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1,2-DIHYDROISOQUINOLINES—V[1]
A SIMPLE BENZO[C]PHENANTHRIDINE RING SYNTHESIS

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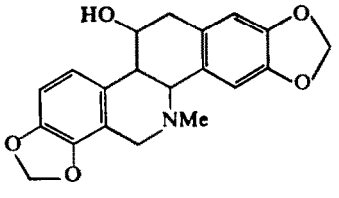
Abstract—The known[2] 2,3,8,9-tetramethoxybenzo[c]phenanthridine (33) has been synthesized in a simple procedure utilizing a 1,2-dihydroisoquinoline and a photochemical ring-closure reaction.

THE benzo[c]phenanthridine ring system is found in a small group of alkaloids,[3] the two main types being exemplified by chelidonine (**1**) and chelerythrine (**2**). The majority possess the 2,3,8,9-tetra-oxygenation pattern shown, but nitidine[4] (**3**) and avicine[5] (**4**) are exceptions. Chelerythrine (**2**) was the first alkaloid of the group to be synthesized,[6] in a ten-step sequence, from opianic acid (**5**). Subsequently both nitidine[7] and avicine[8] were prepared by essentially the same route, but as yet none of the reduced members of type **1** have been synthesized. Benzo[c]phenanthridin eitself was first reported[9] by Graebe, who prepared it from chrysene, and although several



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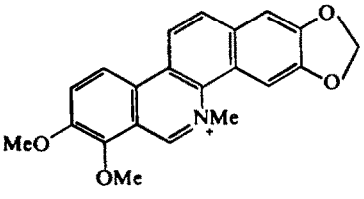

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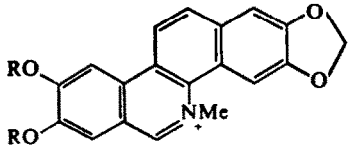
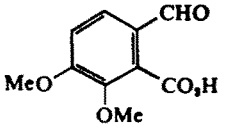


3, R = Me
4, R, R = —CH_2—



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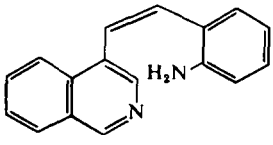
[1] Part IV. M. Sainsbury, S. F. Dyke and A. R. Marshall, *Tetrahedron* **22**, 2445 (1966).
[2] A. S. Bailey, Sir R. Robinson and R. S. Staunton, *J. Chem. Soc.* 2277 (1950).
[3] R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. IV; Chap. 35. Academic Press, New York (1954); R. H. F. Manske, *The Alkaloids* Vol. VII; p. 430, Academic Press, New York (1960).
[4] H. R. Arthur, W. H. Hui and Y. L. Ng, *J. Chem. Soc.* 1840 (1959).
[5] H. R. Arthur, W. H. Hui and Y. L. Ng, *J. Chem. Soc.* 4007 (1959).
[6] A. S. Bailey and C. R. Worthing, *J. Chem. Soc.* 4535 (1956).
[7] H. R. Arthur and Y. L. Ng, *J. Chem. Soc.* 4010 (1959); K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy and N. Viswanathan, *Ibid.* 4012 (1959).
[8] K. W. Gopinath, T. R. Govindachari and N. Viswanathan, *Tetrahedron* **14**, 322 (1961).
[9] C. Graebe, *Liebigs Ann.* **335**, 122 (1904); C. Graebe and F. Honigsberger, *Ibid.* **311**, 257 (1900); C. Graebe and R. Guehm, *Ibid.* **335**, 113 (1904).

methods have been described[10] for the construction of the ring system, very little systematic chemistry has been studied. Of the several attempted ring syntheses since the last review,[10] some successful ones include the Pschorr ring-closure with[11] the amine **6** and the oxidation,[12] via a nitrene intermediate, of the nitrocompound **7**. In neither case is the starting material easily accessible. The tetrahydro derivative **9** has been obtained[13] by cyclodehydration of the anil **8**, and more recently,[14] the ketones **13** (R = H or OMe) have been obtained from the α-naphthylamines **10** (R = H or OMe) as shown in **10** + **11** → **12** → **13**.

We planned to utilize the enamine character of 1,2-dihydroisoquinolines[15] as the basis of a synthesis of the alkaloids of both types **1** and **2**; our unsuccessful attempts to ring-close the model compound **14** (Z = H_2), itself prepared by the C_4-acylation



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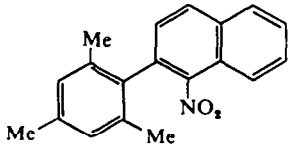

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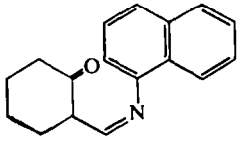

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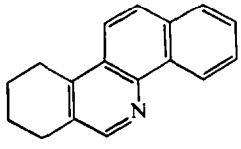

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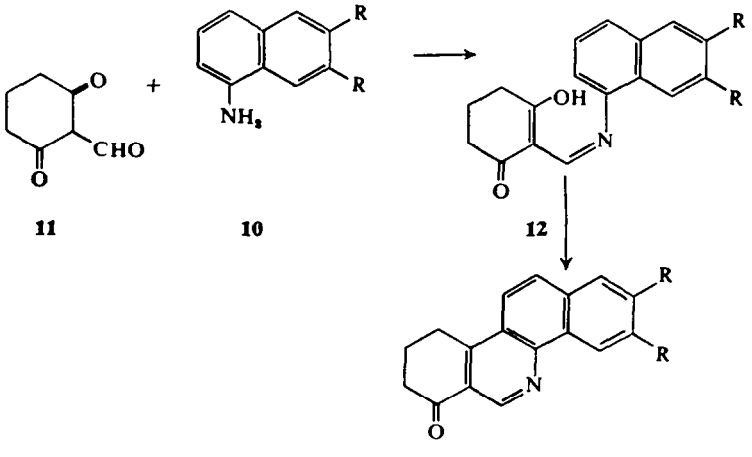

11 **10** **12**

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[10] J. V. Crawford in *The Chemistry of Heterocyclic Compounds: Six Membered Heterocyclic Nitrogen Compounds with Four Condensed Rings* (Edited by C. F. H. Allen) p. 157. Interscience, New York (1951).

[11] R. A. Abramovitch and G. Tertzakian, *Canad J. Chem.* **41**, 2265 (1963).

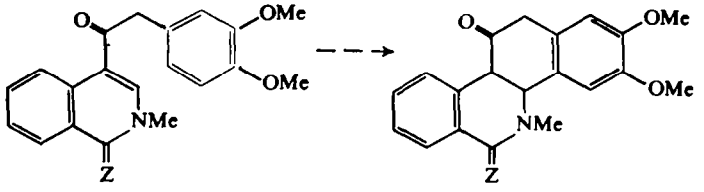
[12] R. A. Abramovitch, O. Newman and G. Tertzakian, *Canad. J. Chem.* **41**, 2390 (1963).

[13] B. L. Hollingsworth and V. Petrow, *J. Chem. Soc.* 1537 (1948).

[14] S. V. Kessar, I. Singh and A. Kumar, *Tetrahedron Letters* 2207 (1965).

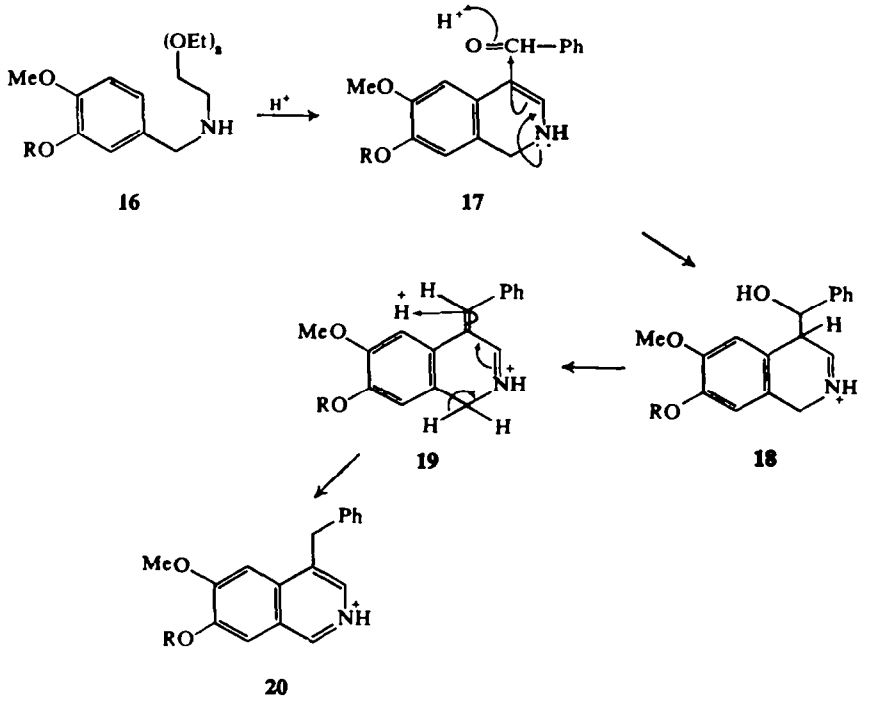
[15] S. F. Dyke and M. Sainsbury, *Tetrahedron* **21**, 1907 (1965) and Refs therein cited.

of a 1,2-dihydroisoquinoline, to the ketone **15** have already been described.[1] We now wish to report a simplified route to the fully aromatic benzo[c]phenanthridine ring system which employs a 1,2-dihydroisoquinoline intermediate, and a photochemical ring-closure reaction. The method will be illustrated for the known[2] 2,3,8,9-tetramethoxybenzo[c]phenanthridine (**33**).



14 **15**

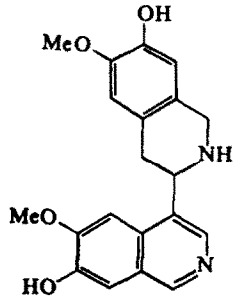
Bobbitt *et al.*[16] have found that 1,2-dihydroiosquinolines (e.g. **17**, R = H) can conveniently be formed by treating aminoacetals such as **16**, (R = H) with mineral acids, and they have shown that these intermediates give 1,2,3,4-tetrahydroisoquinolines by reduction, or 4-benzylisoquinolines by condensation with benzaldehyde, in good yields. The latter reaction proceeds, presumably, as shown in **16** → **20**. In all of the examples reported,[17] a phenolic OH group was present in the 6,7 or 8-position



16 **17** **18** **19** **20**

[16] J. M. Bobbitt, J. M. Kiely, K. L. Khanna and R. Ebermann, *J. Org. Chem.* **30**, 2247 (1965); J. M. Bobbitt, D. P. Winter and J. M. Kiely, *Ibid.* **30**, 2459 (1965).

[17] NMR spectra were measured with a Varian A.60 spectrometer. Chemical shifts are expressed in c/s or ppm downfield from TMS as an internal standard and refer to $CDCl_3$ solns unless otherwise stated. IR spectra were recorded using Nujol nulls.



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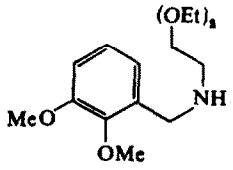

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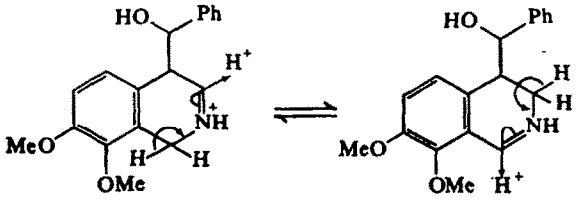
of the 1,2-dihydroisoquinolines, and the only by-products characterized were the expected dimers of the type **21**.

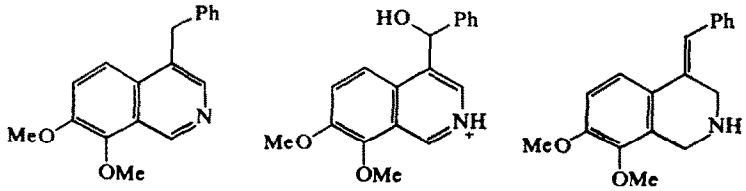
We have now extended this work to the less reactive aminoacetals **16**, (R = Me) and **22**.

With the latter and benzaldehyde a white crystalline hydrochloride quickly formed which could not be obtained analytically pure. Bands at 3400 and 1660 cm^{-1} in its IR spectrum indicated the presence of —OH and $>C{=}\overset{+}{N}H$-groups respectively; the NMR spectrum[17] (taken in CF_3CO_2H soln) is compatible with either structure **23** or **24**. Whereas **23** corresponds to the expected intermediate in the C_4-benzylation reaction,

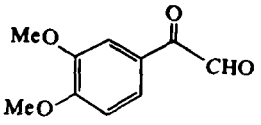


23 24

24 is in accord with the UV evidence (the spectrum suggests the presence of a 3,4-dihydroisoquinolinium salt). The two are, however, easily interconvertible, and the fully aromatic end-product is readily derivable from either. Structure **23** or **24** is supported by the fact that when heated at 70° *in vacuo*, or under reflux with ethanolic KOH, the compound is converted into 7,8-dimethoxy-4-benzylisoquinoline (**25**), a structure confirmed by the analysis, the UV spectrum and the diagnostic NMR spectrum. When the hydrochloride **23** or **24** is boiled with hydrogen chloride in ethanol in the presence of air, the isoquinolinium salt **26** is produced, whereas reduction with sodium borohydride yields **27**, presumably by way of a normal reduction of



25 26 27



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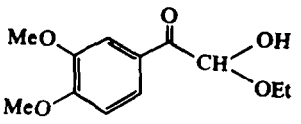

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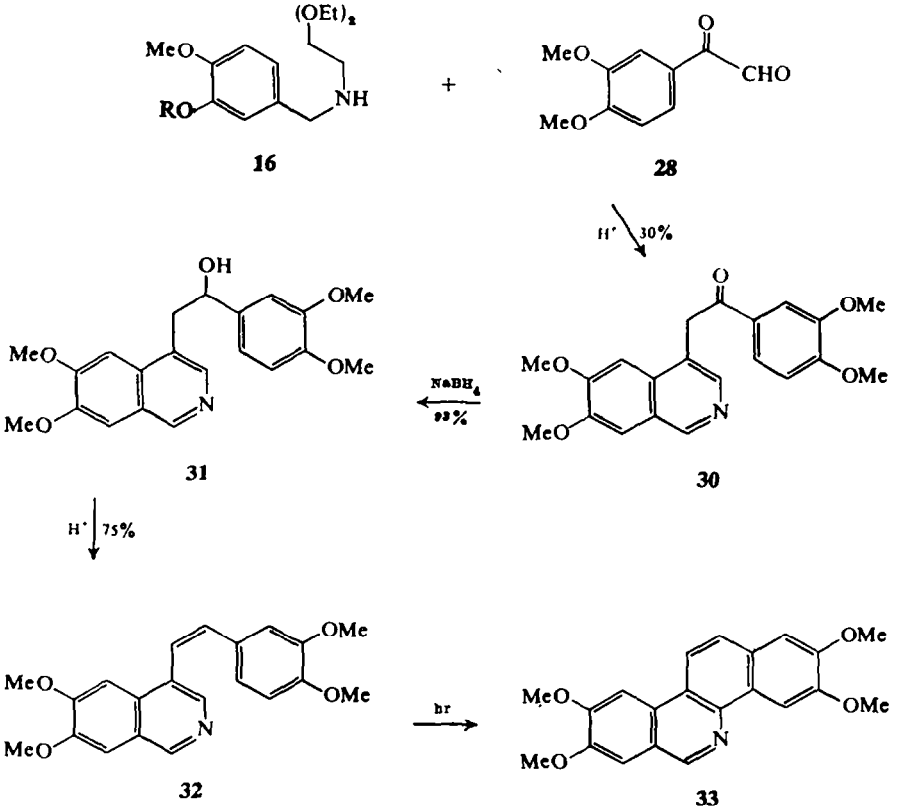
the >C=NH⁺-group and a base-catalysed elimination. A parallel series of experiments with the aminoacetal **16** (R = Me) and benzaldehyde, *p*-methoxybenzaldehyde and *p*-nitrobenzaldehyde was conducted. The nitroaldehyde failed to react under the conditions employed,* but in the other cases intermediates corresponding to **23** or **24** were isolated, together with the expected 4-benzylisoquinolines. The results are summarized in the Experimental.

The new synthesis of 2,3,8,9-tetramethoxybenzo[c]phenanthridine **33** is summarized in the Chart I. The 3,4-dimethoxyphenylglyoxal (**28**) was obtained in 77% yield by the oxidation of acetoveratrone with selenium dioxide. The pale yellow product, m.p. 124–126° was shown by mol. wt determination and by its NMR spectrum to be the hemiacetal **29**, which, on heating above its m.p., reverts to the glyoxal. The interaction of **28** and **16** (R = Me) led to an insoluble hydrochloride which, upon basification

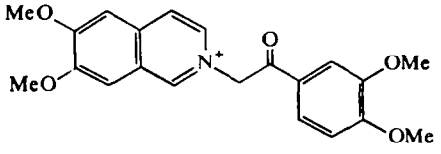
Chart I



* Various nitrobenzaldehydes have now been successfully employed; the results will be described in a later paper.

gave a solid, m.p. 179–180°. This material analysed for $C_{21}H_{21}NO_5$ and its NMR spectrum was diagnostic for the required isoquinoline structure **30**. The base was further characterised as the hydrochloride and methiodide.

The acid filtrate from **30** was evaporated to leave a sticky solid which crystallized from ethanol to give a compound which melted at 80°, with effervescence, solidified, then remelted at 156–160°. The IR spectrum of this compound, tentatively assigned the structure **35**, exhibited bands at 3300 cm^{-1} (—OH), 1675 cm^{-1} (>C=O) and 1640 cm^{-1} (>C=C<). Basification gave an unstable oil, whereas treatment with mineral acid gave a crystalline quaternary salt which possessed a CO group (1683 cm^{-1}), but no OH group. The NMR spectrum of this hydrochloride **35** in CF_3CO_2H was identical with that of the quaternary salt in the same solvent and showed amongst



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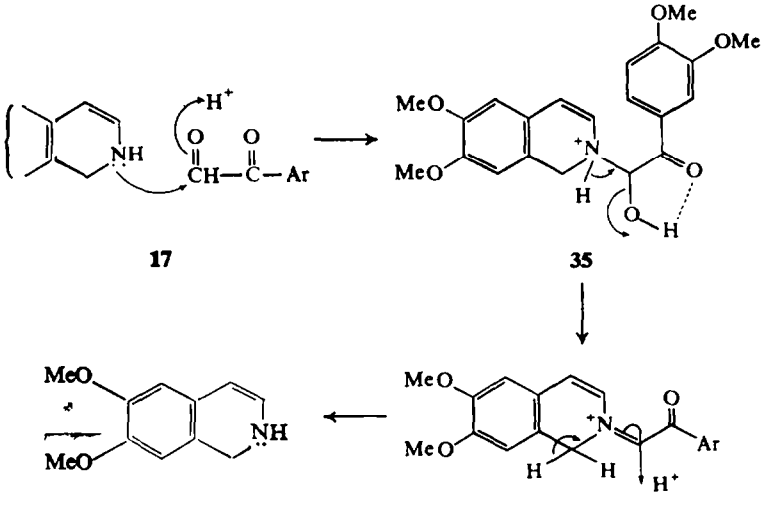
other absorptions, a one proton singlet at 9·0 ppm (C_1—H of an isoquinolinium salt), a broadened two proton singlet at 8·1 ppm ($C_3 + C_4$ hydrogens of an isoquinoline ring) and a two proton singlet at 6·15 ppm (—C(=O)—CH_2—$\overset{+}{N}$<). The structure **34** for the quaternary salt was confirmed by its preparation from 6,7-dimethoxyisoquinoline and ω-bromoacetoveratrone. Hence, as well as C_4-alkylation of the 1,2-dihydroisoquinoline **17**, N-alkylation can occur, at least with an arylglyoxal, to yield **35** which, upon heating, or upon treatment with acids is transformed into **34**, probably via **36**.

Reduction of the ketoisoquinoline **30** [Chart I] with sodium borohydride gave the secondary alcohol **31**, which was easily dehydrated by HCl in chloroform to the styrene



17 **35**

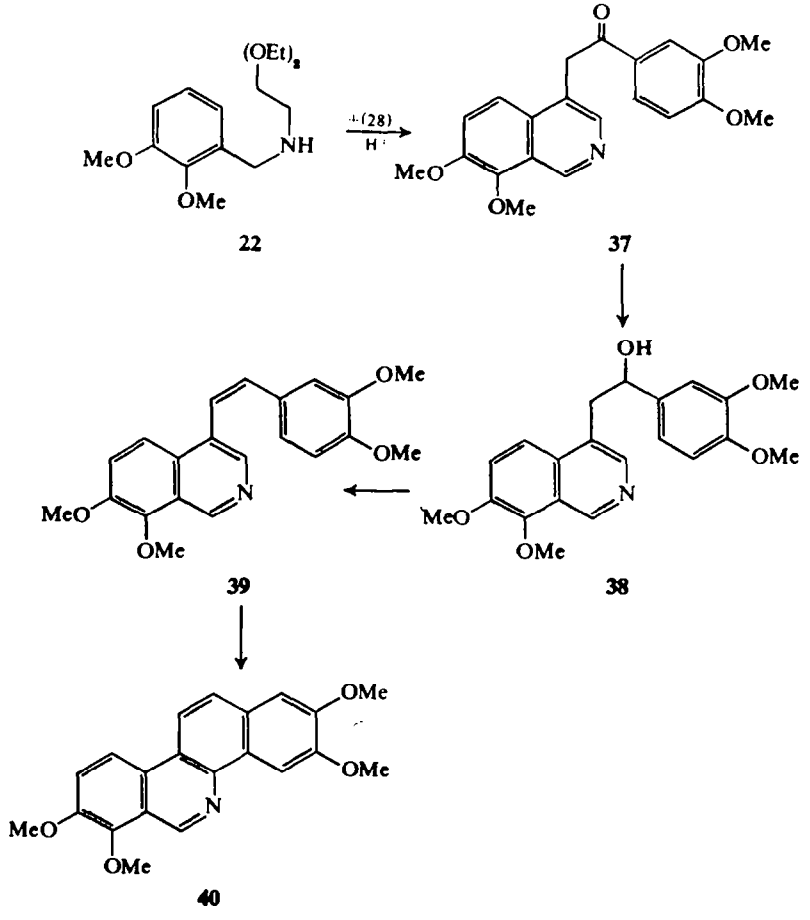
34 **36**

32, and this, when irradiated[18] in ethanol solution according to the conditions used by Timmons[19] caused the precipitation of 2,3,8,9-tetramethoxybenzo[c]phenanthridine (33). Purification was achieved by sublimation and crystallization from pyridine to give a product whose m.p. was undepressed when mixed with an authentic specimen[20] of 33.

A similar sequence of reactions [Chart II] led, from the glyoxal 28 and the isomeric aminoacetal 22, through the ketoisoquinoline 37 and the alcohol 38 to the styrene 39. The conditions for the photochemical ring-closure of 39 were far more critical since the expected product 40 is soluble in the ethanol solvent, but eventually a minute quantity of 2,3,7,8-tetramethoxybenzo[c]phenanthridine (40) was obtained.

The necessary modifications to this route that will lead to the synthesis of the natural alkaloids will be described later.

Chart II



[18] A Hanovia photochemical reactor was used.

[19] We are grateful to Dr. C. J. Timmons for experimental details of his photochemical synthesis of the parent benzo[c]phenanthridine prior to publication.

[20] It is a pleasure to thank Dr. A. S. Bailey for providing a specimen of 2,3,8,9-tetramethoxybenzo[c]-phenanthridine.

EXPERIMENTAL[17]

4-Benzyl-7,8-dimethoxyisoquinoline(25). The acetal **22**, (28·3 g) was dissolved in conc HCl(250 ml) containing EtOH (125 ml) warmed to 60°, then benzaldehyde (21·2 g) was added. After heating under reflux for 1 hr, the dark coloured soln was cooled and stored at 0° for 48 hr; the solid which had separated was then collected. Crystallization first from HCl—EtOH (1:1) and then from water gave **23** or **24** as colourless needles (11 g) m.p. 100–105°. ν_{max} cm^{-1}, 3500 (—OH), 1665 (>C=$\overset{+}{N}$<). λ_{max} (ε) mμ, 236 (13,000), 350 (8,360). NMR singlet 8·5 ppm. [1] (C_1 or C_8), singlet 5·25 ppm [2] (—CH_2—$\overset{+}{N}$<). (Found: C, 64·10; H, 5·62; N, 4·01. $C_{18}H_{19}NO_2HCl$ requires: C, 64·79; H, 6·04; H, 4·20%.)

The filtrate from the above separation was washed with benzene, evaporated to dryness and the residue recrystallized from EtOH to yield 4-benzyl-7,8-dimethoxyisoquinoline hydrochloride as pale yellow needles (10 g) m.p. 178°; ν_{max} cm^{-1}, 1630 (>$\overset{+}{N}$=C<), 1605 (>C=C<); λ_{max} (ε) mμ, 235 (13,500), 255 (8360), 280 (1650), 360 (1360). NMR singlet 8·9 ppm [1] (C_1), singlet 8·0 ppm, [1] (C_8), singlet 3·1 ppm [2] (Ar–CH_2–). (Found: C, 68·54; H, 5·41; N, 4·74; Cl, 11·80. $C_{18}H_{17}NO_2$, HCl requires: C, 68·42; H, 5·70; N, 4·43; Cl, 11·22%.) Basification of this material with aqueous ammonia eventually afforded the free base **25** as a sticky solid which could not be obtained crystalline; ν_{max} cm^{-1}, 1635 (>C=$\overset{+}{N}$<), 1608 (>C=C<); λ_{max} (ε) mμ, 236 (15,800), 270 (1480), 280 (1480), 350 (1640). NMR singlet 8·8 ppm [1] (C_1), singlet 8·3 ppm [1] (C_8), 2·83 ppm, [2] (—CH_2—Ar).

Reduction of this base with $NaBH_4$ in aqueous EtOH gave the 1,2,3,4-tetrahydro base as a colourless liquid which was characterized as the hydrochloride. Colourless needles, m.p. 187–188°, from EtOH. (Found: C, 68·00; H, 6·21. $C_{18}H_{20}NO_2$·HCl requires: C, 68·02; H, 6·35%.)

The alcohol hydrochloride **23** or **24** when heated with methanolic KOH gave 4-benzyl-7,8-dimethoxyisoquinoline which was characterized as the hydrochloride and which is identical with the material described above.

4-(α-Hydroxybenzyl)7,8-dimethoxyisoquinoline hydrochloride(**26**). The alcohol hydrochloride **23** or **24**, (1 g) was boiled with EtOH previously saturated with HCl and after 4 hr the solvent was removed. The residue was recrystallized from EtOH to yield **26** as pale yellow prisms (0·1 g) m.p. 165–170°; ν_{max} cm^{-1}, 3350 (—OH), 1635 (>C=$\overset{+}{N}$<), 1610 (>C=C<), λ_{max} mμ, 240, sh. 255, 350. NMR singlet 8·8 ppm [1] (C_1) singlet 8·4 ppm [1] (C_8), singlet 3·75 ppm [1] (Ar—C(OH)*H*—) (Found: C, 65·01; H, 5·21; N, 4·02. $C_{18}H_{17}NO_2$, HCl requires: C, 65·18; H, 5·47; N 4·23%.)

4-Benzylidene-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**27**). The alcohol hydrochloride **23** or **24**, (5 g) in 90% aqueous EtOH (100 ml) was treated with $NaBH_4$ (5 g), and the mixture heated on a water-bath for 1 hr. After standing overnight the EtOH was removed and water (50 ml) was added. The insoluble material was collected into benzene and subsequent removal of the dried solvent gave **27** as colourless needles (3·5 g), m.p. 144–145°, from benzene; ν_{max} cm^{-1}, 1620 (>C=C<) λ_{max} (ε) mμ, 236 (14,800), 303 (18,600). (Found: C, 76·63; H, 6·73; N, 5·11. $C_{18}H_{19}NO_2$ requires: C, 76·84; H, 6·81; N, 4·98%.)

The hydrochloride was obtained as colourless prisms from EtOH, m.p. 227–228°. (Found: C, 68·16; H, 6·28; N, 4·71; Cl, 11·03. $C_{18}H_{19}NO_2$·HCl requires: C, 68·00; H, 6·34; N, 4·40; Cl, 11·15%.)

Catalytic reduction of **27** in EtOH containing a trace of perchloric acid, using Adam's catalyst, gave 4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline. This substance was characterized as the hydrochloride and was shown to be identical with the compound previously obtained by $NaBH_4$ reduction of **25**.

4-Benzyl-6,7-dimethoxyisoquinoline hydrochloride (**20**, R = Me) [with Miss M. E. Chilton]. A soln of **16** (R = Me, 10 g) in conc HCl (50 ml) containing EtOH (25 ml) was heated to boiling under an atmosphere of N_2 and benzaldehyde (10 g) was added. After heating under reflux for 45 min, the soln was cooled and washed with benzene. Evaporation under reduced press gave a sticky residue which was taken up in a small volume of EtOH and set aside. Compd (**18**, R = Me) was eventually deposited as a microcrystalline orange coloured solid (4·56 g, 34·6%), m.p. 180–185°, ν_{max} cm^{-1}, 3350 (–OH), 1660 (>C=$\overset{+}{N}$<); λ_{max} (ε) mμ, 245 (27, 530). NMR (CD_3SOCD_3), singlet 7·95 ppm [1] (C_1 or C_8), singlet 4·55 ppm [2] (—CH_2—$\overset{+}{N}$<), broad singlet 4·10 ppm [1] (—O*H*) removable by deuteration.

The ethanolic mother liquor from the above experiment was evaporated under reduced press and the residue obtained dissolved in water. After repeatedly washing with benzene the aqueous phase was concentrated to small volume and cooled to 0°, when (**20**, R = Me) was obtained as colourless needles (0·93 g), m.p. 192–194° from water; ν_{max} cm^{-1}, 1630 (>C=$\overset{+}{N}$<), 1610 (>C=C<); λ_{max} (ε) mμ 240, (16,760), 313 (10,000). NMR (CF_3CO_2H), doublet 9·15 ppm [1] J = 6·1 c/s (C_3), doublet 8·20 ppm, [1] J = 6·1 c/s. (C_3), singlet 4·52 ppm [2] (—CH_2—Ar). (Found: C, 68·35; H, 5·79; N, 4·65. $C_{18}H_{18}NClO_3$ requires: C, 68·40; H, 5·72; N, 4·44%.)

Compd (**18**, R = Me) (500 mg) was heated under reflux with 0·5N methanolic KOH (50 ml) for 1 hr. Removal of the solvent and addition of water (5 ml) followed by extraction of the aqueous phase with ether, gave, after removal of the dried ether, 4-benzyl-6,7-dimethoxyisoquinoline (335 mg) as an oil. This compound was characterized as the hydrochloride, and shown to be identical with **20** prepared previously.

4-(p-*Methoxybenzyl*)6,7-*dimethoxyisoquinoline hydrochloride*. In a similar experiment to that described above, **16** (R = Me) was reacted with *p*-methoxybenzaldehyde. The alcohol hydrochloride corresponding to **23** or **24** was obtained in 47% yield as a red crystalline solid, m.p. 155–156°; ν_{max} cm^{-1}, 3250 (—OH), 1665 (>C=$\overset{+}{N}$<), 1610 (>C=C<); λ_{max} mμ 250, 290. NMR (CD_3SOCD_3), singlet 9·5 ppm, [1] (C_1 or C_3), singlet 4·5 ppm, [1] (—*OH*) removed by deuteration. (Found: C, 66·46; H, 5·91; N, 3·43. $C_{19}H_{20}NClO_3$ required: C, 66·00; H, 5·80; N, 4·05%.)

Evaporation of the mother-liquor, from which the alcohol hydrochloride had separated, gave 4-(*p*-methoxybenzyl)6,7-dimethoxyisoquinoline, which was characterized as the hydroiodide, pale yellow prisms, m.p. 188–189° from EtOH; ν_{max} cm^{-1}, 1640 (>C=$\overset{+}{N}$<), 1620 (>C=C<); λ_{max} (ε) mμ 243 (20,050), 313 (15,850). NMR (CF_3CO_2H), doublet 9·3 ppm, [1] J = 5·4 c/s (C_1), doublet 8·1 ppm, [1] J = 5·4 c/s, (C_3), singlet 4·50 ppm, [2] (CH_2—Ar). (Found: C, 52·58; H, 4·74; N, 3·24. $C_{19}H_{20}NIO_3$ requires: 52·30, H, 4·58; N, 3·20%.)

3,4-*Dimethoxyphenylglyoxal* (**28**). Acetoveratrone (72 g) was added rapidly to a well stirred, warm soln of SeO_2 (49 g) in EtOH (240 ml) containing water (9 ml). After heating under reflux for 24 hr the precipitated Se was removed by filtration and the filtrate evaporated under reduced press. The residual liquid was distilled (135–138°/0·15 mm) to yield the monomeric glyoxal as a pale yellow liquid (60 g, 77%); ν_{max} cm^{-1}, 1679, 1660. NMR singlet 9·60 ppm (—*CH*O). On standing, the liquid solidified to a glass, which when triturated with 75% EtOHaq yielded pale yellow prisms (m.p. 124–126° from aqueous EtOH), ν_{max} cm^{-1}, ~3300 (—OH), 1665 (>CO), 1095 (—O—). Analytical results for this compound were inconsistent due to the presence of variable amounts of water, which could not be removed. Heating under vacuum resulted in reformation of the aldehydic monomer, hemiacetal m.p. 77–78° from EtOH. (Found: C, 59·70; H, 6·65; $C_{19}H_{16}O_5$ requires C, 59·99; H, 6·71%)

4-(3,4-*Dimethoxyphenacyl*) 6,7-*dimethoxyisoquinoline* (**30**). A solution of **16**, (R = Me, 5·66 g) in conc HCl (50 ml) was warmed to 80° and molten 3,4-dimethoxyphenylglyoxal (7·76 g) was added together with EtOH (20 ml). The mixture was warmed on a water-bath for 30 min, cooled and stored at 0° for 2 days. The crystalline material (3·1 g) was collected and recrystallized from EtOH to yield 4-(3,4-dimethoxyphenacyl)6,7-dimethoxyisoquinoline hydrochloride as colourless needles (2·80 g), m.p. 224–225°; ν_{max} cm^{-1}, 1668 (>CO), 1635 (>C=$\overset{+}{N}$<), 1610 (>C=C<); λ_{max} (ε) mμ, 240 (48,900), Sh 255 (40, 550), 321 (18,000). (Found: C, 61·35; H, 5·85; N, 3·55; OMe, 28·00. $C_{21}H_{22}NO_5Cl$. C_2H_5OH requires: C, 61·53; H, 6·27; N, 3·11; OMe, 27·58%.) Basification with ammonia afforded **30**, m.p. 179–180° EtOH) as colourless small prisms in 82% yield; ν_{max} cm^{-1}, 1667 (>CO), 1625 (>C=N—), 1600 (>C=C<); λ_{max} (ε) mμ, 237 (50,600), 277 (16,300), Sh 305 (13,250), Sh 325 (8300) NMR, singlet 8·9 ppm, [1] (C_1), singlet 8·3 ppm, [1] (C_3), singlet 4·5 ppm, [2] (—CH_2—CO—). (Found: C, 68·26; H, 5·65; N, 4·0. $C_{21}H_{21}NO_5$ requires: C, 68·65; H, 5·76; N, 3·81%.) The base was characterized as the methiodide m.p. 204–205° (dec), pale yellow prisms from EtOH. (Found: C, 51·40; H, 4·74; N, 2·68. $C_{22}H_{24}NO_5I$ requires: C, 51·87; H, 4·75; N, 2·75%.)

2-(3,4-*Dimethoxyphenacyl*)6,7-*dimethoxyisoquinolinium iodide* (**34**). The original hydrochloric acid filtrate from the above experiment was washed with benzene to remove neutral material and then concentrated to small volume when a sticky brown solid separated. Crystallization from EtOH gave eventually a colourless micro-crystalline solid (7·2 g) m.p. 78–80° (with effervescence, resolidification and remelting at 156–160°); ν_{max} cm^{-1}, 3300 (—OH), 1675 (>C=O), 1640 (>C=C<) λ_{max} mμ,

275, 312. NMR (CF_3CO_2H), — identical with that of **34** in the same solvent. NMR (CD_3OD), singlet 8·3 ppm, [1] (C_1), quartet 8·3 ppm [2] $J = 4·5$ c/s. (C_3 and C_4, AB), singlet 5·0 ppm [2] (—CH_2—Ar). Basification of this material, tentatively assigned the structure **35**, gave an unstable oil which rapidly turned red in air. When boiled with HClaq, followed by addition of KIaq the compound, m.p. 78–80°, gave a crystalline iodide salt, which was recrystallized from EtOH to yield very pale yellow prisms, m.p. 189–190°; ν_{max} cm^{-1}, 1690 (>CO), 1640 (>C=$\overset{+}{N}$<), 1615 (>C=C<). λ_{max} (ε) mμ, 280 (19,500), 310 (16,000), NMR (CF_3CO_2H), singlet 9·25 ppm, [1] (C_1), broad singlet 8·9 ppm, [2] (C_3 and C_4), singlet 7·25 ppm, [2] ($\overset{+}{N}$—CH_2—Ar). (Found: C, 50·71; H, 4·45; N, 3·06. $C_{22}H_{22}NO_5I$ requires: C, 50·90; N, 4·48; N, 2·83%.)

The iodide was shown to be identical (IR, NMR and mixed m.p.) with **34**, obtained by the interaction of 6,7-dimethoxyisoquinoline with 3,4-dimethoxyphenacyl bromide, followed by anion exchange.

Reduction of the iodide with $NaBH_4$ in aqueous EtOH gave 2-(*β*-hydroxy-3,4-dimethoxyphenylethyl) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, m.p. 122°, as colourless needles from EtOH. (Found: C, 67·71; H, 7·18; N, 4·02. $C_{21}H_{27}NO_5$ requires: C, 67·54; H, 7·29; N, 3·75%.) Methiodide m.p. 190–195° from EtOH. (Found: C, 51·01; H, 6·05; N, 2·69. $C_{22}H_{30}NO_5I$ requires: C, 51·26; H, 5·87; N, 2·72%.)

The secondary alcohol, m.p. 122°, was also obtained by the interaction of 6,7-dimethoxy-1,2,3,4-tetrahydrosioquinoline and 3,4-dimethoxyphenacyl bromide, followed by reduction with $NaBH_4$.

4-(*β-Hydroxy*-3,4-*dimethoxyphenylethyl*) 6,7-*dimethoxyisoquinoline* (**31**). The hydrochloride salt of **30** was suspended in EtOH and treated with an equal weight of $NaBH_4$. After heating for 30 min, the solvent was removed and water added to dissolve the salts; then extraction with benzene afforded, after removal of the dried solvent, a colourless gum which crystallized in contact with ether. Recrystallization from EtOH—ether gave colourless plates (m.p. 75–80°) of **31** (93%). ν_{max} cm^{-1}, ~3350 (OH), 1625 (>C=N—), 1610 (>C=C<); λ_{max} (ε) mμ, 239 (12,900), 282 (2675), 316 (1220). NMR singlet 8·6 ppm, [1] (C_1), singlet 8·0 ppm, [1] (C_3), triplet 4·9 ppm, [1] $J = 7·5$ c/s. (CH_2—C*H*(OH)—), doublet 3·5 ppm, [2] $J = 7·5$ c/s (CH_2—CH(OH)—). (Found: C, 68·07; H, 6·15; N, 4·01. $C_{21}H_{25}NO_5$ requires: C, 68·28; H, 6·28; N, 3·79%.)

Methiodide, m.p. 203–204°, pale yellow prisms from EtOH. (Found: C, 51·52; H, 5·13; N, 2·80. $C_{22}H_{28}NO_5I$ requires: C, 51·65; H, 5·13; N, 2·74%.)

4-(3,4-*Dimethoxystyryl*) 6,7-*dimethoxyisoquinoline* (**32**). The alcohol **31** (500 mg) was dissolved in $CHCl_3$ (100 ml) and the soln saturated with HCl during 30 min. Removal of the solvent gave a yellow crystalline hydrochloride which was recrystallized from EtOH to yield yellow needles (362 mg), m.p. 213–215°; ν_{max} cm^{-1} 1640, 1620, 1605. (Found: C, 63·52; H, 6·96; N, 3·53. $C_{21}H_{21}NO_4Cl$, C_2H_5OH requires: C, 63·36; H, 6·54; N, 3·21%.)

Basification of the hydrochloride with aqueous ammonia yielded **32** as colourless needles, m.p. 135°, from AcOEt (82% conversion); ν_{max} cm^{-1}, 1635, 1625, 1605. λ_{max} (ε) mμ, 243 (46,600), 336 (25,400). NMR singlet 8·9 ppm, [1] (C_1), singlet 8·5 ppm, [1] (C_3); seven proton multiplet ~7 ppm. (Found: C, 71·60; H, 5·91; N, 4·20. $C_{21}H_{21}NO_4$ requires: C, 71·78; H, 6·02; N, 3·99%.)

2,3,8,9-*Tetramethoxybenzo*[c]*phenanthridine* (**33**). Compd **32** (684 mg) in EtOH (1000 ml) was irradiated for 16 hr in a Hanovia II photochemical reactor. During this time a quantity of insoluble material (150 mg) separated and this was collected. The EtOH was concentrated to low bulk when a further quantity (31 mg) of solid was obtained. The combined crops were purified, first by sublimation at 210–220°/0·1 mm, and then by recrystallization from pyridine. The pure **33**, colourless needles, had m.p. 306–308° (lit.[8] m.p. 302–304°) ν_{max} cm^{-1}, 1615, 1603, λ_{max} (ε) mμ ($CHCl_3$) 285 (30,200), 335 (10,000). (Found: C, 72·39; H, 5·51; N, 4·00; Calc. for $C_{21}H_{19}NO_4$; C, 72·19; H, 5·48; N, 4·01%.)

Evaporation of the ethanolic mother-liquor gave a gummy residue which upon treatment with AcOEt yielded crystalline **32** (421 mg) (61·8% recovery).

4-(3,4-*Dimethoxyphenacyl*) 7,8-*dimethoxyisoquinoline hydrochloride* (**37**). The condensation between 3,4-dimethoxyphenylglyoxal and **22** was carried out essentially as previously described for **30**. The hydrochloride salt was collected and recrystallized from EtOH as pale yellow plates m.p. 212–214° (37%); ν_{max} cm^{-1}, 1669 (>CO), 1645 (>C=$\overset{+}{N}$<), 1618 (>C=C<); λ_{max} (ε) mμ, 233 (40,500), 275 (14,400), 360 (3300). NMR (CF_3CO_2H), doublet 9·7 ppm, [1] $J = 5$ c/s, (C_1), doublet 8·35 ppm,

[1] J = 5 c/s, (C_8), singlet 5·1 ppm, [2] (—CH_3CO—). (Found: C, 62·19; H, 5·60; N, 3·61. $C_{21}H_{21}NO_5HCl$ requires: C, 62·27; H, 5·48; N, 3·46%.)

4-(*β-Hydroxy*-3,4-*dimethoxyphenylethyl*)7,8-*dimethoxyisoquinoline* (**38**). Reduction of **37** with $NaBH_4$ in EtOH yielded almost quantitatively **38** as a colourless glass which did not crystallise; ν_{max} cm^{-1}, 1625, 1610; λ_{max} mμ, 233, 277, 342, 357. The methiodide was obtained as a pale brown amorphous solid, m.p. 100–102° (from EtOH—ether). NMR singlet 9·5 ppm, [1] (C_1), singlet 8·5 ppm [1] (C_3), singlet 2·6 ppm, [3] (NMe). (Found: C, 51·36; H, 5·04; N, 2·76. $C_{22}H_{26}NO_5I$ requires: C, 51·65; H, 5·13; N, 2·74%.)

4-(3,4-*Dimethoxyphenylstyryl*) 7,8-*dimethoxyisoquinoline* (**39**). A soln of **38** (500 mg) in $CHCl_3$ (100 ml) was saturated with HCl as described for the prep of **32**, and the solvent was then removed to yield **39** as the hydrochloride salt as yellow microprisms m.p. 188–189° (dec) from acetone; ν_{max} cm^{-1}, 1642, 1618, 1608. The free isoquinoline, pale yellow prisms, m.p. 129°, from EtOH, was obtained by basification with aqueous ammonia; ν_{max} cm^{-1}, 1640, 1630, 1605; λ_{max} (ε) mμ, 238 (40,100), 370 (20,410). NMR singlet 9·4 ppm, [1] (C_1), 8·6 ppm [1] (C_3), Complex seven proton multiplet 6·7–7·8 ppm. (Found: C, 71·67; H, 5·90; N, 4·04. $C_{31}H_{31}NO_4$ requires: C, 71·78; H, 6·02; N, 3·99%.)