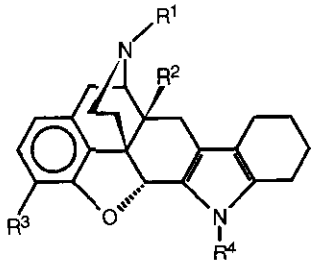
A SYNTHESIS OF PYRROLOMORPHINANS

Peter Schwarz and Helmut Schmidhammer*

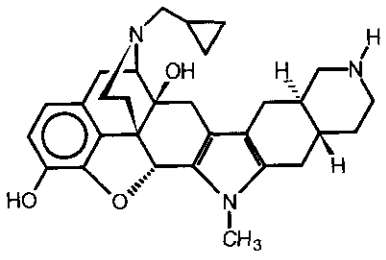
Institute of Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

Abstract - Pyrrolomorphinans (**4**, **10**, and **13**) have been prepared from the corresponding nitro ketones employing the tributylphosphine-diphenyl sulfide deoxygenating system. The nitro ketones (**7**, **9**, and **12**) were obtained either from hydrocodone (**6**) with lithium diisopropylamide and the corresponding nitroalkene, or from hydrocodonepyrrolidine enamine (**11**) by treatment with 2-nitropropene.

Pyrrolomorphinans substituted in the pyrrole moiety (compounds **1** and **2**, respectively) have been prepared from Portoghese and co-workers.[1,2] Preparation was accomplished in low yield by conducting a Piloty-type[3] pyrrole synthesis. An attempt to prepare compound (**3**) by the same route failed.[1] Our efforts to prepare compounds (**4**) and (**5**) by the Piloty process from the corresponding azines were also unsuccessful.[4] Thus we sought for a different route for the synthesis of pyrrolomorphinans of this type. Such compounds have potential as opioid receptor selective ligands and are of interest as pharmacological and biological tools.[1-3]



1 R^1 = CPM, R^2 = R^3 = OH, R^4 = CH_3
3 R^1 = CPM, R^2 = R^3 = OH, R^4 = H
4 R^1 = CH_3, R^2 = R^4 = H, R^3 = OCH_3
CPM = cyclopropylmethyl



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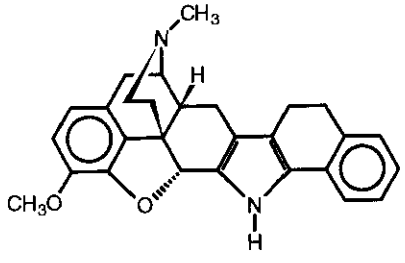

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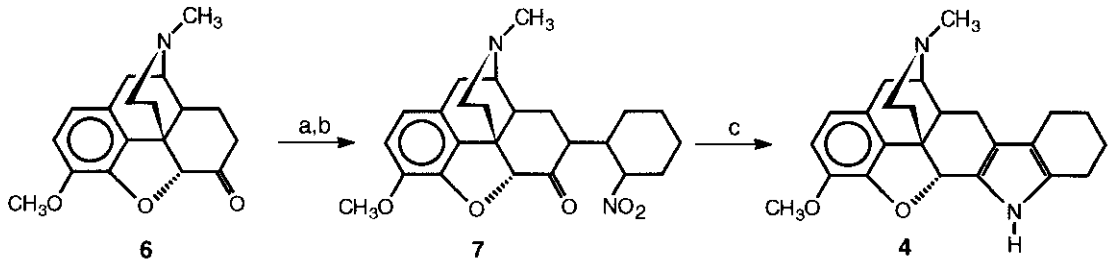
This paper is dedicated with best wishes to Dr. Arnold Brossi on the occasion of his 70th birthday.

RESULTS AND DISCUSSION

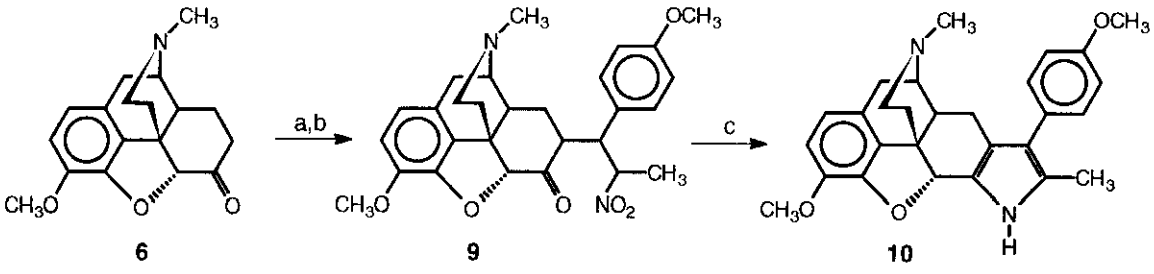
We found that pyrrolomorphinans can be prepared in good yields *via* the corresponding nitro ketones (e. g. compounds **7**, **9**, **12**) employing the tributylphosphine-diphenyl disulfide (Bu_3P, PhSSPh) deoxygenating system.[5-7] The nitro ketones were obtained either directly from dihydrocodeinone (= hydrocodone; **6**) by reaction with lithium diisopropylamide (LDA) and the corresponding nitroalkene, or from hydrocodonepyrrolidine enamine (**11**) by treatment with 2-nitropropene.[8]

Thus, compound (**4**) has been prepared by the following reaction sequence: Hydrocodone (**6**) was treated in THF at -78° C with 1-nitrocyclohexene[9] after formation of the lithium enolate with LDA (obtained from diisopropylamine and BuLi in THF at -40° C) to give nitro ketone (**7**)[10,11] as a mixture of stereoisomers which was not further separated. Subsequent addition of PhSSPh and Bu_3P to a solution of **7** in THF at room temperature yielded pyrrole (**4**)[10,12] (Scheme 1).



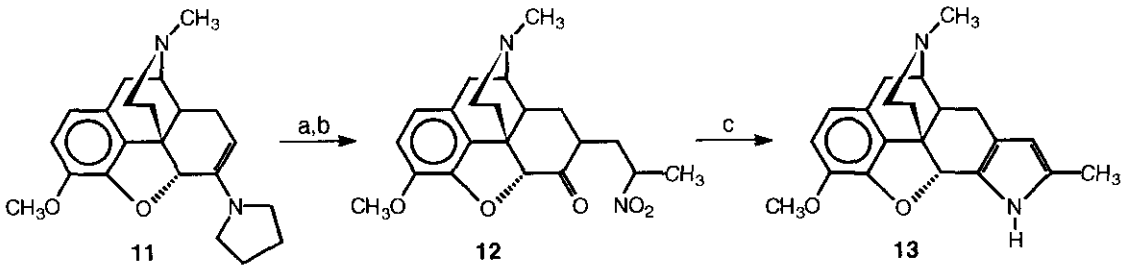
Scheme 1: Reaction conditions and reagents: a) LDA, 1-nitrocyclohexene, THF, -78°C. b) HOAc, -20°C, 76%. c) PhSSPh, $(C_4H_9)_3P$, THF, room temperature, 70%.

The pyrrolomorphinan (**10**)[10,13] has been prepared similarly using nitrostyrene (**8**)[14] instead of 1-nitrocyclohexene. The intermediate nitro ketone (**9**)[10,11] was used as a mixture of stereoisomers for further transformation (Scheme 2).



Scheme 2: Reaction conditions and reagents: a) LDA, 4-CH_3O-C_6H_4-CH=C(NO_2)CH_3 (**8**), THF, -78°C. b) HOAc, -20°C, 57% c) PhSSPh, $(C_4H_9)_3P$, THF, room temperature, 73%.

Compound (**13**) has been synthesized starting from hydrocodonepyrrolidine enamine (**11**) which was obtained by reacting hydrocodone and pyrrolidine at room temperature.[15] Enamine (**11**) was treated with 2-nitropropene[16] in Et_2O at room temperature and gave, after hydrolysis with 10% HCl, nitro ketone (**12**)[10,11] as a mixture of stereoisomers. Compound (**12**) could not be obtained by reaction of the lithium enolate of **6** with 2-nitropropene. Pyrrolomorphinan (**13**)[10,17] was formed as described above using the Bu_3P - PhSSPh system (Scheme 3).



Scheme 3: Reaction conditions and reagents: a) 2-nitropropene, $(C_2H_5)_2O$, room temperature. b) *10%* aq. HCl, *75%*. c) PhSSPh, $(C_4H_9)_3P$, *THF, room temperature, 67%.*

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REFERENCES AND NOTES

1. P. S. Portoghese, H. Nagase, K. E. MaloneyHuss, C.-E. Lin, and A. E. Takemori, *J. Med. Chem.*, 1991, **34**, 1715.
2. C.-E. Lin, A. E. Takemori, and P. S. Portoghese, *J. Med. Chem.*, 1993, **36**, 2412.
3. O. Piloty, *Ber.*, 1910, **43**, 489.
4. H. Schmidhammer and P. Schwarz, *Liebigs Ann. Chem.*, in press.
5. D. H. R. Barton, W. B. Motherwell, and S. Z. Zard, *Tetrahedron Lett.*, 1984, **25**, 3707.

6. D. H. R. Barton, W. B. Motherwell, E. S. Simon, and S. Z. Zard, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2243.

7. D. H. R. Barton, J. Kervagoret, and S. Z. Zard, *Tetrahedron*, 1990, **46**, 7587.

8. A. Risaliti, M. Forchiassin, and E. Valentin, *Tetrahedron*, 1968, **24**, 1889.

9. E. J. Corey and H. Estreicher, *J. Am. Chem. Soc.*, 1978, **100**, 6294.

10. All novel compounds showed satisfactory elemental analyses.

11. The structure assigned to each new nitro ketone was in full accord with its spectral (^{1}H and ^{13}C nmr, ir and mass) characteristics. Each nitro ketone was purified by column chromatography and isolated as foam.

12. **4**: mp 146 - 150° C (AcOEt); ir (KBr): 3400 (NH) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ 7.87 (br s, NH), 6.64 and 6.58 (dd, J = 8.2, 8.2 Hz, 2 arom. H), 5.50 (s, H-C(5)), 3.77 (s, CH_3O), 2.44 (s, CH_3N); ^{13}C nmr (50 MHz, $CDCl_3$): δ 144.6, 143.0, 129.2, 129.0, 127.0, 121.9, 118.7, 118.2, 114.5, 112.6, 86.4, 60.0, 56.0, 46.8, 43.4, 42.9, 41.5, 35.9, 23.3, 23.2, 22.7, 21.3, 20.9, 20.5; EI-ms: m/z 376 (M^+).

13. **10**: mp 118 - 120 ° C (diisopropyl ether); ir (KBr): 3397 (NH) cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 8.15 (br s, NH), 6.95 (m, 4 arom. H), 6.61 and 6.67 (dd, J = 8.2, 8.2 Hz, 2 arom. H), 5.54 (s, H-C(5)), 3.80 and 3.78 (2 s, 2 CH_3O), 2.41 (s, CH_3N), 2.14 (s, CH_3); ^{13}C nmr (75 MHz, $CDCl_3$): δ 157.5, 144.6, 143.0, 130.2, 129.3, 128.2, 127.3, 126.1, 122.1, 119.7, 118.7, 118.4, 113.6, 112.7, 86.2, 59.9, 56.0, 55.2, 46.7, 43.4, 43.0, 41.9, 36.0, 22.6, 20.5, 11.9; CI-ms: m/z 443 ($M^+ + 1$).

14. C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, 1953, **18**, 1.

15. K. A. Kovar and F. Schielein, *Arch. Pharm.*, 1978, **311**, 73.

16. M. Miyashita, T. Yanami, and A, Yoshikoshi, *Org. Synth.*, Coll. Vol. V, **60**, 101.

17. **13**: mp 130 - 133° C (AcOEt); ir (KBr): 3390 (NH) cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$): δ 8.06 (br s, NH), 6.63 and 6.57 (dd, J = 8.2, 8.2 Hz, 2 arom. H), 5.49 (s, 2H), 3.76 (s, CH_3O), 2.42 (s, CH_3N), 2.11 (CH_3); ^{13}C nmr (75 MHz, $CDCl_3$): δ 144.5, 142.9, 129.5, 129.3, 127.2, 122.5, 121.0, 118.3, 112.6, 104.7, 86.1, 59.8, 56.0, 46.7, 43.3, 42.9, 41.8, 35.9, 23.1, 20.4, 12.9; EI-ms: m/z 336 (M^+).

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