1,2-Dihydroisoquinolines. Part XIII.† Synthesis of Sanguinarine Chloride

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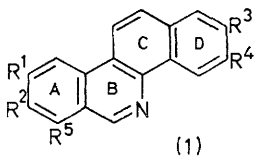
The first synthesis of sanguinarine chloride (2,3:7,8-bismethylenedioxybenzo[*c*]phenanthridine methochloride), from 2-hydroxy-3-methoxybenzaldehyde, is described.

We have previously [1] described the development of the synthetic route followed by Abramovitch and Tertzakian [2] to give the benzo[*c*]phenanthridine ring system, and outlined the preparation of the derivatives (1a—c).



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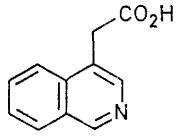
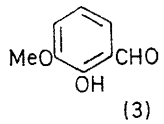


(2)

a; $R^1 = R^2 = R^3 = R^4 = OMe$, $R^5 = H$
b; $R^1R^2 = R^3R^4 = CH_2O_2$, $R^5 = H$
c; $R^1 = R^2 = OMe$, $R^3R^4 = CH_2O_2$, $R^5 = H$
d; $R^1 = H$, $R^2R^5 = R^3R^4 = CH_2O_2$
e; $R^1 = R^2 = R^3 = R^4 = R^5 = H$

The success of the method hinged upon the discovery of a simple, one-step synthesis of isoquinoline-4-acetic acid derivatives (2) from benzylaminoacetaldehyde dimethyl acetals. In principle this route to the benzo[*c*]phenanthridines should be applicable to the 2,3,7,8-tetraoxygenated compounds, as well as to the 2,3,8,9-tetraoxygenated derivatives, and we now [3] describe the first synthesis of the alkaloid sanguinarine chloride, the methochloride of the bismethylenedioxy-derivative (1d). The method called for 2,3-methylenedioxybenzaldehyde (5) as starting material. This was originally obtained by Perkin and Trikojus [4] but our preparation starts from 2-hydroxy-3-methoxybenzaldehyde (3), treatment of which with potassium hydroxide gave 2,3-dihydroxybenzoic acid (4; R = OH).

The potassium salt of (4; R = OH) was then treated with di-iodomethane to yield [5] the acid (4; RR = CH_2O_2), the acid chloride of which was reduced by the Rosenmund method to the aldehyde (5). The overall yield from (3) was 15%. The remaining steps in the



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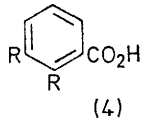

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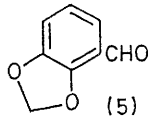


(5)

synthesis of sanguinarine chloride are summarised in Scheme 1, with optimum yields of each step indicated; the overall yield of (1d) from (3) was 0·6%. The final product, the methochloride of (1d), was identical (u.v. and i.r. spectra and mixed m.p.) with an authentic ‡ specimen of sanguinarine chloride.

It is possible to distinguish between a 2,3,8,9-tetraoxygenated benzo[*c*]phenanthridine and the isomeric 2,3,7,8-tetraoxygenated derivatives by a comparison of u.v. spectra. Thus derivatives (1b and c) show $\lambda_{max.}$ 230 and 277 nm., whereas (1d) shows $\lambda_{max.}$ 244 and 282 nm. The n.m.r. spectral data for the benzo[*c*]phenanthridines that we have synthesised are collected in the Table. The methylenedioxy-system on ring D always resonates at a lower field than that attached to ring A. The 6-proton is the one with the highest chemical shift. In each case the 11- and 12-protons resonate as an AB quartet with J 9 Hz.

The mass spectra of (1b) and (1d) are very similar, with the molecular ions as the base peaks. The fragmentation (Scheme 2) consists of a stepwise loss of HCHO and CO followed by expulsion of HCN; this

† Part XII, S. F. Dyke, M. Sainsbury, D. W. Brown, and M. N. Palfreyman, *Tetrahedron*, 1969, **25**, 5345.

‡ Obtained from Dr. J. Slavik, Institute of Medicinal Chemistry, Purkyne University, Czechoslovakia.

[1] S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron*, 1968, **24**, 1467.

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

[3] Preliminary communication, S. F. Dyke, B. J. Moon, and M. Sainsbury, *Tetrahedron Letters*, 1968, 3933.

[4] W. H. Perkin and V. M. Trikojus, *J. Chem. Soc.*, 1926, 2925.

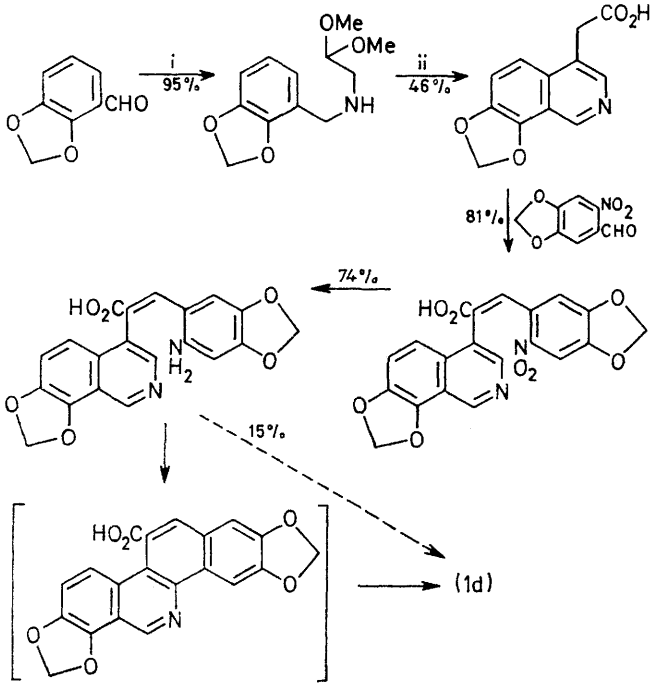
[5] W. Bonthrone and J. W. Cornforth, *J. Chem. Soc.* (*C*), 1969, 1202.

interpretation is substantiated by the appearance of the corresponding metastable ions and doubly charged species. The mass spectra of (1a) and (1c) are more

N.m.r. spectra of benzo[*c*]phenanthridines (1b—d) (p.p.m. downfield from internal tetramethylsilane; solvent trifluoroacetic acid)

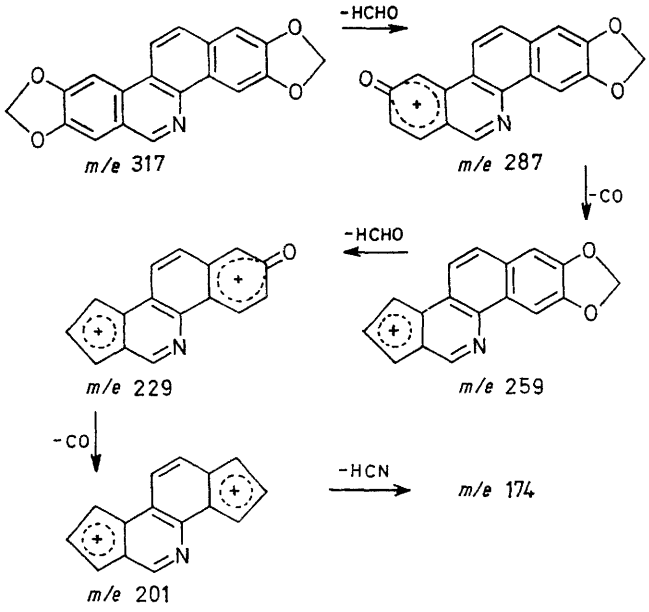
	(1b)	(1c)	(1d)
H-1	7·23	7·34	7·28
H-4	7·54	7·73	8·26
H-6	9·10 (d, *J* 6 Hz)	9·30 (d, *J* 6 Hz)	9·38
H-7	7·91	8·10	
H-9			8·18 (d, *J* 10 Hz)
H-10	7·73	7·97	7·65 (d, *J* 10 Hz)
H-11	8·12 (d, *J* 9 Hz)	8·36 (d, *J* 9 Hz)	8·33 (d, *J* 9 Hz)
H-12	7·84 (d, *J* 9 Hz)	8·04 (d, *J* 9 Hz)	7·90 (d, *J* 9 Hz)
8-OMe		4·25 and 4·39	
9-OMe			
Ring D CH_2O_2	6·21	6·22	6·24
Ring A CH_2O_2	6·40		6·53

complex than those of the bis-methylenedioxy-compounds, owing to the fact that methoxy-groups can

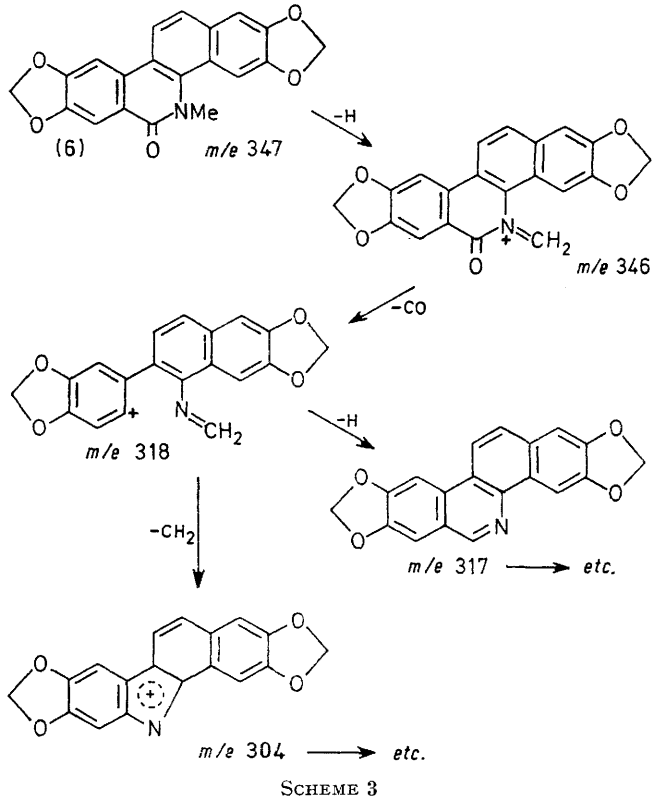


SCHEME 1 Reagents: i, (a) $H_2N{\cdot}CH_2{\cdot}CH(OMe)_2$, (b) H_2–Pt; ii, $OHC{\cdot}CO_2H$

fragment in more than one way, and it has not proved possible to formulate detailed fragmentation schemes in these cases. The mass and n.m.r. spectra of some metho-salts, *e.g.* of (1d), and of some pseudo-salts derived from these, have been discussed previously.[6] The mass spectrum of oxyavicine (6) exhibits an intense (M — 1) peak (85%); this ion shows loss of CO and then of a proton. The fragmentation shown in Scheme 3 is supported by the observation of the appropriate meta-stable ions. The fragmentations of the ions at *m/e* 317 and 304 are similar to those observed for (1b); presumably similar processes are involved.



SCHEME 2



SCHEME 3

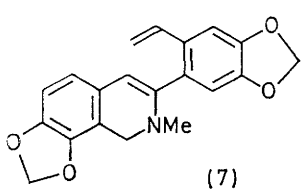
Since completion of our work, some new syntheses of the benzo[*c*]phenanthridine ring system [7,8] and a second

[6] J. Slavik, L. Dolejs, V. Hanus, and A. D. Cross, *Coll. Czech. Chem. Comm.*, 1968, **33**, 1619.

[7] S. V. Kessar and M. Sing, *Tetrahedron Letters*, 1969, 1155.

[8] I. Ninomiya, T. Naito, and T. Mori, *Tetrahedron Letters*, 1969, 3643.

synthesis of sanguinarine chloride, involving photolysis of anhydroprotopine (7), have been reported.[9] Some new benzo[*c*]phenanthridine alkaloids recently described[10] contain 'extra' methoxy-groups [*e.g.* macarpine (8)]; we are currently investigating synthetic routes to them.



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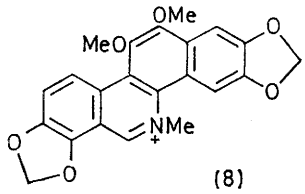

(8)

EXPERIMENTAL

U.v. spectra were measured for solutions in ethanol and i.r. spectra for Nujol mulls. N.m.r. spectra were recorded with a Varian A60 spectrometer; chemical shifts are expressed in p.p.m. downfield from internal tetramethylsilane. Mass spectra were recorded with an A.E.I. MS902 instrument.

2,3-*Dihydroxybenzoic Acid.*—A mixture of sodium hydroxide (28 g.), potassium hydroxide (111 g.), and water (17 ml.) was heated to 160° in a stainless steel beaker (1 l.). 2-Hydroxy-3-methoxybenzaldehyde (50 g.) was added with stirring over five min. After the exothermic reaction (CHO ⟶ CO_2H), the temperature was raised to 250° and maintained there for 30 min., after which the vigorous reaction (OMe ⟶ OH) had subsided. The mixture was cooled to 160° with stirring and water was added (330 ml.). It was then transferred to a beaker (3 l.) and water (170 ml.) was added. Sulphur dioxide was passed through for 2 min. (to prevent excessive colouring) and then 6N-hydrochloric acid (500 ml.) was added. After 48 hr. at 1°, the product was collected and dried under reduced pressure. This gave 2,3-dihydroxybenzoic acid (35·5 g, 71%) as buff-coloured needles, m.p. 200—202° (lit.,[4] 200°).

2,3-*Methylenedioxybenzoic Acid.*—2,3-Dihydroxybenzoic acid (95 g.) was suspended in water (180 ml.). Nitrogen was passed through the apparatus to expel air, and potassium hydroxide (103 g.) in water (400 ml.) was added slowly, followed by methylene iodide (50 ml.) and ethanol (250 ml.). This mixture was heated under reflux and stirred vigorously to disperse the methylene iodide for 18 hr. under nitrogen. It was then steam-distilled to remove the excess of methylene iodide, cooled under a stream of nitrogen, and acidified with concentrated hydrochloric acid. The product gave 2,3-methylenedioxybenzoic acid (44·2 g., 43%) as tan-coloured prisms, m.p. 226—227° (from ethanol) (lit.,[4] 227°). 2,3-Methylenedioxybenzoic acid (33·0 g.) was heated under reflux with thionyl chloride for 2 hr. The excess of thionyl chloride was distilled off and the crude product was distilled under reduced pressure (160°/20 mm.) to give 2,3-methylenedioxybenzoyl chloride (31·2 g., 85%), which yielded colourless needles, m.p. 116° (from xylene) (lit.,[4] 116°).

2,3-*Methylenedioxybenzaldehyde.*—2,3-Methylenedioxybenzoyl chloride (30·0 g.) was dissolved in sodium-dry xylene (500 ml.). 5% palladium–barium sulphate (3·5 g. was added, together with fresh quinoline-S catalyst poison [0·35 ml.; prepared by heating flowers of sulphur (1 g.) and quinoline (6 ml.) under reflux for 6 hr. and then diluting the product to 100 ml. with sodium-dry xylene]. The solution was hydrogenated under reflux with rapid stirring until evolution of hydrogen chloride ceased. The catalyst was filtered from the hot solution, and the xylene was distilled off under reduced pressure to leave the crude aldehyde, which was steam distilled. The aqueous distillate was extracted with ether, dried (Na_2SO_4), and evaporated to give 2,3-methylenedioxybenzaldehyde (13·9 g., 57%) as an oil which gradually solidified to a colourless solid (lit.,[4] m.p. 34°), δ 6·05 (2H, s, CH_2O_2) 7·0 (3H, m, aromatic protons), and 10·07 (1H, s, CHO) p.p.m.

2,3-*Methylenedioxybenzylaminoacetaldehyde Dimethyl Acetal.*—2,3-Methylenedioxybenzaldehyde (13·5 g.) and aminoacetaldehyde dimethyl acetal (9·5 g.) were condensed in ethanol (100 ml.). Adams platinum oxide (0·1 g.) was added and the mixture was hydrogenated at atmospheric pressure. After removal of the catalyst and ethanol, the residue was distilled (120°/0·15 mm.) to give the aminoacetal (20·5 g., 95%) as a colourless oily liquid, δ (CCl_4) 1·60 (1H, s, NH, exchangeable), 2·63 (2H, d, CH_2·CH<), 3·26 (6H, s, 2 × OMe), 3·7 (2H, s, CH_2·NH), 4·38 (1H, t, >CH·CH_2), 5·85 (2H, s, CH_2O_2), and 6·7 (3H, m, aromatic protons) p.p.m.

7,8-*Methylenedioxyisoquinolin*-4-*ylacetic Acid Hydrochloride.*—2,3-Methylenedioxybenzylaminoacetaldehyde dimethyl acetal (20 g.) in 6N-hydrochloric acid (400 ml.) was stirred at room temperature for 24 hr. under nitrogen. The solution was then heated on a water-bath for 10 min. and glyoxylic acid (8·5 g.) was added in 2N-hydrochloric acid (20 ml.). The mixture was heated for 1 hr. under nitrogen on a water-bath. The product was collected and recrystallised from 2N-hydrochloric acid to give the *isoquinolinylacetic acid hydrochloride* (10·3 g., 46%) as orange needles, m.p. 209° (decomp.) (Found: C, 54·1; H, 3·7; N, 5·5. $C_{12}H_{10}ClNO_4$ requires C, 53·9; H, 3·8; N, 5·2%), $\nu_{max.}$ 1700 (CO_2H) cm.$^{-1}$, $\lambda_{max.}$ 210 (ε 21,000), 240 (23,700), 302 (2200), and 379 (2500) nm., $\lambda_{min.}$ 224 (9700) and 335 (800) nm., δ (CF_3·CO_2H) 4·45 (2H, s, CH_2), 6·52 (2H, s, CH_2O_2), 7·99 (2H, s, aromatic protons), 8·44 (1H, s, H-3), and 9·61 (1H, s, H-1).

trans-4,5-*Methylenedioxy*-α-(7,8-*methylenedioxyisoquinolin*-4-*yl*)-2-*nitrocinnamic Acid.*—7,8-Methylenedioxyisoquinolin-4-ylacetic acid hydrochloride (6·0 g.), 2-nitro-4,5-methylenedioxybenzaldehyde[11] (4·2 g.), sodium acetate (1·8 g.), acetic anhydride (90 ml.), and triethylamine (60 ml.), were heated for 2 hr. under reflux. The resulting solution was poured hot into boiling water (300 ml.), and the mixture was boiled with rapid stirring for 10 min. On cooling the product separated, and was collected and dried to give a yellow solid (7·4 g., 81%). This material, as the hydrochloride, crystallised from 2N-hydrochloric acid as yellow *needles*, m.p. 238° (decomp.) (Found: C, 52·3; H, 3·4; N, 6·0. $C_{20}H_{13}ClN_2O_8,H_2O$ requires C, 51·9; H, 3·3; N, 5·8%), $\nu_{max.}$ 1710 (CO_2H) and 2580 (NH^+) cm.$^{-1}$, $\lambda_{max.}$ 209 (ε 34,100), 243 (34,500), and 373 (7600) nm., $\lambda_{min.}$ 225 (21,500) and 329 (5500) nm., δ (CF_3·CO_2H) 6·01 (2H, s, CH_2O_2 on ring D), 6·43 (1H, s, CH=C), 6·48 (2H, s, CH_2O_2 on ring A), 7·67 (1H, s, cinnamic 6-H), 7·89 (2H, s, isoquinoline 5- and 6-H), 8·21 (1H, s, isoquinoline 3-H), 8·90 (1H, s, cinnamic 3-H), and 9·52 (1H, s, isoquinoline 1-H).

[9] M. Onda, K. Yonezawa, and K. Abe, *Chem. and Pharm. Bull. Japan*, 1969, **17**, 404.

[10] J. Slavik, L. Slavikova, and K. Haisova, *Coll. Czech. Chem. Comm.*, 1967, **32**, 4420.

[11] A. H. Salway, *J. Chem. Soc.*, 1909, **95**, 1163.

trans-2-*Amino*-4,5-*methylenedioxy*-α-(7,8-*methylenedioxyisoquinolin*-4-*yl*)*cinnamic Acid*.—A hot solution of iron(II) sulphate (12 g.) in water (40 ml.) was added to a hot solution of the nitro-compound just described (2·0 g.) in ammonia (*d* 0·880; 60 ml.) with vigorous stirring. The mixture was heated on a water-bath for 10 min. and filtered. The filtrate was neutralised with glacial acetic acid and left for 24 hr. This gave the amino-acid as a brown solid (1·37 g., 74%), $\nu_{max.}$ 3350 and 3200 (N·CH_2) cm.$^{-1}$, which could not be purified for analysis and was not sufficiently soluble in trifluoroacetic acid or any of the other available solvents for an n.m.r. spectrum to be obtained.

2,3,7,8-*Bismethylenedioxybenzo*[c]*phenanthridine*.—The aforementioned amino-acid (3·0 g.) in 2N-hydrochloric acid (180 ml.) was diazotised with sodium nitrite (0·80 g.) in water (60 ml.). The excess of nitrous acid was decomposed with urea, and copper powder (3·0 g.) was added. The mixture was stirred for 5 hr. at room temperature and filtered. This product was dried under reduced pressure, and heated at 230° for 20 min. in quinoline; decarboxylation took place. Water was added and the mixture was steam-distilled to remove the quinoline (20 ml.). The solid residue was dried and extracted (Soxhlet) with chloroform for 48 hr. The chloroform was removed and the residue was sublimed (240°/0·05 mm.). Recrystallisation of the sublimate from pyridine gave 2,3:7,8-bismethylenedioxybenzo[*c*]phenanthridine (0·375 g., 15%) as pale yellow needles, m.p. 280—281° (decomp.) (Found: C, 72·1; H, 3·5; N, 4·5. Calc. for $C_{19}H_{11}NO_4$: C, 71·9; H, 3·5; N, 4·4%), $\nu_{max.}$ 1645 (C=N) cm.$^{-1}$, $\lambda_{max.}$ 215 (ε 20,100), 244 (46,300), and 282 (35,800) nm., $\lambda_{min.}$ 224 (16,800) and 265 (22,600) nm., $\lambda_{infl.}$ 295 (27,700) and 330 (15,300) nm.

Sanguinarine Chloride.—2,3,7,8-Bismethylenedioxybenzo[*c*]phenanthridine (100 mg.) was heated under reflux with dry xylene (20 ml.). Freshly distilled dimethyl sulphate (0·5 ml.) was added and the mixture was heated under reflux for 1 hr., then cooled. The orange precipitate was collected, washed with benzene and petroleum (b.p. 40—60°), and dried to give the methosulphate (121 mg.), m.p. 238—240° (decomp.). This was heated under reflux with water (20 ml.) for 15 min.; the solution was then filtered, acidified with a few drops of concentrated hydrochloric acid, and left overnight. Fine orange needles which separated gave sanguinarine chloride, m.p. 273—274° (decomp.) (from 2N-hydrochloric acid), identical with the natural product from *Sanguinaria canadensis* (mixed m.p. and i.r. and u.v. spectra). The m.p. is sensitive to the rate of heating (Found: C, 59·4; H, 4·5. Calc. for $C_{20}H_{14}ClNO_4,2H_2O$: C, 59·5; H, 4·5%), $\nu_{max.}$ 1640 (C=N) and 3340 (H_2O) cm.$^{-1}$, $\lambda_{max.}$ 277 (ε 45,100) and 330 (34,800) nm., $\lambda_{min.}$ 302 (14,600) nm.

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