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CHLORINATION OF 1-BENZYL- OR 1-PHENETHYLTETRAHYDROISOQUINOLINES via A p-QUINOL ACETATE

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Reaction of p-quinol acetates derived from 1-benzyl-(Ib and Ic) or 1-phenethyl-(Id, Ie and If) tetrahydroisoquinolines with conc. hydrochloric acid gave the corresponding 8-chloro derivatives in fair yields.

In continuation of our study on the synthesis of kreysigine[1)] and/or O-methylandrocymbine[2)] via a p-quinol acetate, we found the reaction of the p-quinol acetate with conc. hydrochloric acid yielding none of the desired but a chlorinated product.

As far as we aware, halogenation reaction of p-quinol acetates was rare. Therefore, the present paper reports a study of the general utility of the reaction; namely reaction of the p-quinol acetate from corypalline (Ia) with hydrochloric, hydrobromic or hydroiodic acid and of p-quinol acetate from 1-benzyl or 1-phenethyltetrahydroisoquinolines[1,3)] (Ib, Ic, Id, Ie or If) with hydrochloric acid.

To a solution of phenolic tetrahydroisoquinoline (If)(100 mg) in acetic acid (3 ml) was added lead tetraacetate (250 mg) in one portion and the whole was stirred at room temperature for 30 min to give a diastereoisomeric mixture of p-quinol acetates

(142 mg) , which without purification was treated with conc. hydrochloric acid (5 ml) for 2 h under stirring at room temperature. Usual work-up of the reaction mixture afforded an amorphous mass (100.5 mg), whose purification on preparative t.l.c.[4] gave a crystalline compound (IVc)[5] (62 mg, 57%), mp 134-140°. N.m.r.[6] δ: 2.42 (3H, S, NMe), 3.82 (12H, S, OMe X 4), 5.31 (1H, bs, OH), 6.47 (2H, S, aromatic H), 6.50 (1H, S, aromatic H); i.r.[7] ν_{max} cm^{-1}: 3520 (OH); m.s.[8] m/e: 421 (M^+), 423 ($M^+ + 2$); 226, 228[9] (each base peak). Two sets of characteristic peaks (relative intensity = 3:1) due to a monochloride structure in mass spectrum together with other spectral data and elemental analysis strongly suggested the structure of IVc as 5- or 8-chloro derivative of If.

To confirm the exact substitution pattern, a model experiment was undertaken. Namely, a p-quinol acetate from Ia was treated with 48% hydrobromic acid at room temperature for 2 h to leave a bromo-corypalline (IIb)(106 mg, 75%), mp 189-191°, whose recrystallization from isopropanol gave pale yellow needles of mp 193.5-194.5°. IIb was identical in all respects with an authentic sample[10] (mp 189-191°) of 8-bromocorypalline both by mixed fusion and i.r. comparison. Accordingly the structure of IVc was proved, though indirect, to be (±)-8-chloro-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxy)phenethylisoquinoline by analogy with the reaction mode in the case of Ia.

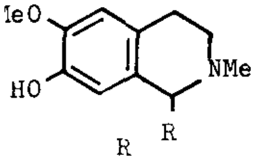
Similar reaction of p-quinol acetates from Ia, Ib, Ic, Id and Ie with conc. hydrochloric acid gave the corresponding 8-chloro derivatives, respectively. Yield of products and the melting point of their analytical samples were listed in

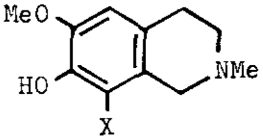
Table I.

	Yield, %	mp
IIa	78	196 - 198°
IIIa	43*	162 - 164°
IIIb	70.5*	145 - 147°
IVa	44*	100 - 103°
IVb	49*	109 - 111°
IVc	57*	145 - 146°

* After purification of the reaction mixture on preparative t.l.c.

Table I





R

Ia: H

Ib: 3,4-dimethoxybenzyl

Ic: 3,4-methylenedioxybenzyl

Id: 3,4-dimethoxyphenethyl

Ie: 3,4-methylenedioxyphenethyl

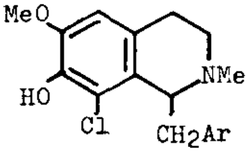
If: 3,4,5-trimethoxyphenethyl

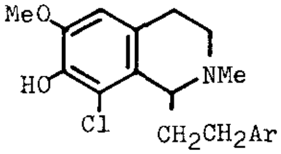
X

IIa: Cl

IIb: Br

IIc: I





Ar

IIIa: 3,4-dimethoxyphenyl

IIIb: 3,4-methylenedioxyphenyl

Ar

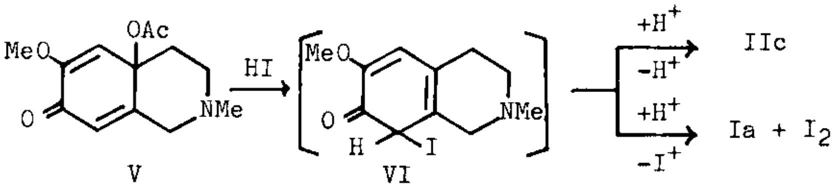
IVa: 3,4-dimethoxyphenyl

IVb: 3,4-methylenedioxyphenyl

IVc: 3,4,5-trimethoxyphenyl

Iodination of Ia by similar reaction deserved of special comment. When a p-quinol acetate from Ia was stirred with 38% hydroiodic acid under water-cooling, a reddish-violet oil deposited indicating that iodine was liberated in the reaction. Usual work-up followed by preparative t.l.c. furnished two products, in which the more polar was Ia (17 mg, 17%), mp 161-166°, and the less polar the expected iodo derivative (IIc) (18 mg, 11%), mp 147-153°, whose recrystallization from isopropanol gave pale yellow prisms, mp 159-160°. N.m.r. δ: 2.49 (3H, S, NMe), 3.43 (2H, S, C_1-H), 3.83 (3H, S, OMe), 5.50 (1H, bs, OH), 6.59 (1H, S, aromatic H); i.r. ν_{max} cm^{-1}: 3520 (OH); m.s. m/e: 319 (M^+), 318 (M^+-1 , base peak).

Since p-quinol acetate formation was complete as monitored by t.l.c., Ia in the products should surely be originated from the reaction. As an explanation, S_N2' reaction was assumed to give rise to an intermediate such as VI, which would readily undergo deprotonation leading to IIc, otherwise deiodination giving back to Ia (Scheme I). Mechanistically, the same suggestion as above would be acceptable even in the case of chlorination or bromination except that dechlorination or debromination was not a facile process.



Scheme I

Attempted synthesis of chloro-morphinandienones or -homomorphinandienones is currently investigated by acid treatment of p-quinol acetates from the 8-chloro compound (IIIa, IIIb, IVa, IVb or IVc).

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3. O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Pharm. Bull. (Tokyo)*, 1974, **22**, 1302; O. Hoshino, H. Hara, N. Serizawa, and B. Umezawa, manuscript in preparation.
4. T.l.c. or preparative t.l.c. was run on silica gel G or GF_{254} (Merck); developing solvent: $CHCl_3$-MeOH = 20:1.
5. All new compounds gave satisfactory analytical data.
6. N.m.r. spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 Spectrometer in deuteriochloroform solution (5-10%) by using tetramethylsilane as internal standard.

7. I.r. spectra were run on a Hitachi 215 spectrometer in chloroform solution.

8. Mass spectra were measured with a Hitachi Model RMU-6E mass spectrometer.

9. See H. Budzickiewicz, C. Djerassi, and D.H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. 1: Alkaloids, Holden-Day, Inc., San Francisco, London, Amsterdam, 1964, pp. 173-175.

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