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SYNTHETIC ANALGESICS: PREPARATION OF RACEMIC 6,7-BENZOMORPHANS

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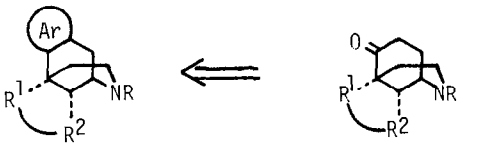
Abstract: A simple preparation of 2-carbomethoxy-2-azabicyclo[3.3.1]nonan-6-one (7) and its conversion to the racemic benzomorphans: 9, 10, 14 are described.

With a few notable exceptions, past as well as current synthetic approaches to the morphine related analgesics, including the morphinans and benzomorphans, have relied on the acid-catalyzed cyclization of 2-(arylmethyl)-tetrahydropyridines, chemistry pioneered by Grewe in the 1940's[2,3]. In addition to the limitations this places on the aryl portion of these systems, this and related synthetic approaches often lack effective stereocontrol and restrict the potential for the preparation of natural and synthetic analgesics in the desired optically pure form[3].

In recent communications, we have described the development and application of several different aryl annulations and in each instance a keto group served as the necessary functionality for the introduction of the aryl ring, equation 1[4].

Eqn. (1)

As the first stage in the development of new, and potentially useful, synthetic approaches to the morphine related analgesics we would like to report a simple and direct preparation of racemic 6,7-benzomorphans based on this preliminary work, equation 2 and scheme I-II.



Eqn. (2)

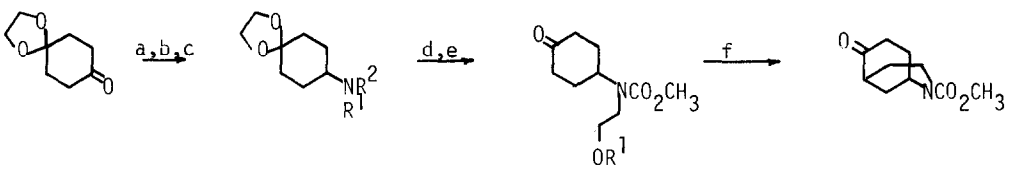
R^1/R^2 = H, alkyl:benzomorphan

R^1/R^2 = $-(CH_2)_4-$:morphinan

Lithium aluminum hydride reduction of the imine formed by condensation of allylamine with the mono-ethylene ketal of 1,4-cyclohexadione[5] afforded 2. Carbamate formation followed by ozonolysis and sodium borohydride reduction gave alcohol 4. Ketal hydrolysis and mesylate formation preceded a base catalyzed intramolecular alkylation to give 2-carbomethoxy-2-azabicyclo[3.3.1]nonan-6-one (7)[6], a key intermediate capable of conversion to a number of synthetic benzomorphans, scheme I.

The final conversion of 7 to a series of racemic 6,7-benzomorphans required the introduction of appropriately substituted aromatic rings, typified by a phenol, and thus required the simple implementation of our aryl annulations, scheme II. Conversion of 7 to the β-keto sulfoxide 12[6] followed by treatment with methyl vinyl ketone afforded 3-carbomethoxy-8-hydroxy-6,7-benzomorphan (9)[6] in modest yield[4a]. A more satisfactory introduction of a phenol ring was

Scheme I



1

2 R^1 = $CH_2CH{=}CH_2$, R^2 = H

3 R^1 = $CH_2CH{=}CH_2$, R^2 = CO_2CH_3

4 R^1 = CH_2CH_2OH, R^2 = CO_2CH_3

5 R^1 = H

6 R^1 = SO_2CH_3

7

(a) 10.0 equiv. allylamine, 4Å mol. sieves, C_6H_6, 40°C, 40 h; 4.0 equiv. $LiAlH_4$, THF, 60°C, 18 h, 80%. (b) 20 equiv. K_2CO_3, 1.2 equiv. $ClCO_2CH_3$, THF, 25°C, 12 h, 88%. (c) O_3, EtOH, -78°C; CH_3SCH_3, 25°C, 4 h; 3.3 equiv. $NaBH_4$, 25°C, 4 h, 93%. (d) 3:1 HOA_c: H_2O, 25°C, 17 h. (e) 1.5 equiv. Et_3N, 1.2 equiv. $ClSO_2CH_3$, CH_2Cl_2, -20°C, 3 h. (f) 1.25 equiv. t-BuOLi, THF, 25°C, 4 h, 26% from 4.

accomplished employing the inverse electron demand Diels-Alder reaction of 3-carbomethoxy-2-pyrones[4d] with 1,1-dimethoxyethylene. Thus, conversion of 7 to the α-pyrone 8 followed by treatment with 1,1-dimethoxyethylene afforded 3,9-dicarbomethoxy-8-methoxy-6,7-benzomorphan (10)[6] in high yield. Ester hydrolysis followed by decarboxylation[7] and phenol demethylation[7] gave 9[6] in excellent yield (97%). In addition, treatment of the pyrrolidine enamine of 7 with 1,3,5-triazine in dioxane[4c] afforded the pyrimidine substituted benzomorphan 14 (50%)[6].

Thus, the late introduction of a phenol or aryl ring provided a sound premise for the preparation of a series of typical, racemic benzomorphans. Extrapolation of this work to accommodate each class of natural and synthetic analgesics, to address the problem of effective stereocontrol, and for the implementation of a synthetic approach to optically pure analgesics are the focus of current efforts.

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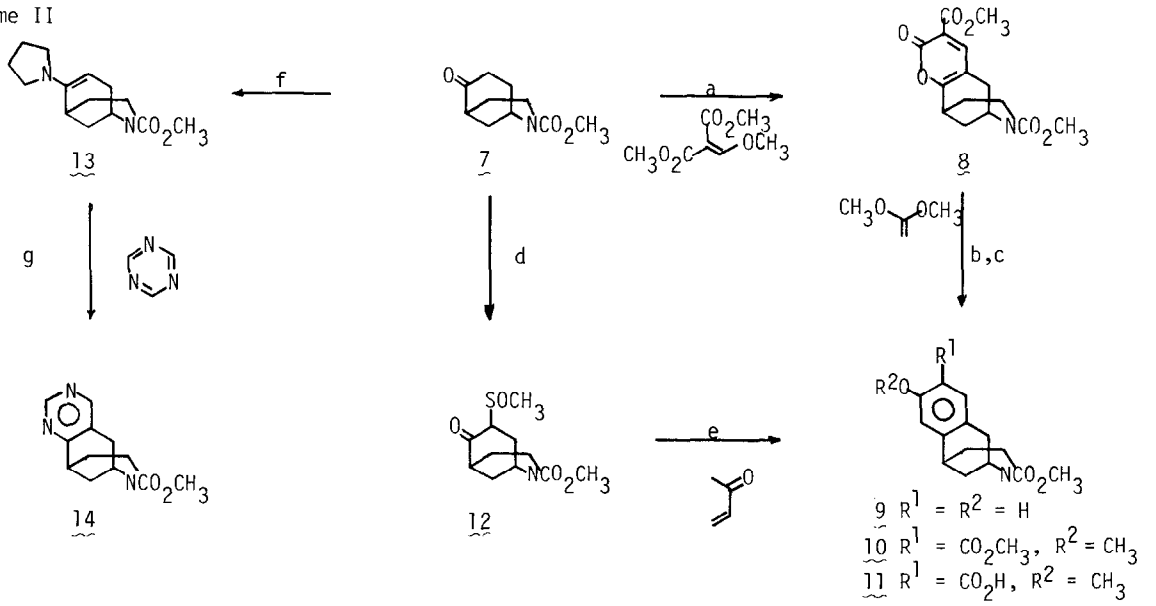
Scheme II



(a) 1.2 equiv. lithium diisopropylamide (LDA), THF, -78°C to -25°C, 1.5 h; 1.2 equiv. dimethylmethoxymethylenemalonate, -25°C to 25°C, 4 h, 47%. (b) 10.0 equiv. 1,1-dimethoxyethylene, toluene, 120°C, 13 h, 80%. (c) 2.0 equiv. 0.67 N aq. NaOH, THF, 25°C, 15 h; 10.0 equiv. copper powder, quinoline, 220°C, 1 h, 97%. (d) 2.2 equiv. LDA, -78° to -15°C, 1.5 h; 2.2 equiv. CH_3SSCH_3, HMPA, -20° to 25°C, 4 h; 1.0 equiv. $NaIO_4$, CH_3OH/H_2O, 25°C, 8 h, 60%. (e) 1.4 equiv. methyl vinyl ketone, 0.1 equiv. CH_3ONa/CH_3OH, 0°C, 24 h; 1.2 equiv. CH_3ONa, 25°C, 35 h, 19-27%. (f) 3.0 equiv. pyrrolidine, 4Å mol. sieves, C_6H_6, 80°C, 18 h. (g) 1.2 equiv. 1,3,5-triazine, dioxane, 90°C, 20 h, 50% from 7.

References and Notes

1. (a) Chicago Community Trust Co./Searle Scholar Recipient, 1981-1984; (b) National Institutes of Health predoctoral fellow, 1981-1984 (NIH GM 07775).
2. For recent reviews and discussion of morphine related analgesics, see: (a) Lednicer, D.; Mitscher, L. A. "Organic Chemistry of Drug Synthesis", John Wiley and Sons, Inc., New York, N. Y., 1977, Vol. 1, pp. 285-310; 1980, Vol. 2, 314-337; (b) Johnson, M. R.; Milne, G. M.; "Burger's Medicinal Chemistry", fourth edition, Part III, Wolfe, M. E., ed., John Wiley and Sons, Inc., New York, N. Y., 1981, pp. 700-758.
3. For a discussion of benzomorphan analgesics and recent synthetic work, see: (a) May, E. L. J. Med. Chem. 1980, 23, 225; (b) Palmer, D. C.; Strauss, M. J. Chem. Rev. 1977, 77, 1; (c) Bosch, J.; Bonjoch, J. Heterocycles 1980, 14, 505; Idem J. Org. Chem. 1981, 46, 1538; Bosch, J.; Bonjoch, J.; Serret, I. Tetrahedron Lett. 1982, 23, 1297; (d) Rapoport, H.; Gless, R. D. J. Org. Chem. 1979, 44, 1394; (e) Watanabe, K.; Wakabayashi, T. ibid 1980, 45, 357; (f) DeStevens, G. Pure and Applied Chem. 1969, 19, 89. For recent advances in the preparation of optically pure, synthetic analgesics, see: (g) Rice, K. C. J. Org. Chem. 1980, 45, 3135; Chemical and Engineering News, April 9, 1982, pg. 41; Science 1982, 216, 398.
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5. Lambert, J. B. J. Am. Chem. Soc. 1967, 89, 1836.
6. 7: ^{1}H-NMR ($CDCl_3$) δ 4.48 (m, 1 H), 4.10-3.75 (m, 1 H), 3.72 (s, 3 H), 3.25 (dt, J = 12, 7 Hz, 1 H), 2.70-2.35 (m, 3 H), 2.20-1.60 (m, 6 H); ^{13}C-NMR ($CDCl_3$), δ 213.5 (s, C-6, C=O), 156.3 (s, $-CO_2CH_3$), 52.6 (q, OCH_3), 44.8 (d, C-1), 42.3 (d, C-5), 38.9 (t, C-3), 37.7 (t, C-7), 31.0 (t, C-4/C-8/C-9), 29.0 (t, C-4/C-8/C-9), 27.0 (t, C-4/C-8/C-9); IR (film) ν_{max} 2940, 2860, 1705, 1685, 1440, 1200, 1085, 930, 755 cm^{-1}; mass spectrum, m/e: 197 (M^+).
   8: ^{1}H-NMR ($CDCl_3$) δ 8.01 (s, 1 H), 4.65 (m, 1 H), 4.15-3.25 (m, 1 H), 3.90 (s, 3 H), 3.72 (s, 3 H), 3.15-2.85 (m, 4 H), 2.15-1.60 (m, 4 H); IR ($CHCl_3$) ν_{max} 2960, 1770, 1710, 1695, 1550, 1445, 1220, 1090, 780 cm^{-1}; mass spectrum, m/e: 307 (M^+).
   9: ^{1}H-NMR ($CDCl_3$) δ 6.93 (d, J = 6 Hz, 1 H), 6.63 (d, J = 6 Hz, 1 H), 6.58 (s, 1 H), 4.59 (m, 1 H), 4.11-3.55 (m, 2 H), 3.70 (s, 3 H), 3.10-2.45 (m, 4 H), 2.20-1.40 (m, 4 H); IR ($CHCl_3$) ν_{max} 3440, 3010, 2950, 1615, 1605, 1495, 1445, 1405, 1260, 1210, 1095, 1040, 935, 895 cm^{-1}; mass spectrum, m/e: 247 (M^+).
   10: ^{1}H-NMR ($CDCl_3$) δ 7.54 (s, 1 H), 6.69 (s, 1 H), 4.65 (m, 1 H), 4.15-3.65 (m, 1 H), 3.89 (s, 6 H), 3.72 (s, 3 H), 3.23-2.47 (m, 4 H), 2.15-1.60 (m, 4 H); IR (film) ν_{max} 2950, 1725, 1690, 1605, 1445, 1400, 1070, 710 cm^{-1}; mass spectrum, m/e: 319 (M^+).
   12: ^{1}H-NMR ($CDCl_3$) δ 4.75 (m, 1 H), 4.25-3.82 (m, 1 H), 3.75 (s, 3 H), 3.25-2.25 (m, 4 H), 2.61 (s, 3 H), 2.15-1.70 (m, 5 H); IR (film) ν_{max} 2960, 1700, 1450, 1270, 1105, 1050, 1020, 770 cm^{-1}; mass spectrum, m/e: 196 (base, M^+ - 63).
   14: See reference 4c.
7. Decarboxylation and demethylation of 11 were found to occur upon treatment with copper powder in quinoline at 220°C. Trost, B. M.; Kinson, P. L. J. Org. Chem. 1972, 37, 1273.

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