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THE TOTAL SYNTHESIS OF THE 4,5-DIOXOAPORPHINE ALKALOID PONTEVEDRINE[1]

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Pontevedrine (Ia) (2,3) is a member of the small group of 4,5-dioxoaporphine alkaloids which have been postulated to be directly related to the aristolactams and aristolochic acids (4) of known antitumor activity (5). Its structure has been established on the basis of spectral and chemical evidence (2,3). Only partial syntheses of cepharadione B (6) and pontevedrine (7) have been achieved by photochemical oxidation of the corresponding dehydroaporphines though in low yield.

Further to our synthetic study on the dioxoaporphine alkaloids, we can now report the first total synthesis of pontevedrine (Ia) by a route starting from the readily prepared ketoacid (IIa) using the novel photooxidation of the lactam (IIId) and the photocyclization of the 1-(6'-bromobenzylidene)-isoquinoline-3,4-dione (IVb) in the key stages. As pontevedrine (Ia) could easily be converted into the corresponding N-methyl aristolactam (3) by decarbonylation, this synthetic route appears to have a great potential capacity of application in the total synthesis of both types of related compounds.

It seemed to us that an attractive precursor of pontevedrine (Ia) could be the known lactam (IIIa) (8,9), which is readily prepared from the ketoacid (IIa) and in turn is made from the self condensation of homoveratric acid.

Nitration of (IIIa) with fuming nitric acid in glacial acetic acid afforded the nitro compound (IIIb) (10) as a yellow solid, m.p. 202-205°C., in 40% yield. Catalytic hydrogenation of IIIb (MeOH/Pd-C) gave the aminolactam (IIIc) and this without further purification was refluxed with 10% aq. HCl in methanol for about half an hour to give the 1-(benzylidene)-isoquinoline-3,4-dione (IVa) (11), m.p. 255-60°C., in 60% yield, which was isolated as a mixture of the E and Z isomers (2:8 ratio). It was expected that this mixture (IVa), having a stilbene-like system and the nitrogen atom protected as lactam (12) would undergo photocyclization to the pontevedrine skeleton. However, cis-trans isomerization appeared to be the only process observed.

To induce the photocyclization, the presence of Br at the 6' position

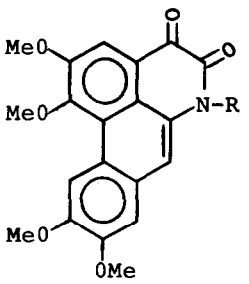
of IVa seemed to be the most promising approach. Since any attempt to brominate IIIa was unsuccessfull at that position, it was decided to introduce the bromine atom at the early stage of the ketoacid (IIa). Treatment of IIa with bromine in acetic acid gave IIb, m.p. 193-95°C., in 85% yield, which by reaction with ammonium acetate in acetic acid afforded the bromolactam (IIId), m.p. 261-62°C., in 95% yield. The nitration of this bromolactam (HNO_3/HOAc) gave the nitro compound (IIIe), m.p. 233-35°C., in 70% yield. Attempt to reduce the nitro group of IIIe by catalytic hydrogenation (MeOH/Pd-C) was accompanied by debromination, resulting IVa. Therefore, an alternative approach to functionalize ring B of the lactam (IIId) seemed necessary. Since it is known that 3-isoquinolones can act as dienes in Diels-Alder reactions (9), we expected that singlet oxygen could add to the lactam (IIId) to give the endoperoxide (V), a suitable intermediate to the desired dioxocompound (IVb).

A solution of the lactam (IIId) in methanol saturated with oxygen was irradiated with a medium pressure mercury lamp until complete disappearence of the starting material; removal of the solvent afforded in 95% yield the dioxo compound (VI) (13) [m.p. 196-97°C.; IR(KBr) $\nu_{max.}$ 1690 (broad, C=0) cm^{-1}; UV (EtOH) $\lambda_{max.}$ (log.ε) 213 (4,29), 245 (4,02), 292 (3,69), 340 (3,45) nm; pmr, δ($CDCl_3$) 7.45, 6.91, 6.87 and 6.26 (1H each,s,ArH), 6.68 (1H,bs,NH), 3.97, 3.94, 3.79 and 3.59 (3H each,s,Ar-OCH_3), 3.42(2H,dd,ArCH_2) and 3.17 ppm (3H,s,-C-OCH_3); m/e 479, 481 (M^+) and 250 (base peak)] . The C-13 nmr spectrum confirmed the structure (VI) by showing besides the methylene (49.71 ppm) and the alifatic methoxy group (51.07 ppm), a strongly deshielded tetrasubstituted carbon atom at 89.15 ppm.

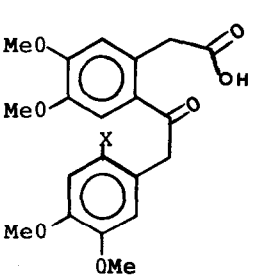
The formation of the dioxocompound (VI) can be regarded as proceeding by the opening of the endoperoxide (V) by the solvent (14). As expected, the dioxocompound (VI) readily eliminates MeOH under acid conditions (dioxane/10 % aq. HCl at 60°C. for a half an hour) to give a mixture of the E-Z isomers (IVb) in 95 % yield, from which the pure Z isomer was isolated by fractional crystallization [m.p. 252-54°C.; UV(EtOH) $\lambda_{max.}$ (log.ε) 244 (4.27), 296 (4.26) and 402 (4.08) nm; pmr, δ($CDCl_3$) 8.44 (1H,bs,NH), 7.61, 7.31, 7.12, 6.84 and 6.71 (1H each,s,ArH and C=CH), 4.06, 3.99, 3.90 and 3.87 ppm (3H each,s,OMe); m/e 447, 449 (M^+)] .

The photocyclization of the dioxocompound (IVb) was carried out in an ethanolic alkali solution (0.1M NaOH), under an argon atmosphere with Pyrex filtered light. From the reaction mixture, norpontevedrine (Ib) was isolated by preparative tlc in 43 % yield as a red compound [m.p. 284-86°C.; UV(EtOH) $\lambda_{max.}$ (log.ε) 238 (4.60). 313 (3.99), 325 (4.24) and 478 (3.95) nm; pmr, δ(DMSO-d_6) 8.92, 8.08, 7.43 and 7.37 (1H each,s,ArH), 4.06 (6H,s,2xOMe) and 3.93 ppm (6H,s,2xOMe); m/e 367 (M^+)] .

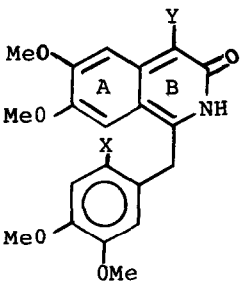
Finally, treatment of norpontevedrine (Ib) with NaH in dry DMF to prevent the decarbonylation of pontevedrine (Ia) (3), followed by the addition of methylfluorosulphonate at room temperature afforded in 76 % yield pontevedrine (Ia), identical in all respects with authentic specimen from natural sources (mp, tlc,



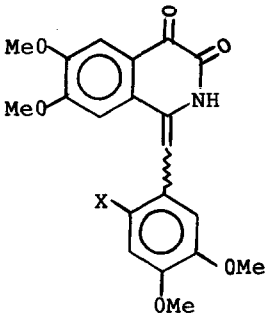
Ia, R=Me
Ib, R=H



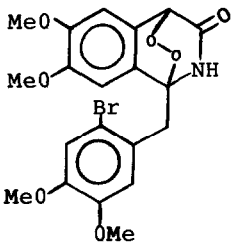
IIa, X=H
IIb, X=Br



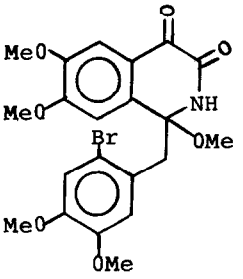
IIIa, X= Y= H
IIIb, X=H, Y=NO_2
IIIc, X=H, Y=NH_2
IIId, X=Br, Y=H
IIIe, X=Br, Y=NO_2



IVa, X=H
IVb, X=Br



V



VI

IR and NMR). Under these conditions, the competitive O-methylation of norpontevedrine was practically avoided.

According to the sequence IIId⟶ VI ⟶ IVb⟶ Ib, and once it was confirmed that VI could be converted into IVb under the mild basic conditions (MeOH/NaOH) required for the photocyclization step (IV ⟶ Ib), a "one pot" transformation of IIId into Ib should be achieved. In fact, irradiation of a solution of IIId in 0.1M NaOH methanolic solution, under oxygen atmosphere, gave norpontevedrine Ib in 23% yield.

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