 3.45 (1 H, s, (5-H), 4.35 (1 H, s, 8-H), 4.86 (1 H, d, *J* 4 Hz, C*H*OH), 6.2 (3 H, s, 6-OMe), 6.22 (1 H, d, *J* 4 Hz, C*H*NMe), 6.7 (3 H, s, 7-OMe), and 7.35 (3 H, s, NMe); *m/e* 206 (M^+ — ArCHOH).

1-(*4-Chloro-α-hydroxybenzyl*)-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (10) was obtained as a single diastereoisomer, after crystallization, m.p. 109—112 °C (benzene); τ ($CDCl_3$) 2.80 (2 H, d, *J* 8 Hz, 3'-H and 5'-H), 3.0 (2 H, d, *J* 8 Hz, 2'-H and 6'-H), 3.5 (1 H, s, 5-H), 4.36 (1 H, s, 8-H), 5.0 (1 H, d, *J* 4 Hz, C*H*OH), 6.23 (6 H, s, OMe), 6.32 (1 H, d, *J* 4 Hz, C*H*NMe), 6.65 (3 H, s, 7-OMe), and 7.41 (3 H, s) (Found: C, 65.4; H, 6.4; Cl, 10.2; N, 3.9. $C_{19}H_{22}ClNO_3$ requires C, 65.6; H, 6.3; Cl, 10.2; N, 4.0%).

1-(α-Hydroxy-3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (7) was obtained as two diasteroisomers, m.p. 128—130 °C (aqueous methanol) (lit.,[10] 108 °C from benzene). The two diastereoisomers, in the ratio 5 : 3, gave τ ($CDCl_3$) 3.48 (1 H, s, 5-H), 4.22 (1 H, s, 8-H), 4.95 (1 H, d, *J* 4 Hz, C*H*OH), 6.28 (1 H, d, *J* 4 Hz, C*H*NMe), and 7.46 (3 H, s, NMe); and 3.45 (1 H, s, 5-H), 4.62 (1 H, s, 8-H), 5.68 (1 H, d, *J* 9 Hz, C*H*OH), 6.68 (1 H, d, *J* 9 Hz), and 7.39 (3 H, s, NMe), respectively; *m/e* 373 (M^+) and 206 [M^+ — $(MeO)_2$ArCHOH] (Found: C, 67.4; H, 7.4; N, 3.7. Calc. for $C_{21}H_{27}NO_5$: C, 67.7; H, 7.2; N, 3.8%).

The Acid Catalyzed Rearrangement of the Isoquinoline (8) *to give the Benzazepines* (12) *and* (14).—The aforementioned alcohol (8) (2.85 g) was heated in refluxing formic acid (30 ml) for 36 h, cooled, added to water, and neutralized. The products were extracted with chloroform. The chloroform extracts were washed with water and dried (Na_2SO_4), and evaporated to give a gum which was separated by column chromatography (SiO_2 with ethyl acetate and ethyl acetate–methanol as eluants). The first product eluted was crystallized from methanol to give 5-(3,4-*dimethoxyphenyl*)-8-*methoxy*-3-*methyl*-2,3-*dihydro*-1H-3-*benzazepine* (12) (0.35 g, 13%), m.p. 125—126 °C; $\nu_{max.}$ 1 615 cm^{-1}; τ ($CDCl_3$) 3.22br (4 H, s, Ar-H), 3.42 (2 H, s, Ar-H), 3.88 (1 H, s, C*H*NMe), 6.15 (3 H, s, OMe), 6.23 (3 H, s, OMe), 6.27 (3 H, s, OMe), 6.62 (2 H, m, Ar-CH_2), 7.06 (2 H, m, CH_2NMe), and 7.15br (3 H, s, NMe); *m/e* 325 (M^+) (Found: C, 73.45; H, 7.2; N, 4.3. $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.1; N, 4.3%). A second fraction gave 1-(3,4-*dimethoxyphenyl*)-7-*methoxy*-3-*methyl*-2,3,4,5-*tetrahydro*-1H-3-*benzazepine* (14); $\nu_{max.}$ 1 605 cm^{-1}; τ ($CDCl_3$) 3.18 (1 H, d, *J* 9 Hz, 5'-H), 3.25—3.40 (3 H, m, Ar-H), 3.44br (2 H, s, 8- and 9-H), 5.78 (1 H, dd, *J* 2 and 8 Hz, 1-H), 6.17 (3 H, s, OMe) 6.22 (3 H, s, OMe), 6.30 (3 H, s, OMe), 6.96 (1 H, dd, *J* 2 and 12 Hz, C*H*NMe), 7.24 (1 H, dd, *J* 8 and 12 Hz, C*H*NMe), 7.0—7.3 (4 H, m, CH_2CH_2NMe), and 7.65 (3 H, s, NMe); *m/e* 327 (M^+), 283 (M^+ — 44), 270 (M^+ — 57), 269 (M^+ — 58), 253 (M^+ — 74), 239 (M^+ — 88), 176 (M^+ — 151), and 163 (M^+ — 164). The base formed an oxalate (2 g, 58%) (which crystallized from isopropyl alcohol), m.p. 187 °C (Found: C, 63.2; H, 6.7; N, 3.5. $C_{20}H_{25}NO_3(CO_2H)_2$ requires C, 63.2; H, 6.47; N, 3.35%).

Similarly, from the alcohol (7) (2.8 g) was obtained, after refluxing in formic acid for 24 h, 5-(3,4-dimethoxyphenyl)-7,8-dimethoxy-3-methyl-2,3-dihydro-1*H*-3-benzazepine (11) (375 mg, 14%), m.p. 112—113 °C (methanol) (lit.,[5] m.p. 115—116 °C); $\lambda_{max.}$ (ethanol) 254 (ε 14 600) and 310 nm (14 600); τ ($CDCl_3$) 6.12 (6 H, s, OMe), 6.17 (3 H, s, OMe), 6.40 (3 H, s, 7-OMe), and 7.0br (3 H, NMe); *m/e* 325 (M^+) and the known [5] 1-(3,4-dimethoxyphenyl)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13); $\nu_{max.}$ 1 605 and 1 590 cm^{-1}; τ ($CDCl_3$) 3.15 (1 H, d, *J* 9 Hz, 5'-H), 3.2—3.35 (2 H, m, Ar-H), 3.36 (1 H, s, 6-H), 3.73 (1 H, s, 9-H), 5.78 (1 H, dd, *J* 2 and 8 Hz, 1-H), 6.18 (3 H, s, OMe), 6.20 (3 H, s, OMe), 6.24 (3 H, s, OMe), 6.44 (3 H, s, 8-OMe), 6.96 (1 H, dd, *J* 2 and 12 Hz, C*H*NMe), 7.16 (1 H, dd, *J* 8 and 12 Hz, C*H*NMe), 7.0—7.3 (4 H, m, CH_2CH_2NMe), and 7.66 (3 H, s, NMe); *m/e* 357 (M^+), 300 (M^+ — 57), 283 (M^+ — 74), 269 (M^+ — 88), 206 (M^+ — 151), 193 (M^+ — 164), and 165 (M^+ — 192). The base formed an oxalate in ethanol (2.5 g, 74%), m.p. 198—199 °C. Crystallization from isopropyl alcohol raised the m.p. to 201—202 °C [Found: C, 61.7; H, 6.7; N, 3.0. Calc. for $C_{21}H_{27}NO_4$-$(CO_2H)_2$: C, 61.7; H, 6.5; N, 3.1%].

1-(3,4-*Dimethoxybenzyl*)-6-*methoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (33).—The imine hydrochloride (18) (800 mg, 2.3 mmol), described above, was partitioned under nitrogen between saturated aqueous sodium hydrogencarbonate and ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), and treated at room temperature with an excess of methyl iodide for 24 h. The mixture was evaporated to dryness and the residue crystallized from ethanol to give the yellow *methiodide* (850 mg, 81%), m.p. 162—164 °C (decomp.) (Found: C, 53.1; H, 5.3; N, 3.0. $C_{20}H_{24}H_{24}NO_2I$ requires C, 52.9; H, 5.3; N, 3.0%). The 1-(3,4-dimethoxybenzyl)-6-methoxy-2-methyl-3,4-dihydroisoquinolinium iodide (500 mg) in ethanol at room temperature was reduced with an excess of sodium borohydride. After evaporation to low bulk the mixture was diluted with water, acidified, and stirred for 10 min. The mixture was neutralized and the product was extracted with chloroform to give, after drying (Na_2SO_4) and evaporation, the 1-benzyltetrahydroisoquinoline (33) (quantitative yield), m.p. 70 °C (lit.,[10] m.p. 72 °C); $\nu_{max.}$ 1 605 and 1 590 cm^{-1}; *m/e* 327 (M^+) and 176 [M^+ — $(MeO)_2ArCH_2$]; τ ($CDCl_3$) 3.28 (1 H, d, *J* 8 Hz, 5'-H), 3.35—3.55 (5 H, complex Ar-H), 6.19 (3 H, s, OMe), 6.28 (6 H, s, OMe), 6.30 (1 H, dd, *J* 4 and 8 Hz, 1-H), 6.8—7.4 (6 H, complex), and 7.52 (3 H, s, NMe). The base formed an *oxalate*, m.p. 157—158 °C (methanol) (Found: C, 63.3; H, 6.2; N, 3.0. Calc. for $C_{20}H_{25}NO_3(CO_2H)_2$: C, 63.2; H, 6.45; N, 3.35%].

[2/202 *Received*, 4*th February*, 1982]

REFERENCES

[1] F. Santavy, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, London, 1970, vol. XII, p. 333.
[2] C. Schöpf and M. Schweickert, *Chem. Ber.*, 1965, **98**, 2566.
[3] C. Reby and M. J. Gardent, *Bull. Soc. Chim. Fr.*, 1972, 1574.
[4] H. Irie, S. Tani, and H. Yamane, *Chem. Commun.*, 1970, 1713.
[5] T. Kametani, S. Hirata, S. Shibuya, and K. Fukumoto, *J. Chem. Soc. C*, 1971, 1927.
[6] S. Ruchirawat, Ph.D. Thesis, Liverpool University, 1969.
[7] J. A. Weisbach, J. L. Kirkpatrick, E. Macko, and B. Douglas, *J. Med. Chem.*, 1968, **11**, 752.
[8] G. C. Morrison, R. O. Waite, and J. Shavel, *Tetrahedron Lett.*, 1967, 4055.
[9] G. Mahuzier and M. Hamon, *Bull. Soc. Chim. Fr.*, 1969, 687.
[10] K. W. Bentley and A. W. Murray, *J. Chem. Soc.*, 1963, 2487.
[11] M. Tomita, H. Furukawa, T. Kikuchi, A. Kato, and T. Ibuka, *Chem. Pharm. Bull.* (*Jpn.*), 1966, **14**, 232.
[12] G. Fraenkel, M. P. Cava, and D. R Dalton, *J. Am. Chem. Soc.*, 1967, **89**, 329.