PREPARATION AND ANALGESIC ACTIVITY OF SOME 3,4-DISUBSTITUTED N-METHYLMORPHINANS OF THE (-) SERIES

Mohamad F. Rahman[1] and Arnold Brossi*

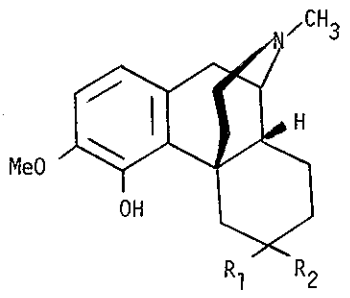
Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Maryland 20014, USA

Some reactions of (-)-3-methoxy-4-hydroxy-N-methylmorphinan (2) obtained from dihydrothebainone (1) were investigated. The analgesic properties of compounds 2,3,4,5 and 6 compared to morphine hydrochloride and levorphenol are reported.

Much knowledge has been accumulated regarding the structure activity relationship of 3-hydroxymorphinans its N,O-substituted derivatives[2] and the 2 and 4-hydroxy isomers[3]. Similar concise information is lacking for most aromatic dioxygenated analogs. The 3,4-disubstituted compounds are of particular importance since they possess the oxygen functions at the same position as most naturally derived analgesics of the morphine group. We now report the preparation and analgesic activity of several closely related compounds belonging to this series. They are obtained by much improved procedures to those already reported in the literature.

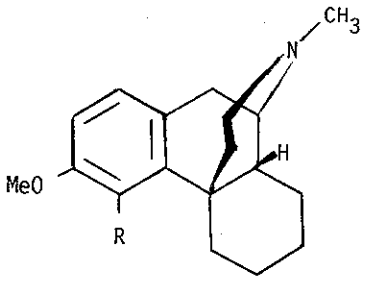
---

*In memory of Hans Schmid, Professor of Organic Chemistry at the University of Zürich, Switzerland, who passed away on Sunday December 19, 1976.



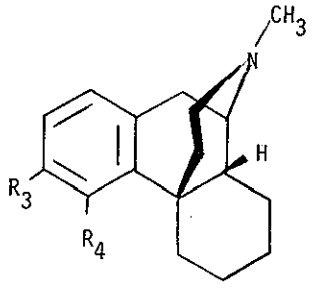
1 R_1R_2 = O

2 R_1R_2 = H



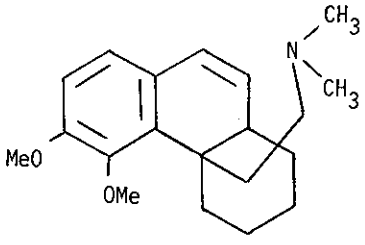
3 R = OAc

4 R = OMe



5 R_3 = R_4 = OH

6 R_3 = R_4 = OAc



7

The starting material (-)-dihydrothebainone (1) can be easily obtained by acid catalysed hydrogenolysis of thebaine[4,5] or by total synthesis[6]. We utilized material prepared from thebaine, thus eliminating the possibility of enantiomeric contamination. The compounds shown below were prepared in the following way: removal of 6-keto group in (1) could be achieved by Clemmensen reduction in 50-60% yield affording the known 3-methoxy-4-hydroxy-N-methyl-morphinan[7] (2). Acetylation with acetic anhydride and pyridine to (3) could easily be accomplished affording an oily base ($[\alpha]_D^{20}$ = -12.2°, c = 0.82, CH_3OH; HCl m.p. 115°). The oily 3-4-dimethoxy-N-methylmorphinan[7] (4) is made conveniently by treatment of (2), sodium hydride, dimethylformamide and methyl p-toluenesulfonate at ice bath temperature, ($[\alpha]_D^{20}$ = -30.4°, c = 1.43, CH_3OH; 48% yield; HCl m.p. 242-244°). At elevated temperatures 4 is contaminated with its Hofmann elimination product[8] (7) separated by preparative thin layer chromotography on silica gel and characterized as its hydrochloride (m.p. 145°; UV maximum 268 mμ, m/e 315). The catechol (5) is obtained in good yield by O-demethylation of 2 with boron tribromide in methylene chloride solution at ice bath temperature (m.p. 242°; $[\alpha]_D^{20}$ = -62.12°, c = 0.82, CH_3OH; HCl m.p. 267-268°) and identical with material obtained in low yield by O-demethylation of (2) with 48% hydrobromic acid[4]. Acetylation of this light-sensitive catechol affords the diacetoxy derivative 6 (m.p. 118-120°, $[\alpha]_D^{20}$ = 0°, c = 0.94, CH_3OH; ($[\alpha]300$ = -578°, $[\alpha]290$ = -603°, c = 0.013, C_2H_5OH). Acid hydrolysis of the diacetoxy compound 6 affords the catechol 5, identical with an authentic sample. An attempt to selectively cleave the 3-methoxy group in 4 afforded the catechol as the only product. It is interesting to note from the above data that introduction of larger groups in the 3,4-positions lowers the sign of the optical rotation considerably. The catechol 5 shows the highest-optical rotation whereas

the $[\alpha]_D^{20}$ of the diacetoxy morphinan 6 is zero when measured in methanol. The latter shows, however, high negative values when measured in ethanol at different wave lengths.

ANALGESIC POTENCY

Compounds·HCl	ED_{50}	O^c	p^d	D^e
2	6,2 (4.3-8.8)	3.3	19.5	141
3	3,8 (2.7-5.4)	3.0	15.3	119
4	0,33 (0.20-0.55)	3.2	21.7	155
5	1,9 (1.5-2.6)	3.5	17.8	148
6[f]	2,6 (1.9-3.4)	4.1	33.0	161
Morphine Sulfate	1,1 (0.8-1.5)	3.3	32.6	183
Levorphanol Tartrate	0,17 (0.11-0.27)	4.7	29.2	142
Levomethorphan Base[f]	ca. 1,5			

[a]Numbers in parentheses represent 95% confidence limits as obtained by probit analysis. [b]Subcutaneous injection in mice, milligrams per kilogram, using the hot-plate assay (see Refs. 9 and 10). [c]Onset of analgesia in minutes. [d]Peak time at which maximal analgesic response is observed in minutes. [e]Duration of analgesia in minutes. [f]Free base dissolved in stoichiometric amount of dilute hydrochloric acid.

With the exception of compound 4, all other 3,4-disubstituted morphinans are weaker analgesics than morphine. The dimethyl ether 4 is several times more active than morphine and almost as active as levorphanol. This unexpected finding prompts us to further investigate this interesting morphinan derivative.

ACKNOWLEDGEMENT The authors wish to thank Dr. K. C. Rice for helpful suggestions, Dr. A. E. Jacobson and Louise Atwell for planning and carrying out the analgesic screening.

REFERENCES AND NOTES

1 Visiting Associate on leave from the Regional Research Laboratory, Hyderabad, India.

2 J. Hellerbach, O. Schnider, H. Besendorf and B. Pellmont, "Synthetic Analgesics Part II (A) Morphinans". International Series of Monographs in Organic Chemistry, Vol. 8, 1966, Pergamon Press.

3 E. Mohacsi and W. Leimgruber (Hoffmann-La Roche, Inc.) US patent 3914232 issued 21 October 1975; Chem. Abstr., 1976, 84, 74488.

4 L. F. Small and R. E. Lutz in "Chemistry of Opium Alkaloids", U. S. Treasury Department, Public Health Service, Government Printing Office, Washington, D. C. 1932.

5 C. Schöpf and L. Winterhalder, Ann., 1927, 452, 232.

6 H. Beyerman, T. S. Lie, L. Maat, H. H. Bosman, E. Buurman, E. J. M. Bijsterved and H. J. M. Sinnige, Recl. Trav. Chim., 1976, 95, 24.

7 L. F. Small and F. L. Cohn, J. Amer. Chem. Soc., 1932, 54, 802.

8 A. Grüssner, J. Hellerbach, A. Brossi and O. Schnider, Helv. Chim. Acta, 1956, 39, 1371.

9 N. B. Eddy and D. Leimbach, J. Pharmacol. Exp. Ther., 1953, 107, 385.

10 A. E. Jacobson and E. L. May, J. Med. Chem., 1965, 8, 563.

Received, 11th April, 1977