A NEW HETEROCYCLE WITH ANALGESIC ACTIVITY: 2,6-EPOXY-1,2,3,4,5,6-HEXAHYDRO-3-METHYL-3-BENZAZOCINE

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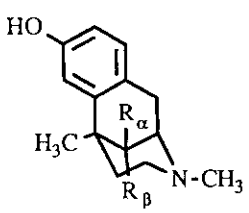
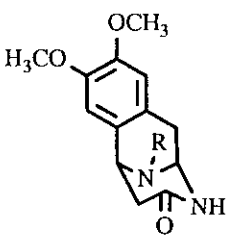
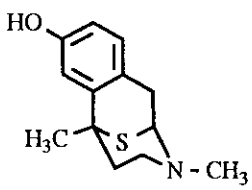
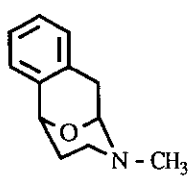
Abstract - The title compound (**4**) was prepared in five steps, starting with the benzaldehyde derivative (**5**). In the mouse writhing-test **4** showed strong analgesic activity.

Substitution of the methano bridge in benzomorphans can dramatically influence the analgesic activity: Compound (**1a**) with two hydrogen atoms at the methano bridge shows ca. 14% of the morphine analgesia in the mouse hot-plate-test. An α-methyl group[1] (**1b**) increases the analgesic activity fivefold (70% of morphine-analgesia), while the diastereomeric compound (**1c**) with a β-methyl group is ca. five times as active as morphine.[2]









1 a: $R_\alpha = R_\beta = H$

b: $R_\alpha = CH_3, R_\beta = H$

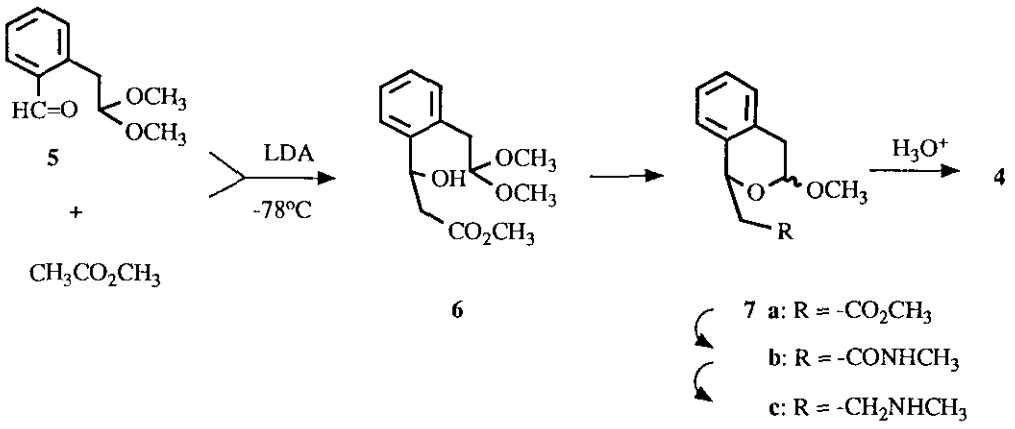
c: $R_\alpha = H, R_\beta = CH_3$

2 ($R = -COC_6H_5$)

3

4

We are interested in the pharmacological effects of benzomorphan derivatives, where the methano-C-atom is substituted by a heteroatom (N,S,O). The synthesis of the aza-derivative (**2**) was reported in 1968[3] and, very recently (in 1990), the corresponding thia-analogue (**3**) was prepared by Hori and colleagues.[4] But neither **2** nor **3** were reported to be tested for pharmacological activities. We wish to report the synthesis and CNS effects of the corresponding oxa-derivative (**4**).



The lithium enolate of methyl acetate was added to the homophthalaldehyde monoacetal (**5**)[5] at -78°C. After careful workup with ammonium chloride at -78°C, we isolated the hydroxy ester (**6**, colourless oil) in 92% yield.[6] Cyclisation of **6** under standard conditions (p-toluenesulfonic acid, methanol, 4 h, room temp.)[5] and subsequent aminolysis with methylamine (23 h, room temp.) resulted in formation of amide (**7b**, m p 118 - 122°C), which was reduced by $LiAlH_4$ (Et_2O, 5 h, room temp.) to the amine (**7c**, colourless oil). Finally, hydrolysis of **7c** with dilute HCl (20 h, room temp.) afforded the epoxybenzazocine (**4**)[7] in 21% overall yield starting from **5**.

At first, **4** was tested for analgesic activity. In the mouse writhing-test,[8] we determined an ED_{50} of 13.5 mg/kg,[9] which is comparable with the ED_{50} of tramadol (ED_{50} = 7.8 mg/kg), a central active analgesic. Then, we watched mice for anomalous behaviour caused by application of **4**.[10] At a dose of 50 mg/kg, we noted the Straub-tail-phenomenon and mydriasis. Increasing the dose to 100 mg/kg led to convulsions and dyspnoea in addition to the above symptoms.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. For the terms α and β see: N. B. Eddy and F. L. May," Organic Chemistry", Vol. 8, Synthetic Analgesics, Pergamon, New York, 1966, p. 113.
2. G. R. Lenz, S. M. Evans, D. E. Walters, and A. J. Hopfinger, "Opiates", Academic Press, New York, London, 1986, p. 250 ff.
3. S. Shiotani, T. Hori, and K. Mitsuhashi, Chem. Pharm. Bull., 1968, **16**, 239.
4. M. Hori, H. Ozeki, T. Iwamura, H. Shimizu, T. Katoaka and N. Iwata, Heterocycles, 1990, **31**, 23.
5. B. Wünsch, Arch. Pharm. (Weinheim), 1990, **323**, in press.
6. All new compounds gave satisfactory physical and analytical data.
7. **4**: Colourless oil, b $p_{0.05}$ 150 - 180°C. Ir (Film): 2930, 1095 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): δ(ppm) = 1.18 (ddd, J = 12.7, 3.0,1.2 Hz, 1H, H-5 equatorial), 2.51 - 2.56 (m, 1H, H-4 equatorial), 2.645 (s, 3H, N-CH_3), 2.65 (tt, J = 12.7, 4.8 Hz, 1H, H-5 axial), 2.92 (d, J = 18.0 Hz, 1H, H-1), 3.01 (td, J = 12.7, 3.0 Hz, 1H, H-4 axial), 3.31 (dd, J = 18.0,7.3 Hz, 1H, H-1), 4.73 (d, J = 7.3 Hz, 1H, H-2), 5.00 (d, J = 4.8 Hz, 1H, H-6), 6.97 - 6.99 (m, 1H, aromat.), 7.13 - 7.22 (m, 3H, aromat.).
8. R. Koster, N. Anderson, and E. J. de Bur, Fed. Proc., 1959, **18**, 412.
9. With 95% probability the ED_{50} is between 5.6 and 32.4 mg/kg.
10. S. Irwin, Science, 1962, **136**, 123.

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