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SYNTHESIS OF ANHYDROLYCORINE AND DIMETHYLAPOERYSOPINE

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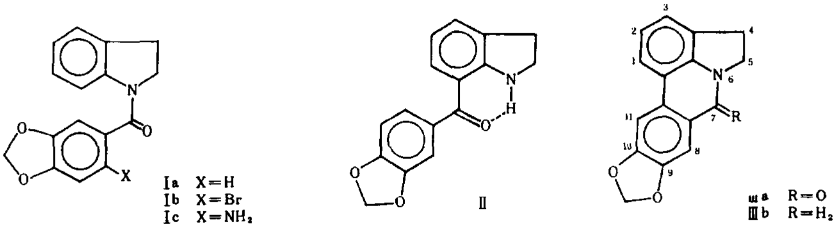
Recently photochemical reactions$^{1)}$ for the formation of biphenyl linkage were extensively studied to lead to the novel synthesis of aporphine alkaloids. From these facts photolysis of N-acylindolines was expected to give rise to lycorine derivatives. Therefore we undertook a preliminary experiment along these lines. Namely, N-piperonyloyl-, N-(6'-bromopiperonyloyl)- and N-(6'-bromohomoveratroyl)-indoline [(Ia), (Ib) and (IV)] were employed as the starting material and the results were obtained as follows.



Ia X=H
Ib X=Br
Ic X=NH$_2$

II

IIIa R=O
IIIb R=H$_2$

Chart 1.

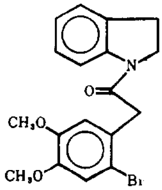
First, a solution of Ia (300 mg) in tetrahydrofuran (400 ml) was irradiated with a high pressure mercury lamp$^{2)}$ (400W) under nitrogen stream for 2 hr to afford an oil on usual work-up. The oil was chromatographed over silicic acid (Mallincrodt) to give, when eluted with chloroform, indole (31 mg, 23.5%) and 7-piperonyloylindoline$^{3)}$ (II) (32.3 mg, 11.2%) as yellow prisms, mp 116-118° (benzene-n-hexane), M^+ 267$^{4)}$; IRν_{Max}^{KBr}cm^{-1}: 3400, 1618; NMRτ ($CDCl_3$ at 100 MHz): 6.93 (2H, t, J=8.75 Hz, C_3-H), 6.23 (2H, t, J=8.75 Hz, C_2-H), 3.98 (2H, s, O-CH_2-O), 3.50 (1H, t, J=7.50 Hz, C_5-H), 3.15 (1H, d, J=7.50 Hz, aromatic H) and 2.88-2.66 (4H, m, aromatic H).

Further elution with chloroform gave piperonylic acid (8.7 mg, 4.7%).

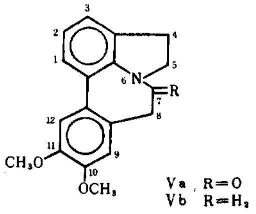
Thus it was apparent that in the reaction photo-Fries rearrangement was predominant over photocyclization. Change of solvent [isopropanol or tetrahydrofuran-benzene (1:1)] or addition of iodine did not alter the reaction course.

As a photo-Fries product, two isomeric structures could be considered. The following spectroscopic observation, however, would eliminate one of them, the p-structure; 1) peak due to C_7-H in the NMR spectrum of Ia was clearly lacking in that of II and 2) bands due to NH and C=O in the IR spectrum of solid state did not show any shift on successive dilution in carbon tetrachloride or chloroform suggesting the presence of an intense intramolecular hydrogen bond.

To induce effective photocyclization, dehydrobromination[1,5)] by photolysis was next examined. A solution of Ib (100 mg) in isopropanol (90 ml) was similarly photolyzed for 1 hr to afford, on usual work-up followed by purification over preparative TLC (silica gel), anhydrolycorin-7-one (IIIa) (51.4 mg, 67%) as pale yellow prisms, mp 232-234° (chloroform-methanol), M^+ 265[4)]; $IR\nu_{Max}^{KBr}cm^{-1}$: 1642; NMRτ ($CDCl_3$ at 100 MHz): 6.59 (2H, t, J=8.5 Hz, C_4-H), 5.53 (2H, t, J=8.50 Hz, C_5-H), 3.85 (2H, s, O-CH_2-O), 2.90-2.65 (2H, m, aromatic H), 2.49 (1H, s, aromatic H), 2.28 (1H, d, J=7.00 Hz, aromatic H) and 2.09 (1H, s, aromatic H). Structure of IIIa was proved unequivocally by mixed fusion with an authentic sample[6)] mp 232-234°, prepared by Pschorr reaction of the corresponding amino compound (Ic). $LiAlH_4$ reduction (15 hr, reflux) of IIIa in a mixture of tetrahydrofuran and ether (1:1) led to anhydrolycorine (IIIb), mp 108-111° (lit.[6)] mp 111-112°), in 65% yield.



IV



Va , R=O
Vb R=H_2

Chart 2.

Furthermore, to extend the reaction to a homologous series, the similar photolysis of IV was carried out. Contrary to the case of Ib, however, the reaction was unsuccessful. Finally, a solution of IV (376 mg) and sodium bisulfite$^{1c)}$ (125 mg) in a mixture of methanol (400 ml) and water (1 ml) was photolyzed similarly for 3 hr to furnish dimethylapoerysopin-7-one (Va) (13 mg, 4.4%), when purified over silicic acid (elution with chloroform) and subsequently on preparative TLC, as colorless prisms, mp 170-172° (acetone-n-hexane), IRν_{Max}^{KBr}cm^{-1}: 1655; NMRτ ($CDCl_3$ at 100 MHz): 6.87 (2H, t, J=7.50 Hz, C_4-H), 6.50 (2H, s, C_8-H), 6.16 (6H, s, OCH_3), 5.78 (2H, t, J=7.50 Hz, C_5-H), 3.09 (1H, s, aromatic H), 2.93, 2.82-2.65 (2H, m, aromatic H) and 2.46 (1H, q, J=7.00 Hz and 2.00 Hz, aromatic H). $LiAlH_4$ reduction (7 hr, reflux) of Va (60 mg) in a mixture of tetrahydrofuran and ether provided, after separation on preparative TLC (silica gel), dimethylapoerysopine (Vb) (20 mg, 35%) as colorless prisms, mp 107-109.5° (ether); picrate, mp 191-192.5° (methanol) (lit.$^{7)}$ mp 191-192°).

The structure was firmly established by comparision of its infrared spectrum (both free base and picrate) with that of an authentic sample and by mixed fusion of our picrate with Mondon's authentic one. Though the yield of Vb was not good enough, the present synthesis would be noted in its simplicity when compared to the known methods$^{8)}$.

Thus photocyclization of brominated N-acylindolines was proved successful to give readily anhydrolycorine or apoerysopine skeleton. It would be worthy for comment that formation of anhydrolycorine meant a formal synthesis of γ-lycorane and choice of a suitably substituted member of Ib would give a promise for a convenient construction of lycorine type alkaloids.

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2. Nikko Seiki Works, Tokyo, Model NY was used.
3. Satisfactory analyses were obtained for new compounds.
4. We thank Prof. S. Sakai, Chiba University, for measurement of mass spectrum.
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