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ELIMINATION OF THE 4-HYDROXYL GROUP OF THE ALKALOIDS RELATED TO MORPHINE—VII

SYNTHESIS OF THE ACTIVE 2'-HYDROXY-2-METHYL-5,9-DIETHYL-6,7-BENZOMORPHAN DERIVATIVES

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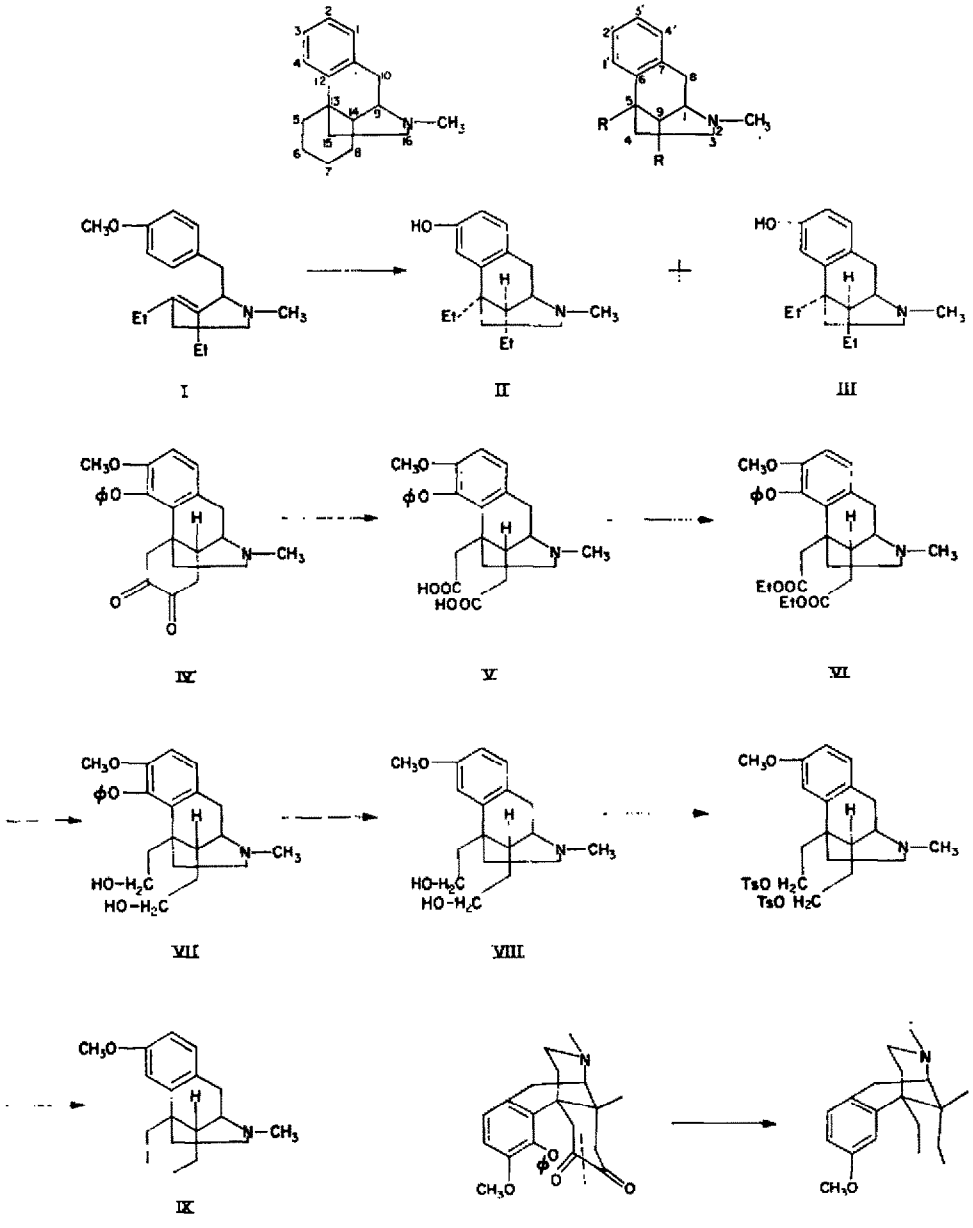
Abstract—Active 2'-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan derivatives have been synthesized from thebaine and also from sinomenine.

IN THE search for an effective analgesic agent with minimal addiction liability and toxicity our attention has centered on 2'-hydroxy-2-methyl-5,9-dialkyl-6,7-benzomorphan derivatives which have been synthesized by May *et al.* either by means of Grewe's synthesis[1] or through β-tetralone derivatives.[2] It was reported[3] that the acid-catalysed cyclization of 3,4-diethyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (I) gave 2'-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan, m.p. 248–249° and the diastereo isomer, m.p. 214–215°, differing in configuration at C_9. It was also stated[4] that the high melting racemic form, predominantly produced, has the configuration II (5·9 *cis*) and the low melting racemic form the configuration III (5·9 *trans*) and that the absolute stereochemistry implied in the structural formulae is that related to morphine. In the previous paper[5] the oxidation of 7-oxo-dihydrothebainone phenyl ether (IV; the antipode of phenylsinomeninone) to dibasic acid V (the antipode of phenylsinomeninic acid) is reported.

The present paper is concerned with the preparation of active 2'-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphans from the natural alkaloids. The dibasic acid (V) was converted to the diethylester (VI) in 62% yield. LAH reduction of the ester VI gave (−)-2'-methoxy-2-methyl-1'-phenoxy-5,9-di-(β-hydroxyethyl)-6,7-benzomorphan (VII) in 83% yield. Elimination of the phenoxyl group at $C_{1'}$ was effected by sodium–liquid ammonia reduction to yield (−)-2'-methoxy-2-methyl-5,9-di-(β-hydroxyethyl)-6,7-benzomorphan (VIII) in 74% yield. Tosylation of the diol VIII was achieved by the tosyl chloride–pyridine method. Though the crude products showed 5 spots in the thin layer chromatogram, the tosylates were reduced with LAH. The crude diethyl compounds still showing 3 spots in the thin layer chromatogram were

[1] E. L. May and E. M. Fry, *J. Org. Chem.* **22**, 1366 (1957); E. L. May and J. H. Ager, *Ibid.* **24**, 1432 (1959); J. H. Ager and E. L. May, *Ibid*, **27**, 245 (1962); S. E. Fullerton, J. H. Ager and E. L. May, *Ibid*, **27**, 2554 (1962); J. H. Ager, S. E. Fullerton and E. L. May, *J. Medicinal Chem.* **6**, 322 (1963); J. H. Ager, S. E. Fullerton, E. M. Fry and E. L. May, *J. Org. Chem.* **28**, 2470 (1963).
[2] S. Saito and E. L. May, *J. Org. Chem.* **26**, 4536 (1961).
[3] J. H. Ager and E. L. May, *J. Org. Chem.* **27**, 245 (1962).
[4] S. E. Fullerton, E. L. May and E. D. Becker, *J. Org. Chem.* **27**, 2144 (1962).
[5] Y. K. Sawa, N. Tsuji, K. Okabe and T. Miyamoto, *Tetrahedron* **21**, 1121 (1965).



purified as the picrate, from which (−)-2′-methoxy-2-methyl-5,9-diethyl-6,7-benzomorphan (IX) was obtained in a yield of 55% based on the diol VIII. Demethylation of IX gave the desired phenolic compound, m.p. 212–213°.

This optically active compound has already been obtained, presumably by resolution of the racemate, by May *et al.*[6]

However, to date no properties except methiodide formation rate have been

[6] S. E. Fullerton, E. L. May and E. D. Becker, *J. Org. Chem.* **27**, 2144 (1962).

reported. For the preparation of (+)-2′-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan, a sequence of similar reactions was carried out starting from phenylsinomeninone.[7]

The racemic form of 2′-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan, m.p. 246–247°, was prepared from these enantiomers. The properties and configuration assigned to this compound agree with the racemate α named by May *et al.*[2] Moreover, (−)-2′-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan, m.p. 211–212°, was prepared from 7-oxo-dihydrothebainone (B/C *cis*) as described above.

EXPERIMENTAL

All m.ps are uncorrected. Microanalyses were carried out by Messrs. K. Miyahara and T. Ieki of this laboratory. The IR spectra were determined on a Nippon Bunko DS-201 IR spectrophotometer.

The antipode of diethyl phenylsinomeninate (VI). A solution of 9·24 g IV and 2·9 ml 30% v H_2O_2 in 46 ml glacial acetic acid was heated on a steam bath for 1 hr. The excess reagents were removed by distillation and the residue dissolved in 70 ml water. The solution was made basic with $NaHCO_3$ and extracted with benzene. The water layer was made acidic with 10% HClaq until the solution became clear.

The acidic solution was evaporated to dryness under red. press. and the residue treated with abs. EtOH to remove inorganic material. The solution was concentrated to about 100 ml, saturated with dry HCl and allowed to stand overnight. The solution was refluxed for 1 hr and then concentrated until the crystalline material separated. The crude hydrochloride (7·58 g; 62·0%) melted at 257–258° (dec). A small sample was recrystallized from EtOH, m.p. 267° (dec); $[\alpha]_D^{28}$ +24·2° ± 6° (*c*, 0·363, alc.). (Found: C, 64·85; H, 7·05; N, 2·71; Cl, 7·10. $C_{28}H_{35}O_6N.HCl$ requires: C, 64·92; H, 7·01; N, 2·70; Cl, 6·84%.)

Liberation of the hydrochloride with 30% NH_4OHaq gave an oily ester which on standing did not crystallize.

Oxidation of phenylsinomeninone (H_2O_2) and esterification of the dibasic acid gave diethyl phenylsinomeninate hydrochloride in 62% yield, m.p. 259–260° (dec); $[\alpha]_D^{24}$ −21·7° ± 7° (*c*, 0·332, alc.).

(−)-2′-*Methoxy*-2-*methyl*-1′-*phenoxy*-5,9-*di*-(β-*hydroxyethyl*)-6,7-*benzomorphan* (VII). To a suspension of 1·19 g LAH in 85 ml ether, a solution of 6·53 g of the antipode of diethyl phenylsinomeninate in 85 ml ether was added dropwise and the mixture gently refluxed for 3 hr. The excess reagent was destroyed with ethyl acetate. The ether solution was washed with dil. NaOHaq and then water. Evaporation of the ether gave 5·2 g of crude amorphous product, which was crystallized from EtOH to give 4·97 g the ethanol adduct (83%), m.p. 116–118° (dec). A small sample was recrystallized from EtOH, m.p. 118–119° (dec); $[\alpha]_D^{24.5}$ −3·8° ± 2° (*c*, 0·734, alc.). (Found: C, 70·40; H, 8·53; N, 3·19. $C_{24}H_{31}O_4N.C_2H_5OH$ requires: C, 70·40; H, 8·41; N, 3·16%.)

LAH reduction of diethyl phenylsinomeninate gave (+)-2′-methoxy-2-methyl-1′-phenoxy-5,9-di-(β-hydroxyethyl)-6,7-benzomorphan in 84% yield. The ethanol adduct had m.p. 118–118·5° (dec), $[\alpha]_D^{25}$ +2·0° ± 2° (*c*, 0·668, alc.).

(−)-2′-*Methoxy*-2-*methyl*-5,9-*di*-(β-*hydroxyethyl*)-6,7-*benzomorphan* (VIII). The ethanol adduct of VII (8·3 g) was dissolved in toluene and the EtOH removed by distillation. The toluene solution was added dropwise to 300 ml liquid ammonia at −55° to −60° and the mixture treated with 1·0 g metallic Na under stirring until the blue colour persisted for ½ hr. The toluene solution after evaporation of the liquid ammonia was washed with dil. NaOHaq and then water. The separated crystalline material (5·1 g) was recrystallized from EtOH to give 4·24 g the desired diol, m.p. 208–209°, 74%; $[\alpha]_D^{24}$ −55·3° ± 6° (*c*, 0·378, alc.). (Found: C, 70·52; H, 9·06; N, 4·49. $C_{18}H_{27}O_3N$ requires: C, 70·79 H, 8·91; N, 4·59%.) The residue (0·42 g) from the toluene solution was crystallized from EtOH giving 0·12 g crystalline product, m.p. 236–240°. No attempt was made to elucidate the structure.

The sodium–liquid ammonia reduction of the solvate of (+)-2′-methoxy-2-methyl-1′-phenoxy-5,9-di-(β-hydroxyethyl)-6,7-benzomorphan gave (+)-2′-methoxy-2-methyl-5,9-di-(β-hydroxyethyl)-6,7-benzomorphan, m.p. 208–209°, $[\alpha]_D^{22.5}$ +49·5° ± 7° (*c*, 0·313, alc.), in 69·7% yield and a small amount of the high melting substance, m.p. 243–244°.

[7] Y. K. Sawa, N. Tsuji and S. Maede, *Tetrahedron* **15**, 144 (1961).

(−)-2′-*Methoxy*-2-*methyl*-5,9-*diethyl*-6,7-*benzomorphan* (IX). To a suspension of 3.7 g VIII in 12 ml pyridine, cooled to 0°, a solution of 5·77 g tosyl chloride in 15 ml pyridine was added and the mixture kept under stirring for 3 hr. The reaction mixture was poured onto 80 ml ice-water and the solution was made basic with dil. alkali. Extraction with benzene and evaporation of the solvent gave 7·43 g of an oily tosylate. To a suspension of 1·84 g LAH in 90 ml tetrahydrofuran was added a solution of the foregoing tosylate in 90 ml tetrahydrofuran and the mixture refluxed for 3 hr. The excess reagent was decomposed with ethyl acetate and the solution washed with dil. alkali and then with water. The crude products (3·48 g) were distilled to give 2·15 g oily bases, b.p.$_{0.085}$ 170° (bath temp). The distillate was converted to the picrate, which was crystallized from EtOH to yield 3·43 g pure picrate of the desired 5,9-diethyl-6,7-benzomorphan derivative, m.p. 151–152°. (Found: C, 57·67; H, 6·20; N, 11·16. $C_{18}H_{27}ON.C_6H_3O_7N_3$ requires: C, 57·36; H,6·02; N, 11·15%). Liberation of the picrate and crystallization from ether gave pure IX, m.p. 86–87° (55%); $[\alpha]_D^{24.5}$ −54·5° ± 2° (*c*, 1·00, alc.). (Found: C, 78·96; H, 9·99; N, 5·06. $C_{18}H_{27}ON$ requires: C, 79·07°; H, 9·95; N, 5·12%.)

Similar treatment of (+)-2′-methoxy-2-methyl-5,9-di-(β-hydroxyethyl)-6,7-benzomorphan gave (+)-2′-methoxy-2-methyl-5,9-diethyl-6,7-benzomorphan, m.p. 86–88°, $[\alpha]_D^{23.5}$ +54·7° ± 2° (*c*, 1·047, alc.) in 51% yield. The methiodide was prepared in ether and recrystallized from acetone, m.p. 246–247°, $[\alpha]_D^{25.5}$ +26·9° ± 2° (*c*, 1·076, alc.). (Found: C, 54·82, H, 7·31; N, 3·42; I, 30·41. $C_{18}H_{27}ON{\cdot}CH_3I$ requires C, 54·94; H, 7·28; N, 3·37; I, 30·56%).

(−)-2′-*Hydroxy*-2-*methyl*-5,9-*diethyl*-6,7-*benzomorphan*. A solution of 1·6 g IX in 24 ml 48% HBraq was refluxed for 1 hr. The excess reagent was removed by distillation under red. press. and the residue dissolved in water. The solution was made basic with dil. NH_4OHaq and extracted with $CHCl_3$.

The crude phenolic compound was crystallized from EtOH to yield 1·414 g (−)-2′-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan, m.p. 211–212°, (93·1%), $[\alpha]_D^{25.5}$ −60·1° ± 2° (*c*, 1·056, alc.). (Found: C, 78·66; H, 9·76; N, 5·49. $C_{17}H_{25}ON$ requires: C, 78·71; H, 9·72; N, 5·40%.) Demethylation of (+)-2′-methoxy-2-methyl-5,9-diethyl-6,7-benzomorphan gave (+)-2′-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan, m.p. 211–212°, $[\alpha]_D^{23.5}$ +59·6° ± 3° (*c*, 0·726, alc.). Methylation of this phenolic compound with Rodinov's reagent gave the original 2′-methoxy derivative, m.p. 83–84°, in 60% yield.

Rac. 2′-*Methoxy*-2-*methyl*-5,9-*diethyl*-6,7-*benzomorphan*. (+)-2′-Methoxy-2-methyl-5,9-diethyl-6,7-benzomorphan (0·453 g) and (−)-2′-methoxy-2-methyl-5,9-diethyl-6,7-benzomorphan (0·453 g) were combined. Recrystallization of the mixture from ether gave the racemic compound, m.p. 63–64°.

Rac. 2′-*Hydroxy*-2-*methyl*-5,9-*diethyl*-6,7-*benzomorphan*. (+)-2′-Hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan (0·488 g) and (−)-2′-hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan (0·488 g) were combined and the mixture was recrystallized from EtOH to yield the racemate, m.p. 246–247°.

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