The Synthesis of Some Substituted Pyoluteorins

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The syntheses of *NOO*-trimethylpyoluteorin, *N*-methylpyoluteorin, and N-benzylpyoluteorin are described.

HALOGENO-SUBSTITUTED pyrroles are rare in nature; all known examples are bacterial products. Three of these compounds: pyoluteorin (Ia), pyrrolnitrin [1] (II), and isopyrrolnitrin [2] (III) are metabolites of *Pseudomonas* spp. and are chloropyrroles. The fourth compound (IV), isolated from marine bacteria, is a bromopyrrole.[3]

Pyoluteorin (Ia), isolated by Takeda from certain strains of *Pseudomonas aeruginosa* grown on a bouillon containing chloride ion, has powerful antibiotic properties.[4] The structure (Ia) was elucidated by Birch, Takeda, and their collaborators.[5,6]

Previous synthetic approaches to pyoluteorin (Ia) terminated at didechloro-*OO*-dimethylpyoluteorin (V), since this compound could not be either demethylated or chlorinated in the desired manner.[6] An attractive route to *NOO*-trimethylpyoluteorin involves aroylation of the readily accessible 1-lithio-2,6-dimethoxybenzene (VIa). Birch, Takeda, and their collaborators investigated the benzoylation of this derivative without success.[6] This result appeared anomalous in view of the work of Baeyer, who claimed that the Grignard reagent derived from 1-iodo-2,6-dimethoxybenzene (VIb) reacted as expected with ethyl formate.[7]

Consequently we have reinvestigated the aroylation route. Treatment of a suspension of 1-lithio-2,6-dimethoxybenzene (VIa) in ether with 4,5-dichloro-1-methylpyrrole-2-carbonyl chloride (VIIa) gave *NOO*-trimethylpyoluteorin (Ib) (45%). The synthetic trimethyl compound was identical with the trimethyl derivative of the natural material.

If the acid chloride (VIIa) was treated with a large excess of 1-lithio-2,6-dimethoxybenzene, nucleophilic replacement of the 5-chlorine atom occurred in addition to replacement of the chlorine on the side-chain, and the benzoylphenylpyrrole (VIII) formed was identified from its spectroscopic properties. In particular the large bathochromic shift (50 mμ) of the long-wavelength absorption band in the electronic spectrum [cf. *NOO*-trimethylpyoluteorin (Ia)] is characteristic of 5- rather than 4-aryl substitution.[8] The marked shielding of the *N*-methyl protons in the n.m.r. spectrum can only be accounted for by the presence of an adjacent aryl ring, twisted slightly from the plane of the pyrrole nucleus by steric interaction. This confirms the position of the 2′,6′-dimethoxyphenyl group.

In a similar manner 1-lithio-2,6-di(tetrahydropyranyloxy)benzene (VIc) (1 mol.) was treated separately with the acid chloride (VIIa) and the acid chloride (VIIb); aqueous acidic hydrolysis of the products led to *N*-methylpyoluteorin (Ic) and *N*-benzylpyoluteorin (Id), respectively. Attempts to produce pyoluteorin (Ia) by debenzylation of the latter compound under a wide variety of conditions resulted in recovery of the starting material, or in extensive degradation of the molecule.

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[3] F. M. Lovell, *J. Amer. Chem. Soc.*, 1966, **88**, 4510; S. Hanessian and J. S. Kaltenbroom, *ibid.*, p. 4509.

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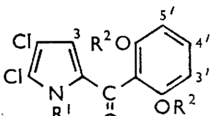
[5] R. Takeda, *J. Amer. Chem. Soc.*, 1958, **80**, 4749; *Bull. Agric. Chem. Soc. Japan*, 1959, **23**, 126, 165.

[6] A. J. Birch, P. Hodge, R. W. Rickards, R. Takeda, and T. R. Watson, *J. Chem. Soc.*, 1964, 2641.

[7] A. Baeyer, *Annalen*, 1910, **372**, 80.

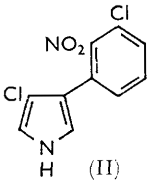
[8] R. W. Guy and R. A. Jones, *Austral. J. Chem.*, 1966, **19**, 1871.

The reaction of 1-lithio-2,6-di(tetrahydropyranolyoxy) benzene (VIc) with 4,5-dichloropyrrole-2-carbonyl chloride (VIIc) did not give pyoluteorin.



(I)

a ; $R^1 = R^2 =$ H
b ; $R^1 = R^2 =$ Me
c ; $R^1 =$ Me , $R^2 =$ H
d ; $R^1 = CH_2Ph$, $R^2 =$ H



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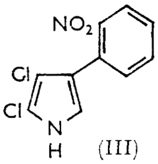

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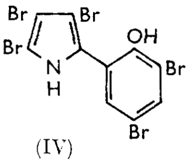
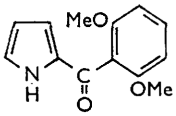
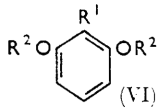


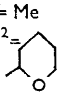
(IV)

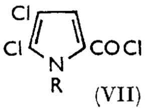


(V)



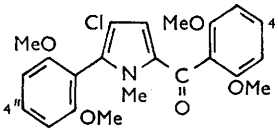
(VI)

a; $R^1 =$ Li, $R^2 =$ Me
b; $R^1 =$ I, $R^2 =$ Me
c; $R^1 =$ Li, $R^2 =$ 



(VII)

a ; R = Me
b ; R = CH_2Ph
c ; R = H



(VIII)

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus, infrared spectra with a Perkin-Elmer 257 grating spectrophotometer, and ultraviolet spectra (ethanol) with a Cary model 14-50 spectrophotometer. N.m.r. spectra were determined at 60 or 100 Mc./sec. Molecular weights were determined by mass spectrometry on an A.E.I. MS 9 instrument by the direct insertion technique. Silicic acid was Mallinckrodt 100 mesh analytical reagent, unless stated otherwise.

NOO-*Trimethylpyoluteorin* (Ib).—To a stirred suspension of 1-lithio-2,6-dimethoxybenzene in absolute ether (5 ml.), prepared from 1,3-dimethoxybenzene [9] (0·7 g.), was added, in 1 portion, 4,5-dichloro-1-methylpyrrole-2-carbonyl chloride [6] (1·0 g.) in benzene (1·0 ml.). A vigorous exothermic reaction ensued. The reaction mixture was set aside at room temperature for 1·5 hr., and was then poured into water. The organic layer was extracted into ether, and the ethereal solution was washed twice with dilute ammonia and several times with water, and dried ($MgSO_4$). The extract was concentrated and adsorbed on to a column of silicic acid (25 × 2·5 cm.). The column was eluted with 30% ether in pentane and 100-ml. fractions were collected. Fractions 5 and 6 yielded the *trimethyl compound* (0·66 g., 45%) as prisms, m. p. and mixed m. p. 136—137° [from ether (charcoal)] (lit.,[5] 135—136°) (Found: C, 53·7; H, 4·15; Cl, 23·0; N, 4·2%; *M*, 313, 315. $C_{14}H_{13}Cl_2NO_3$ requires C, 53·5; H, 4·15; Cl, 22·6; N, 4·45%; *M*, 313, 315), $\nu_{max.}$ (CCl_4) 1650 cm.$^{-1}$ (C=O), $\lambda_{max.}$ 258 and 304 mμ (ε 6800 and 18,600), τ ($CDCl_3$) 6·26 (6H, *O*-methyl), 5·92 (3H, *N*-methyl), 3·57 (1H, singlet, 3-H), 3·40 and 3·41 (2H pair of doublets, *J* = 7·5 and 9·0 c./sec., 3'- and 5'-H), and 2·67 (1H quartet, *J* = 7·5 and 9·0 c./sec., 4'-H).

4-*Chloro*-2-(2,6-*dimethoxybenzoyl*)-5-(2,6-*dimethoxyphenyl*)-1-*methylpyrrole* (VIII).—This compound was prepared in a similar manner to *NOO*-trimethylpyoluteorin except for the use of 4 equiv. of the lithio-compound. The residue from concentration of the dried ether extract yielded the *ketone* (70%) as pale yellow prisms, m. p. 221—223° [from chloroform–methanol (charcoal)] (Found: C, 63·0; H, 5·35; Cl, 8·25; N, 3·2%; *M*, 415, 417. $C_{22}H_{22}ClNO_5$ requires C, 63·55; H, 5·35; Cl, 8·5; N, 3·35%; *M*, 415, 417), $\lambda_{max.}$ 262 and 355 mμ (ε 16,400 and 17,800), $\nu_{max.}$ ($CHCl_3$) 1675 cm.$^{-1}$ (C=O), τ ($CDCl_3$) 7·12 (3H singlet, *N*-methyl), 6·36 and 6·33 (6H singlets, *O*-methyl), 3·50 and 3·42 (4H pair of doublets, 3',5' and 3'',5''-H), 3·23 (1H singlet, 3-H), and 3·66—3·86 (2H, two quartets, 4'- and 4''-H).

Methyl 1-*Benzyl*-4,5-*dichloropyrrole*-2-*carboxylate*.—Methyl 4,5-dichloropyrrole-2-carboxylate [10] (2·6 g.), anhydrous potassium carbonate (5 g.), and benzyl chloride (2 ml.) in acetone (75 ml.) were heated under reflux for 10 hr., and the reaction mixture was worked up in the usual way to give the *ester* (4·0 g., 98%) as prisms, m. p. 88—89° [from light petroleum (b. p. 60—80°) (Found: C, 55·1; H, 3·8; Cl, 24·7; N, 4·5. $C_{13}H_{11}Cl_2NO_2$ requires C, 54·95; H, 3·9; Cl, 24·95; N, 4·9%), $\lambda_{max.}$ 237 and 277 mμ (ε 6700 and 13,100), τ ($CDCl_3$) 6·32 (3H singlet), 4·40 (2H singlet), 3·08 (1H singlet, 3-H), and *ca.* 2·7—3·0 (5H multiplet).

1-*Benzyl*-4,5-*dichloropyrrole*-2-*carboxylic Acid*.—The methyl ester was hydrolysed with aqueous methanolic potassium hydroxide. The *acid* (83%) gave needles, m. p. 159—162° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 53·5; H, 3·4; Cl, 26·75; N, 4·95. $C_{12}H_9Cl_2NO_2$ requires C, 53·35; H, 3·3; Cl, 26·85; N, 5·2%).

N-*Benzylpyoluteorin* (Id).—1-Lithio-2,6-di(tetrahydropyranyloxy)benzene was prepared from 1,3-di(tetrahydropyranyloxy)benzene [11] (1·8 g.). 1-Benzyl-4,5-dichloropyrrole-2-carbonyl chloride was formed by heating the corresponding carboxylic acid (1·69 g.) under reflux with benzene (20 ml.) and thionyl chloride (20 ml.). After 3 hr. the solvents were removed under reduced pressure and traces of thionyl chloride were removed by azeotropic distillation with more benzene. To a stirred solution of the lithio-compound in absolute ether (30 ml.) was added (1 portion) a solution of the acid chloride in absolute benzene (5 ml.). The reaction mixture was stirred at room temperature for 1 hr., and the solvent was removed under reduced pressure. The residue was dissolved in acetone (10 ml.), diluted with 3N-hydrochloric acid (40 ml.), and stirred at room temperature (1·5 hr.). The mixture was then exhaustively extracted with ether and the organic layer was washed with water and extracted with 10% sodium hydroxide (2 × 25 ml.). This extract was washed with ether and acidified. The acidic solution was extracted several times with ether, and the combined extracts were washed with 0·5N-hydrochloric acid, dried ($MgSO_4$), and concentrated. The residue was adsorbed on to a column of silicic acid (B.D.H.; 30 × 2·75 cm.) and eluted with 30% ether in pentane; 100-ml. fractions were collected. Fraction 6 yielded the crude product (0·25 g., 9%), which was rechromatographed on silicic acid (20 × 2 cm.) with 20—25% ether in pentane as eluent to give the *pyoluteorin* as pale yellow needles, m. p.

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[9] G. Wittig, "Newer Methods of Preparative Organic Chemistry," Interscience, New York, 1948, p. 579.

[10] P. Hodge and R. W. Rickards, *J. Chem. Soc.*, 1965, 459.

[11] W. E. Parham and E. L. Anderson, *J. Amer. Chem. Soc*, 1948, **70**, 4187.

137—139° (from ether–pentane) (Found: C, 59·95; H, 3·85; Cl, 19·35; N, 3·7%; *M*, 361, 363. $C_{18}H_{13}Cl_2NO_3$ requires C, 59·7; H, 3·6; Cl, 19·6; N, 3·9%; *M*, 361, 363), $\lambda_{max.}$ 260 and 306 mμ (ε 7000 and 15,800), $\nu_{max.}$ (CH_2Cl_2) 1630 cm.$^{-1}$ (C=O), τ ($CDCl_3$) 4·36 (2H, CH_2), 3·64 and 3·56 (each 1H, 3′- and 5′-H), 3·14 (1H, 3-H), and *ca.* 2·6—3·0 (6H, 4′- and phenyl H).

N-*Methylpyoluteorin* (Ic).—The procedure was identical with that described for *N*-benzylpyoluteorin except that 4,5-dichloro-1-methylpyrrole-2-carbonyl chloride (0·5 g.) was used. *N*-Methylpyoluteorin (0·18 g., 24·5%) was obtained as pale yellow prisms, m. p. 142—144° (decomp.) with sintering at 128°) [from ether–light petroleum (b. p. 40—60°)] (Found: C, 50·4; H, 3·05; Cl, 24·6; N, 4·8%; *M*, 285, 287. $C_{12}H_9Cl_2NO_3$ requires C, 50·35; H, 3·2; Cl, 24·8; N, 4·9%; *M*, 285, 287), $\lambda_{max.}$ 260 and 305 mμ (ε 6400 and 17,300), $\nu_{max.}$ ($CHCl_3$) 3360 (OH) and 1633 cm.$^{-1}$ (C=O), τ (CCl_4) 6·06 (3H singlet, *N*-methyl), 3·42 and 3·43 (2H pair of doublets, *J* = 7·8 and 9·0 c./sec., 3′- and 5′-H) 3·02 (1H singlet, 3-H), and 2·66 (1H quartet, *J* = 7·8 and 9·0 c./sec., 4′-H).

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