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Racemisation. Part I. Racemisation of Protoberberines under the Conditions of Catalytic Hydrogenation

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Treatment of optically active protoberberine alkaloids, namely (−)-coreximine (II), (−)-tetrahydropalmatine (III), and (−)-norcoralydine (IV), with hydrogen in the presence of platinum oxide afforded the corresponding racemic protoberberines. Catalytic hydrogenolysis of (−)-[13,13,13a-D_3]coreximine (VI) and (−)-[13,13,13a-D_3]norcoralydine (VIII) gave racemised products with the expected mass spectra.

In 1944, Kondo and Matsuno [1] reported that catalytic hydrogenation of so-called ' rotundine ' [(—)-tetrahydropalmatine [2]] in glacial acetic acid in the presence of platinum oxide afforded a product whose melting point indicated that racemisation had occurred. We have already reported that no racemisation of protoberberines occurs in treatment with acidic [3] or alkaline [4] solutions.

It has been reported [5] that hydrogenolysis of compounds such as (I) was, in some cases, accompanied by

[1] H. Kondo and T. Matsuno, *J. Pharm. Soc. Japan*, 1944, **64***B*, 113.
[2] M. Kawanishi and S. Sugasawa, *Chem. and Pharm. Bull.* (*Japan*), 1955, **13**, 522.
[3] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), 1966, 2010.
[4] T. Kametani, M. Ihara, and W. Klyne, *J. Chem. Soc.* (*C*), to be published.
[5] W. A. Bonner and J. A. Zderic, *J. Amer. Chem. Soc.*, 1956, **78**, 3218; S. Mitsui and S. Imaizumi, *Bull. Chem. Soc. Japan*, 1961, **34**, 774; S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind.*, 1963, 1354.

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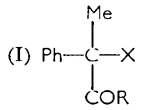
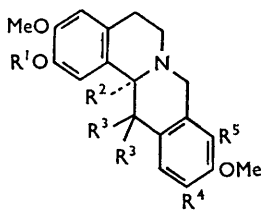
racemisation. However, as far as we know, no reports have been published on racemisation by hydrogenolysis of a carbon–hydrogen (or deuterium) bond. We now report our results on racemisation of protoberberines under various conditions of catalytic hydrogenation.



(I) X = OH, halogen, OMe, SR, or SO_2Ar
R = NH_2, OEt, or OMe

(−)-Coreximine (II),[3] m. p. 261—262°, $[\alpha]_D^{15}$ −418·7° (*c* 0·64 in pyridine) in acetic acid was shaken with hydrogen at room temperature and atmospheric pressure in the presence of Adams catalyst for 165 hours to give (±)-coreximine,[6] m. p. 238—239°, $[\alpha]_D^{14}$ 0° (*c* 0·56 in pyridine). The treatment of (−)-tetrahydropalmatine (III),[4] m. p. 141—142°, $[\alpha]_D^{8}$ −255·2° (*c* 1·78 in methanol) under the same conditions for 42 hours afforded (±)-tetrahydropalmatine.[7] In the case of (−)-norcoralydine (IV),[8] m. p. 177—178°, $[\alpha]_D^{8}$ −281·2° (*c* 1·1 in chloroform), the corresponding racemate [6] was obtained after 36 hours by the same procedure. Furthermore, the treatment of (−)-norcoralydine in ethanol for 42 hours also gave the same racemate.



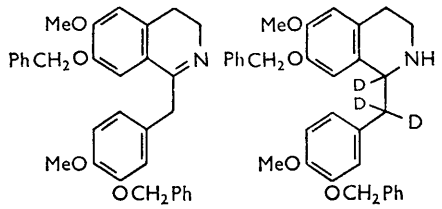
	R^1	R^2	R^3	R^4	R^5
(II)	H	H	H	OH	H
(III)	Me	H	H	H	OMe
(IV)	Me	H	H	OMe	H
(V) *	CH_2Ph	D	D	OCH_2Ph	H
(VI)	H	D	D	OH	H
(VII) *	H	H	D	OH	H
(VIII)	Me	D	D	OMe	H
(IX) *	Me	H	D	OMe	H

* Racemate

However, when palladium oxide was used as catalyst in acetic acid, and palladium–charcoal or W_2-Raney nickel in ethanol, no racemisation occurred. These results are shown in the Table.

In order to examine the mechanism of this racemisation, (−)-[13,13,13a-D_3]coreximine (VI) and (−)-[13,13,13a-D_3]norcoralydine (VIII) were synthesised as described elsewhere.[4] Tetrahydroisoquinoline derivative (XI), which was obtained by reduction of 7-benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline [6] (X) in deuterioacetic acid with zinc powder, was heated with formalin and hydrochloric acid to afford (±)-[13,13,13a-D_3]-*OO*-debenzylcoreximine (V). Optical resolution [3] of the above racemate with (+)-di-*p*-toluoyltartaric acid, followed by debenzylation with 20% ethanolic hydrochloric acid solution, afforded (−)-[13,13,13a-D_3]coreximine (VI).

When both trideuterioprotoberberines (VI) and (VIII) were shaken with hydrogen in the presence of Adams catalyst, racemisation occurred and at the same time the deuterium atom at the 13a-position was replaced by hydrogen. This is established by comparison of the mass spectra of racemised products with those of the starting trideuterioprotoberberines.

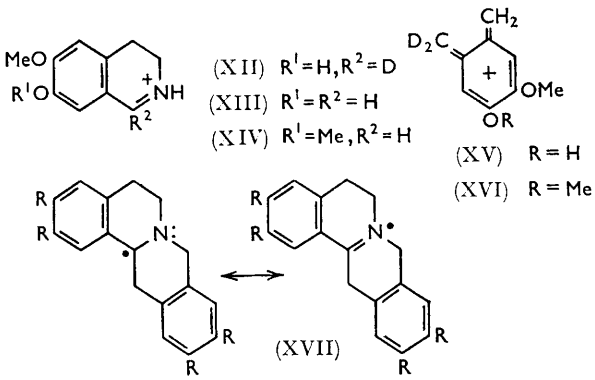


(X) (XI)

The mass spectrum of (VI) showed the ions corresponding to M^+, $M^+ - 1$, and $M^+ - 15$ at *m/e* 330, 329, and 315. The base peak (XII) appeared at *m/e* 179, from which the ion at *m/e* 177 was derived by dehydrogenation. Furthermore, the ion (XV), which was formed by a retro-Diels–Alder reaction, was observed at *m/e* 152, and a further demethylated ion at *m/e* 137.

On the other hand, the mass spectrum of (VII) showed the ions of M^+, $M^+ - 1$, and $M^+ - 15$ at *m/e* 329, 328, and 314. The ions (XIII) and its 3,4-dehydro-derivative were observed at *m/e* 178 and 176 with a decrease of one mass unit, whereas the ions at *m/e* 152 and 137 showed the same mass unit as in the case of (VI).

The mass spectrum of (−)-[13,13,13a-D_3]norcoralydine (VIII) has been reported,[4] and its racemised product (IX) showed the ions of M^+, $M^+ - 1$, $M^+ - 15$ and 3,4-dehydro-(XIV) at *m/e* 357, 356, 342, and 190 with a decrease of one mass unit, whereas the ions (XVI) and (XVI) − 15 at *m/e* 166 and 151 showed the same mass unit as in case of (VIII).



(XII) R^1 = H, R^2 = D
(XIII) R^1 = R^2 = H
(XIV) R^1 = Me, R^2 = H
(XV) R = H
(XVI) R = Me
(XVII)

However, in the case of catalytic hydrogenation of (−)-[13,13,13a-D_3]norcoralydine with palladium oxide, palladium charcoal, or W_2-Raney nickel, no racemisation occurred and the deuterium atoms were not exchanged. It is therefore considered that protoberberines are absorbed on Adams catalyst and then the C(13a)–H bond is ruptured homolytically to afford compound (XVII) which is hydrogenated to the racemate. On the other hand palladium and nickel catalysts seem to have less affinity than platinum for protoberberines.

[6] T. Kametani and M. Ihara, *J. Pharm. Soc. Japan*, 1967, **87**, 174.
[7] T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), 1967, 530.
[8] H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, 1956, **39**, 889.

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EXPERIMENTAL

General Procedure.—The catalyst (PtO_2 or PdO) in solvent was shaken with hydrogen for about 30 min. and then a nearly equal weight of protoberberine was added. The mixture was shaken at room temperature and atmospheric pressure for a few days. After filtration and removal of solvent, the residue was made basic with 10% ammonium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over K_2CO_3, and evaporated, and the residue was recrystallised from methanol. The conditions of racemisation are shown in the Table.

Compound	Catalyst	Solvent	Time (hr.)	Yield of racemate (%)
(−)-Norcoralydine (IV)	PtO_2	AcOH	36	90
	PtO_2	EtOH	42	92
	PdO	AcOH	55	0
	Pd–C	EtOH	52	0
	W_2-Raney Ni	EtOH	40—85	0
(−)-Coreximine (II)	PtO_2	AcOH	165	80
(−)-Tetrahydro-palmatine (III)	PtO_2	AcOH	42	91

(−)-[13,13,13a-D_3]*Coreximine* (VI).—7-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline (X) (0·7 g.) was dissolved in deuterioacetic acid [prepared from acetic anhydride (5 ml.) and deuterium oxide (5 ml.)], and zinc powder (1·8 g.) was added. The mixture was then heated on a water-bath for 7 hr. After cooling and filtration, the filtrate was made basic with 10% sodium hydroxide solution and extracted with ether. Removal of the dried (K_2CO_3) solvent gave a colourless oil (XI) (0·5 g.), which was used in the following Mannich reaction without purification. A mixture of this oil, water (5 ml.), 37% formalin (5 ml.), and concentrated hydrochloric acid (0·2 ml.) was treated as usual,[8] and (±)-[13,13,13a-D_3]*OO*-dibenzylcoreximine (V) (0·35 g.) was obtained as colourless needles, m. p. 136—137°. This base (0·35 g.) and (+)-di-*p*-toluoyltartaric acid (0·27 g.) were dissolved in methanol (30 ml.). The salt which crystallised was recrystallised twice from methanol to afford (−)-[13,13,13a-D_3]OO-*dibenzylcoreximine* (+)-*di*-p-*toluoyltartrate* (0·25 g.), m. p. 189—190° (decomp.) (Found: C, 70·85; H + D, 5·75. $C_{53}H_{48}D_3NO_{12}$ requires C, 70·95; H + D, 6·05%).

The base (V) (150 mg.), recovered from the above salt, was added to 20% ethanolic hydrochloric acid (10 ml.). After refluxing for 2 hr., most of the ethanol was distilled off. The residual solution was washed with ether, basified with concentrated ammonium hydroxide solution, and extracted with chloroform. Removal of the washed and dried (Na_2SO_4) solvent gave a powder, which was recrystallised from methanol to give (−)-[13,13,13a-D_3]*coreximine* (VIII) as prisms, m. p. 258—260° (Found: C, 69·4; H + D, 6·9. $C_{19}H_{18}D_3NO_4$ requires C, 69·1; H + D, 7·3%), $[\alpha]_D^9$ −408·2° (*c* 0·51 in pyridine).

[7/911 *Received, July 24th*, 1967]