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FORMATION OF PROTOBERBERINES BY DEBENZYLATION AND PHOTOLYSIS OF TETRAHYDROISOQUINOLINES[†]

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Treatment of 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinolines (1, 5 and 6) with hydrochloric acid in ethanol without formalin gave the corresponding phenolic isoquinolines (2, 8 and 9) and the tetrahydroprotoberberines (3, 11 and 12). The former products (2, 8 and 9) on photolysis also gave the tetrahydroprotoberberines (3, 11 and 12) together with the normal products, aporphines.

A classic synthesis of tetrahydroprotoberberines is Mannich reaction of 1-benzyl-1,2,3,4-tetrahydroisoquinoline with formaldehyde in the presence of acid.[1,2] In this condensation, formaldehyde provides so-called "berberine bridge", a carbon atom at 8-position in a protoberberine system. However, we have found a

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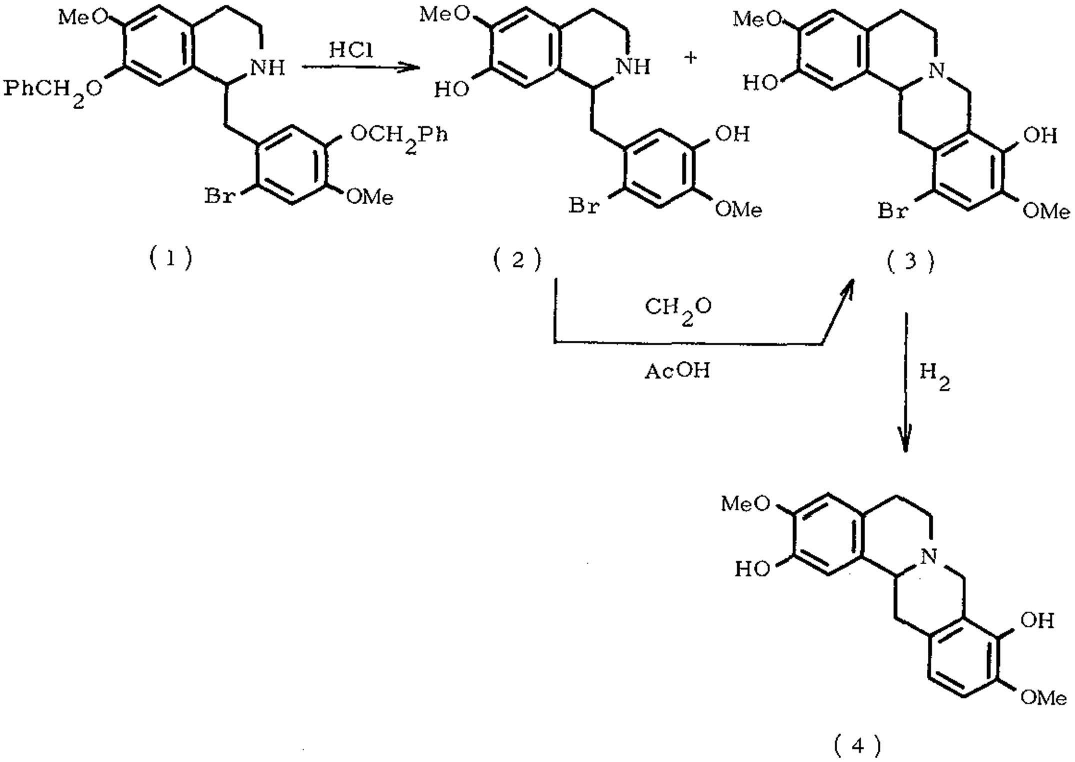
[†] Dedicated to Professor T. R. Govindachari on this 60th birthday.

protoberberine formation from 1-benzyl-1,2,3,4-tetrahydroisoquinolines in the absence of C_8 source in berbine system in a ground state and excited state, and here wish to report this result.

Firstly, heating 7-benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (1) (2 g) with concentrated hydrochloric acid (100 ml) in a boiling purified ethanol (100 ml) for 12 hr gave the objective 2'-bromonorreticuline (2), m.p. 205°, in 80 % yield (1.1 g) in addition to unexpected compound (15 mg), m.p. 156 - 158° (chloroform-methanol),[3] both of which were separated on silica gel chromatography. The latter product has molecular formula $C_{19}H_{20}NO_4Br$ by mass spectrometry [m/e 407 and 405 (M^+), 326 (M^+ - Br) and microanalysis (Found: C, 54.72; H, 5.59; N, 3.62. $C_{19}H_{20}NO_4Br.0.5H_2O$ requires C, 54.95; H, 5.10; N, 3.37 %)], which showed an incorporation of one carbon atom after debenzylation. The ir [ν_{max} (KBr) 2700 - 2850 cm^{-1} (Bohlmann bands)[4]] and uv [λ_{max} (EtOH) 235 ^{sh} and 286 nm (log ε 4.11 and 3.84), λ_{max} (EtOH + NaOH) 249 and 302 nm (log ε 4.19 and 3.99)] suggested this product to be a phenolic tetrahydroprotoberberine, which was supported by mass spectrum[5] showing m/e 230 , 228, 178, and 176. Moreover, nmr spectrum (δ in DMSO-d_6) revealed one of C_8-protons at 4.09 as a doublet showing $\underline{J}$ = 16 Hz and three aromatic protons at 6.64, 6.70, and 7.06 as each singlet together with two methoxyl (3.78 and 3.81) and hydroxyl (8.72 disappeared on D_2O addition) groups. On the basis of these data the unexpected product should be assigned 12-bromoscoulerine (3), whose structure was proved by a direct comparison with the authentic sample (700 mg, 68.5 % yield) prepared from 2'-bromonorreticuline (2) (1 g) and 37 % formalin (5 ml) in refluxing glacial acetic acid (5 ml)

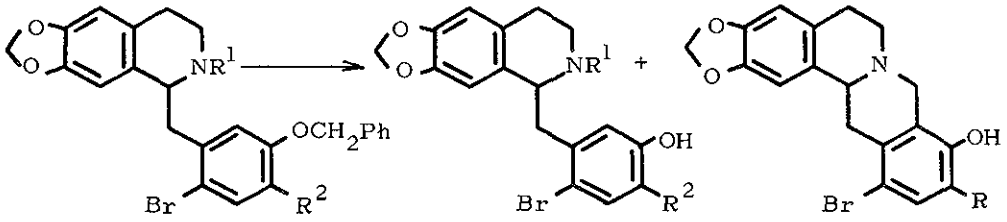
Chart 1



for 20 min by our method.[6] 12-Bromoscoulerine (3) (250 mg) was hydrogenated in the presence of 10 % palladium on carbon (100 mg) in ethanol (250 ml) at 40 - 50 psi to give (±)-scoulerine (4) (100 mg), m.p. 183 - 185°[3] (lit.,[6] m.p. 183 - 185°) which was also identical with the authentic (±)-scoulerine[6] in spectral comparisons.

Same reaction of the 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline (5 and 6) with concentrated hydrochloric acid in ethanol gave the corresponding phenolic isoquinolines (8, 80 % yield, m.p.

Chart 2



	R^1	R^2
(5)	H	OMe
(6)	H	H
(7)	Me	OMe

	R^1	R^2
(8)	H	OMe
(9)	H	H
(10)	Me	OMe

(11) R=OMe

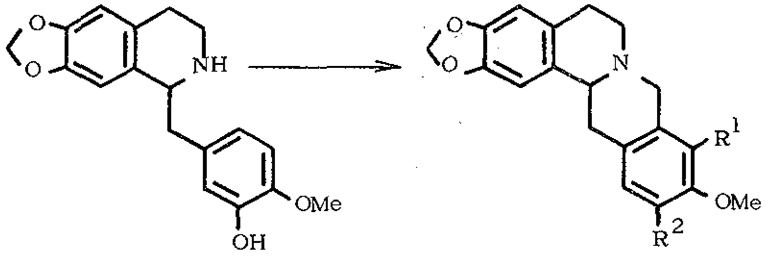
(12) R=H

230 - 231° and 9, 71.5 % yield, m.p. 236°) and phenolic 12-bromoprotoberberines (11, 1.2 % yield, m.p. 132°[7] and 12, 1 % yield, m.p. 149 - 150° [8]).

On the other hand, treatment of the N-methylated 1-benzyl-1,2,3,4-tetrahydroisoquinoline (7) with hydrochloric acid under the same conditions gave the corresponding phenolic 1-benzylisoquinoline (10), m.p. 140 - 142°.

Interstingly, 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-methylenedioxyisoquinoline (13) was heated with concentrated hydrochloric acid in ethanol for 24 hr to afford the corresponding protoberberines, nandinine (14) and its isomer (15)[9] which were

Chart 3



(13)

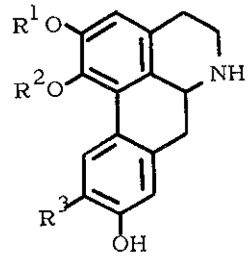
(14) R^1=OH, R^2=H

(15) R^1=H, R^2=OH

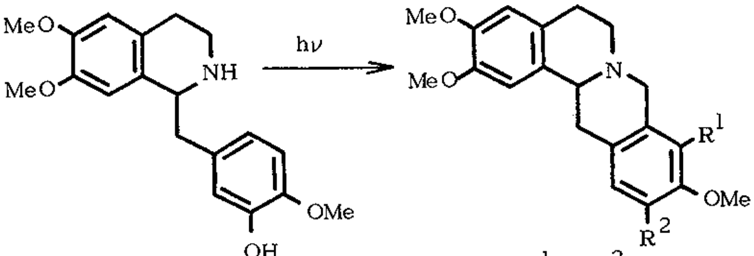
detected by gas chromatography. Treatment of the hydrochloride of 13 with benzyl chloride in boiling ethanol for 24 hr recovered the starting material. These facts revealed that a berberine bridge source would come from either methoxy methyl and/or methylenedioxy methylene group.

Secondly, irradiation of the phenolic isoquinoline (2) hydrochloride (2 g) in distilled water (1200 ml) containing sodium bisulphite (600 mg) with Hanovia mercury lamp surrounded by a pyrex filter at room temperature for 10 hr gave a normal product, (±)-norisoboldine (16), m.p. 211 - 212° (chloroform-methanol),[3] in 8.2 % yield (120 mg) [λ_{max} (EtOH) 280 and 304 nm (log ε 4.08 and 4.07), λ_{max} (EtOH + NaOH) 328 nm (log ε 4.13), m/e 313 (M^+), 312, 298, 296, 284, 282, 269 and 263] and an abnormal product, 12-bromoscoulerine (3) (80 mg), m.p.

Chart 4



	R^1	R^2	R^3
(16)	Me	H	OMe
(17)	$-CH_2-$		OMe
(18)	$-CH_2-$		H



(19)

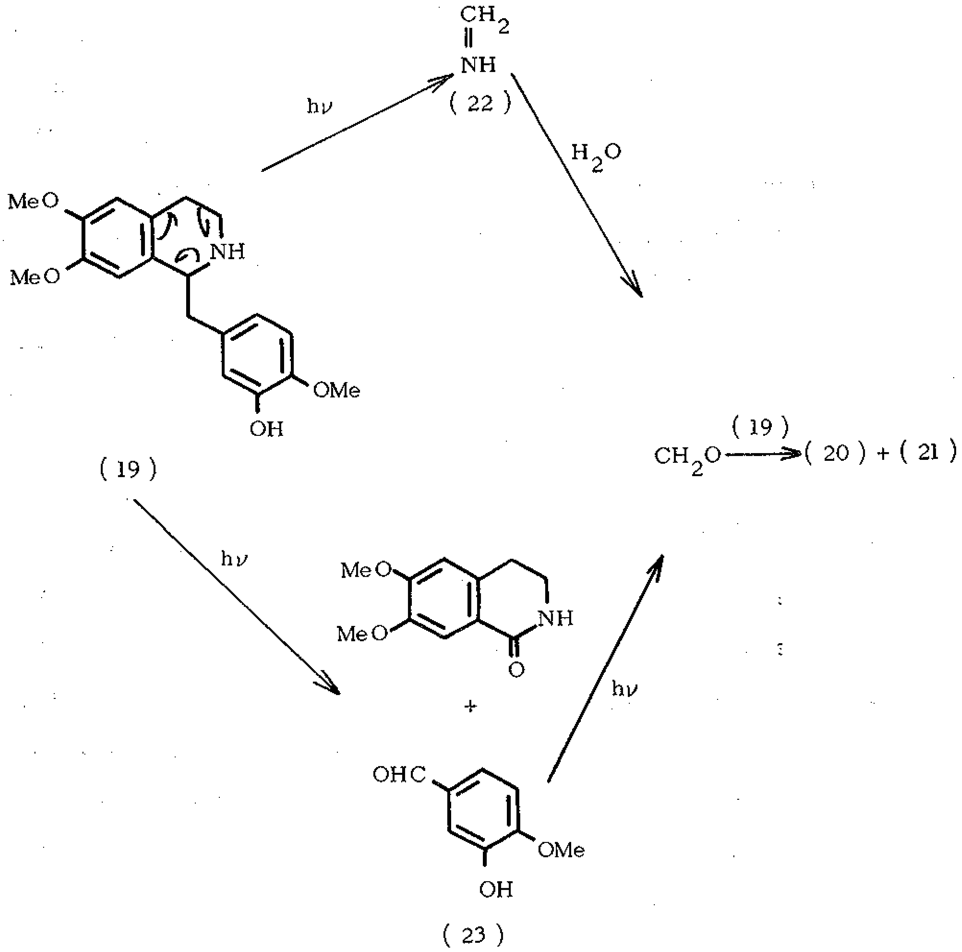
	R^1	R^2
(20)	H	OH
(21)	OH	H

156 - 158°,[3] which was identical with the above sample. Similarly, photolysis of the phenolic benzylisoquinolines (8 and 9) afforded the aporphine alkaloids, actionodaphnine (17, 8.3 % yield), m.p. 195 - 189°[10] and anolobine (18, 8.3 % yield), m.p. 242 - 244°,[8] in addition to 12-bromotetrahydroprotoberberines (11, 5.3 % yield and 12, 12.7 % yield). Moreover, irradiation of 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (19) gave (±)-corytenchine (20)[11] in 4.5 % yield (16.3 % yield based on recovery of starting material), m.p. 235 - 237°, and (±)-schefferine (palmatrubine) (21)[12] in 2 % yield (7.1 % yield base on recovery of starting material), m.p. 144 - 145°, which were identical with the authentic samples in spectral comparisons and melting point test.

The origin of the berberine bridge portion is unclear, but it would be derived from alkoxyl group, C_3-carbon in isoquinoline system or methylene in benzyl residue as shown in Chart 5. Thus, a photo-induced retro-Diels-Alder reaction[13] of 1,2,3,4-tetrahydroisoquinoline would give the imine (22) which provides formaldehyde. Moreover, 1-benzyl-1,2,3,4-tetrahydroisoquinoline on irradiation with uv light formed 1,2,3,4-tetrahydroisocarbostyril and benzaldehyde (23) by a cleavage,[14] and then the latter transformed into formaldehyde by photolysis.

In summary, precaution is necessary in a synthesis of phenolic benzylisoquinolines by debenzylation with acids, expecially in case of preparation of the precursor to protoberberine alkaloids in biosynthetic studies.

Chart 5


hν
CH_2
NH
(22)
H_2O
MeO
MeO
NH
OMe
OH
(19)
(19)
CH_2O
(20) + (21)
hν
MeO
MeO
NH
O
+
hν
OHC
OMe
OH
(23)

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