STUDIES ON THE SYNTHESIS OF 13-METHYLTETRAHYDROPROTOBERBERINE DERIVATIVE

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4-Methylated isocarbostyril derivative (VII) was reduced with lithium aluminum hydride, followed by an acidic treatment to give the trans-13-methyltetrahydroprotoberberine (VIII).

Previously we have reported a synthesis of 8-oxoprotoberberine from isocarbostyril.[1] In this communication we wish to describe a synthesis of 13-methyltetrahydroprotoberberine from homophthalimide via 4-methylisocarbostyril.

Methylation of the homophthalimide (I) with methyl iodide in the presence of NaH gave a mixture of (IIa) and (IIb). Separation of mixture of (IIa) and (IIb) were unsuccessful.

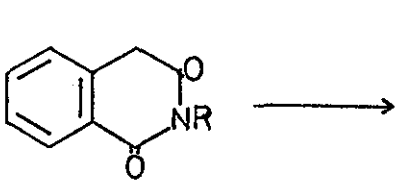
On the other hand, Michael reaction of the homophthalimide (I) with methyl vinyl ketone in the presence of Triton B gave the 4-(3-oxobutyl)homophthalimide (III), m.p. 90-93°, in 90% yield,

ir ν_{max} (nujol) 1700 and 1650 cm^{-1} ; mass m/e 395 (M^+) and nmr $\delta(CDCl_3)$ 2.08 (3H, s, $-COCH_3$), 3.80 and 3.84 (6H, s, $-OCH_3$ x 2), 6.76 (3H, bs, aromatic-H x 3) and 8.21 (1H, d-d, J=12Hz, J=2Hz, C_8-H).

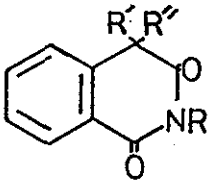
Methylation of (III) with methyl iodide in the presence of NaH affords the 4-(3-oxobutyl)-4-methylhomophthalimide (IV) as an oil in 90% yield, ir ν_{max} (nujol) 1700 and 1650 cm^{-1} ; mass m/e 409 (M^+) and nmr $\delta(CDCl_3)$ 1.58 (3H, s, $-CH_3$), 1.96 (3H, s, $-COCH_3$), 3.80 and 3.84 (6H, s, $-OCH_3$ x 2), 6.80 (3H, bs, aromatic-H x 3) and 8.21 (1H, d-d, J=12Hz, J=2Hz, C_8-H).

The compound (IV) was converted in the usual manner in 90% yield to the ketal (V), then reduced with sodium borohydride to the 4,4-disubstituted 3-hydroxyisocarbostyril (VI), which was heated with p-toluenesulfonic acid in benzene for 1 hr to give 4-methyl-2-[β-(3,4-dimethoxyphenyl)ethyl]isocarbostyril (VII), m.p. 114-116°, in 90% yield, ir ν_{max} (nujol) 1650 cm^{-1} ; mass m/e 323 (M^+) and nmr $\delta(CDCl_3)$ 2.20 (3H, s, $-CH_3$), 3.72 and 3.80 (6H, s, $-OCH_3$ x 2), 6.64 (2H, bs, aromatic-H x 2), 6.74 (2H, s, C_3-H and aromatic-H) and 8.45 (1H, d-d, J=12Hz, J=2Hz, C_8-H).

Unsuccessful attempt was made to cyclize this isocarbostyril (VII) with 12-N hydrochloric acid. Therefore (VII) was reduced with lithium aluminum hydride followed by treatment with 12-N hydrochloric acid at 100° for 1 hr to afford the 13-methyltetrahydroprotoberberine (VIII) as an oil in 80% yield, ir ν_{max} (nujol) 1600 cm^{-1} ; mass m/e 309 (M^+), 190 and 118 and nmr $\delta(CDCl_3)$ 1.48 (3H, d, J=6Hz, $-CH_3$), 3.69 (1H, d, J=8Hz, C_a-H), 3.84 and 3.86

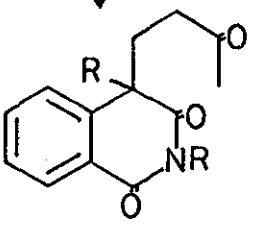


(I)



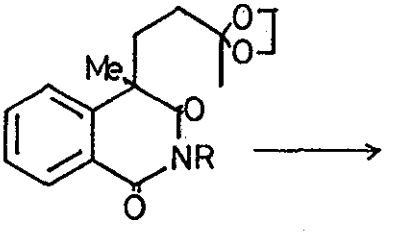
(IIa): R'=Me, R''=H

(IIb): R'=Me, R''=Me

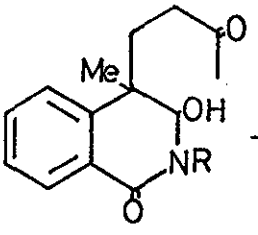


(III): R=H

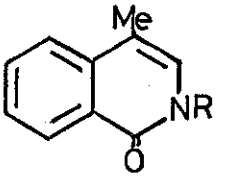
(IV) : R=Me



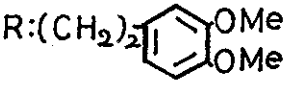
(V)

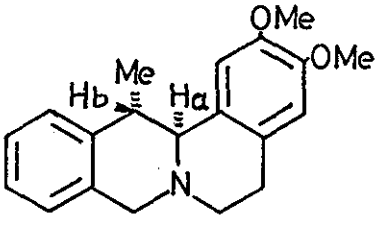


(VI)



(VII)





(VIII)

(6H, s, $-OCH_3$ x 2), 4.21 (1H, d, J=16Hz, C_8-H), 6.62 and 6.67 (2H, s, aromatic-H x 2).

The absence of Bohlmann bands in the infrared spectrum of (VIII), as well as the appearance of the C-13 methyl group as a doublet (J=6Hz) at δ1.48 and proton H_a as a doublet (J_{ab}=8Hz) in the NMR spectrum, establishes the trans relative configuration and cis quinolizine conformation.[2)]

This stereoselective formation of the berberine skelton (VIII) may be able to explain as follow. When a 1,2-dihydroisoquinoline is treated with hydrochloric acid, the C_4-protonated form is susceptible to nucleophilic attack at C_3 from the less hindered, the anti side to the methyl group.

REFERENCE

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2 M. Cushmann, J. Gentry and F.W. Dekow, J. Org. Chem., 1977, 42, 1111.

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