A STEREOSELECTIVE FORMAL TOTAL SYNTHESIS OF EMETINE

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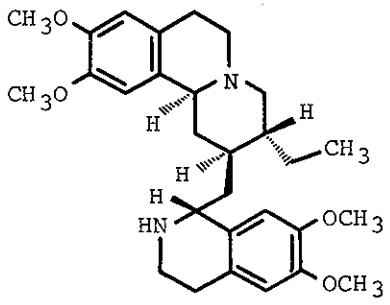
Condensation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (2) with dimethyl 3-methoxyallylidenemalonate (3) gave 2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(β,β-dimethoxyethyl)benzo[a]quinolizin-4-one (4) which was converted to (±)-dihydroprotoemetine (10a). Decarboxylation of the 3-carboxybenzo[a]quinolizin-4-one (6) gave mainly the cis-isomer (7b), whose stereochemistry could be transformed to the thermodynamically stable form (8a) by epimerization at the stage of the hexahydrobenzo[a]quinolizin-4-one (8b).

Recently we reported the one-step formation of benzo[a]quinolizin-4-ones by condensation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (2) and diethyl α,γ-diethoxycarbonylglutaconate.[1] In continuation of this study, a facile route to the benzo[a]-quinolizine derivative (4), an ideal intermediate for a synthesis of emetine (1) and related alkaloids, was developed. We here wish to describe a formal stereoselective synthesis of emetine by

a shorter pathway than any of the reported procedures.[2]



(1)

Treatment of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (2) and dimethyl 3-methoxyallylidenemalonate (3), bp 120 - 125° (0.3 mm Hg), prepared from 1,1,3,3-tetramethoxypropane and dimethyl malonate in an excellent yield,[3] in methanol for 6 days at room temperature followed by refluxing the resulting solution for 12 hr, afforded 2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(β,β-dimethoxyethyl)benzo[a]quinolizin-4-one (4) as a syrup in 88.5 % yield. The mass spectrum of 4 showed a molecular ion peak at m/e 405 and the ir spectrum ($CHCl_3$) exhibited absorptions due to carbonyl groups at 1740 and 1660 cm^{-1}. Proton signals due to three different types of methoxyl group were observed at 3.36 (6H, s), 3.76 (3H, s) and 3.90 (6H, s) in addition to signals at 1.80 (2H, t, J 6.0 Hz, $>CHC\underline{H}_2CH(OMe)_2$), 2.80 (2H, t, J 6.5 Hz, 7-H_2), 4.56 (1H, t, J 6.0 Hz, $-C\underline{H}<^{OMe}_{OMe}$), 5.68 (1H, d, J 5 Hz, 1-H), 6.63 (1H, s, 8-H) and 7.02 ppm (1H, s, 11-H) in the nmr spectrum ($CDCl_3$). Treatment of 4 with ethyl iodide in the presence of sodium hydride in a mixture of benzene and dimethyl-

formamide for 5 hr gave the 3-ethyl compound (5) as crystals, mp 132.5 - 133.5° (isopropyl ether) [$\nu_{max}^{CHCl_3}$ 1725 and 1660 cm^{-1}, δ ($CDCl_3$) 1.00 (3H, t, J 7 Hz, $CH_2\underline{CH}_3$), 2.82 (2H, t, J 6.5 Hz, 7-H_2), 3.38 (6H, s, $CH<^{OCH}_{OC\underline{H}_3}$), 3.62 (3H, s, CO_2Me), 3.90 (6H, s, 2 x OMe), 4.57 (1H, t, J 5 Hz, $C\underline{H}<^{OMe}_{OMe}$), 5.63 (1H, d, J 3.5 Hz, 1-H), 6.63 (1H, s, 8-H) and 7.02 ppm (1H, s, 11-H), m/e 433 (M^+)] in good yield. Hydrolysis of the ester (5) was carried out by heating with potassium hydroxide in aqueous methanol for 2 hr to yield the carboxylic acid (6) as crystals, mp 147.5° (decomp.) [δ ($CDCl_3$) 0.93 (3H, t, J 7 Hz, $CH_2\underline{CH}_3$), 3.26 (6H, s, $CH<^{OCH}_{OC\underline{H}_3}$), 3.93 (6H, s, 2 x OMe), 4.50 (1H, t, J 6 Hz, $C\underline{H}<^{OMe}_{OMe}$), 5.90 (1H, d, J 7 Hz, 1-H), 6.67 (1H, s, 8-H) and 7.06 ppm (1H, s, 11-H), m/e 419 (M^+)] in 92.5 % yield. Spectral and chromatographical analyses verified that only one stereoisomer was obtained in each reaction.

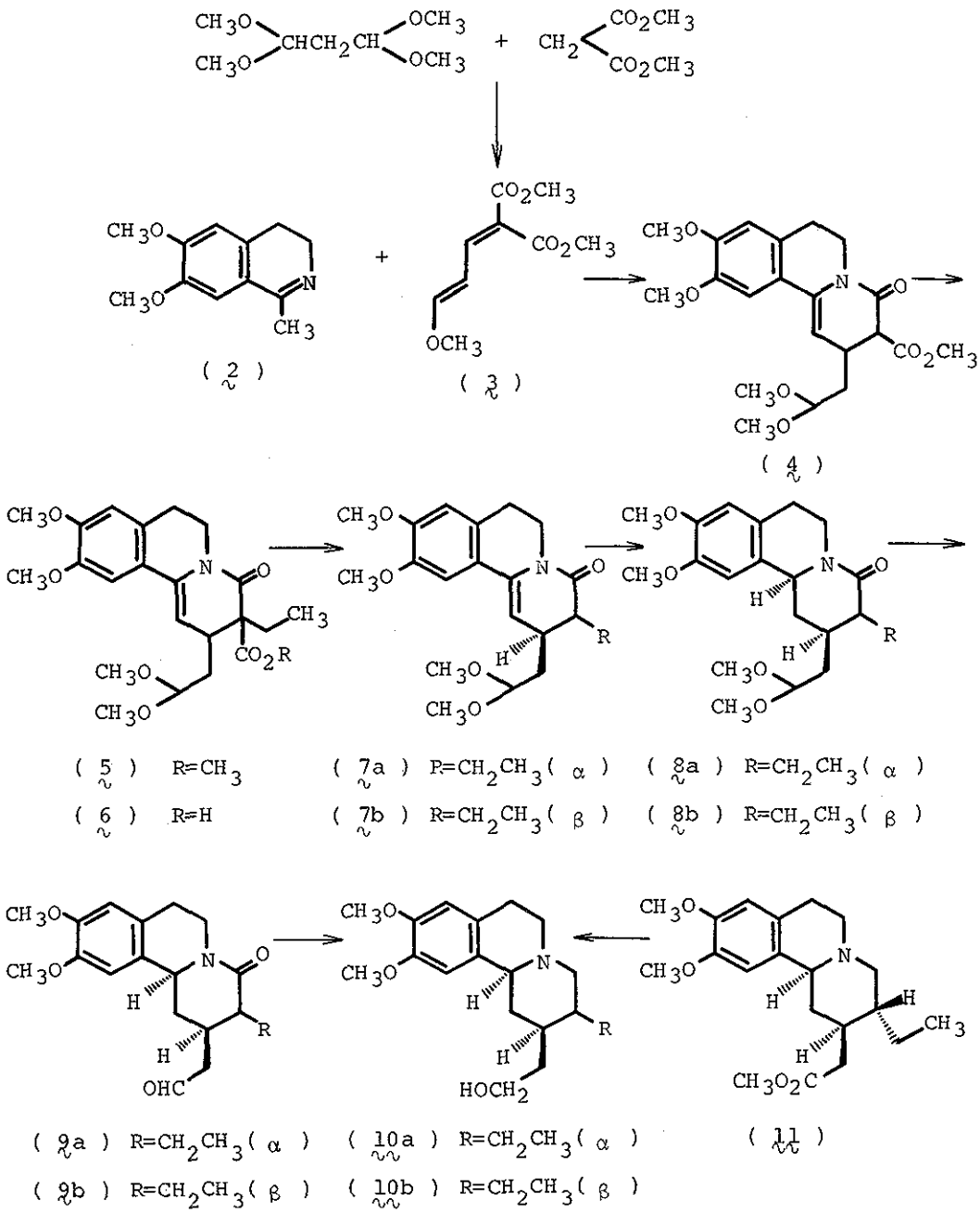
Heating the acid (6) in dimethylformamide at 120 - 130° afforded, in 75.6 % yield, the decarboxylated products (7) [δ ($CDCl_3$) 0.98 (3H, t, J 7 Hz, $CH_2\underline{CH}_3$), 3.33 (6H, s, $CH<^{OCH}_{OC\underline{H}_3}$), 3.92 (6H, s, 2 x OMe), 6.60 (1H, s, 8-H) and 7.03 ppm (1H, s, 11-H), m/e 375 (M^+)], which were hydrogenated in the presence of Adams catalyst in methanol at atmospheric pressure and room temperature to give the lactam (8) in 80.2 % yield. High pressure liquid chromatography (hplc, Hitachi gel 3011, MeOH) revealed that the product was composed of two stereoisomers (8a and 8b) in a ratio of 1 : 5. The major component (8b) was converted to the minor one (8a) by refluxing with sodium hydride in dimethylformamide. Thus, after epimerisation, 8a [$\nu_{max}^{CHCl_3}$, 1660 cm^{-1}, δ ($CDCl_3$) 0.91 (3H, t, J 6 Hz, $CH_2\underline{CH}_3$), 3.35 (6H, s, $CH<^{OCH}_{OC\underline{H}_3}$), 3.86

(6H, s, 2 x OMe), 4.53 (1H, t, J 5 Hz, $CH<^{OMe}_{OMe}$), 6.58 and 6.63 (each 1H, each s, 2 x ArH, m/e 377 (M^+)] was obtained in 62.5 % yield. The stereochemistry was confirmed by the conversion of 8a to (±)-dihydroprotoemetine (10a). Treatment of 8a with dilute hydrochloric acid in acetone formed the aldehyde (9a)[4] [$\nu_{max}^{CHCl_3}$ 1728 and 1620 cm^{-1}, δ ($CDCl_3$) 0.90 (3H, t, J 6 Hz, CH_2CH_3), 3.85 (6H, s, 2 x OMe), and 9.80 (1H, s, CHO), m/e 331 (M^+)] in 78.6 % yield. Reduction of 9a with lithium aluminium hydride in a hot mixture of dioxane and ether gave (±)-dihydroprotoemetine (10a), which was characterised as the perchlorate, mp 178 - 181° (lit.,[4,5] mp 178 - 181°) identical in ir and nmr and hplc behaviour with an authentic sample derived from the ester (11)[6].

It was clear from the above conversion that the decarboxylation of 6 yielded mainly the cis-isomer (7b). By reduction of the mixture (7a and 7b), hydrogen selectively attacked the carbon at the 11b-position from the less hindered α side.

By the same sequence as above but without the epimerisation, the mixture (8a and 8b) was transformed via the aldehydes (9a and 9b) to the alcohols, which were separated into (±)-dihydroprotoemetine (10a) and its stereoisomer (10b) in 1 : 5 ratio by hplc [μ-bondapak C_{18}, MeOH- 0.5 % aqueous ammonium carbonate (3 : 1 v/v)]. The latter gave the perchlorate, mp 202 - 203°.

Since the aldehyde (9a) had already been converted to emetine (1),[4] the formal total synthesis of emetine has thus been accomplished. The transformation of the other intermediates into emetine and related alkaloids is under investigation.



(5) R=CH_3 (7a) R=CH_2CH_3 (α) (8a) R=CH_2CH_3 (α)

(6) R=H (7b) R=CH_2CH_3 (β) (8b) R=CH_2CH_3 (β)

(9a) R=CH_2CH_3 (α) (10a) R=CH_2CH_3 (α) (11)

(9b) R=CH_2CH_3 (β) (10b) R=CH_2CH_3 (β)

ACKNOWLEDGEMENT We thank Prof. S. Takano and Dr. K. Ogasawara, Tohoku University, for a kind gift of the ester (11).

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Received, 21st June, 1977