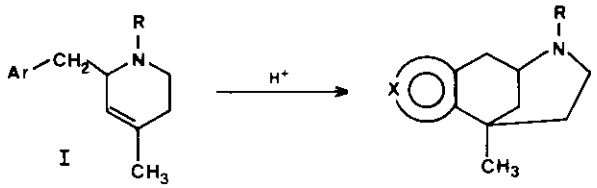
BENZOMORPHAN RELATED COMPOUNDS. XV.[1]
A VERSATILE METHOD FOR THE SYNTHESIS OF HETEROMORPHANS[2].

Joan Bosch*, Josep Bonjoch, and Isabel Serret.
Department of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona, Spain.

From 2-benzoyl-5-methyl-6-oxo-2-azabicyclo[3.3.1]nonane-7-carboxylate the preparation of 5-methyl substituted pyrazolo[3,4-f]-, pyrido[2,3-f]-, and indolo[2,3-f]morphans is described.

Heteromorphan[3] synthesis usually implies the acid-induced final cyclization of a 2-(heteroarylmethyl)tetrahydropyridine. It means that the carbocyclic ring fused to the aromatic heterocycle is formed in the last stage of the synthesis. By this procedure thieno-[4-7], benzo[b]thieno-[8], indolo[2,3-f]-[9,10], pyrido[3,2-f]-[11], and pyrrolo[3,2-f]morphans[1] have been prepared in the last years.



HETEROMORPHAN

Nevertheless, this approach to heteromorphans has some limitations:

a) Those deriving from the inaccessibility of certain starting products in the case of some heterocycles. Thus, it is not possible to obtain indolylmethyl-, pyrrolylmethyl- and furfurylmagnesium[12] halides, required for the preparation of type I systems through condensation with a pyridinium salt and further reduction of the resulting dihydropyridine (Grewe route)[13].

b) It is not applicable to systems which are sensitive to the strong acid medium required in the cyclization, such as for 2-(furylmethyl)tetrahydropyridines[14,15]. Also cyclizations on indole 3-position fail because of its protonation in the reac-

tion conditions[1], as those that would lead to N-benzylpyrrolo[3,2-f]morphans[1].

c) Cyclizations on the less active positions of pentagonal heterocyclic systems, i.e. on thiophene 4-position of 2-(3-thenyl)tetrahydropyridines (synthesis of thieno[3,4-f]morphans), are not observed[4] or take place in low yield[7]. Similarly, cyclizations on 2- and 4-positions of the pyridine ring (synthesis of pyrido[2,3-f]- and [4,3-f]morphans, respectively) are presumably difficult owing to their weak reactivity towards electrophilic agents in acid medium.

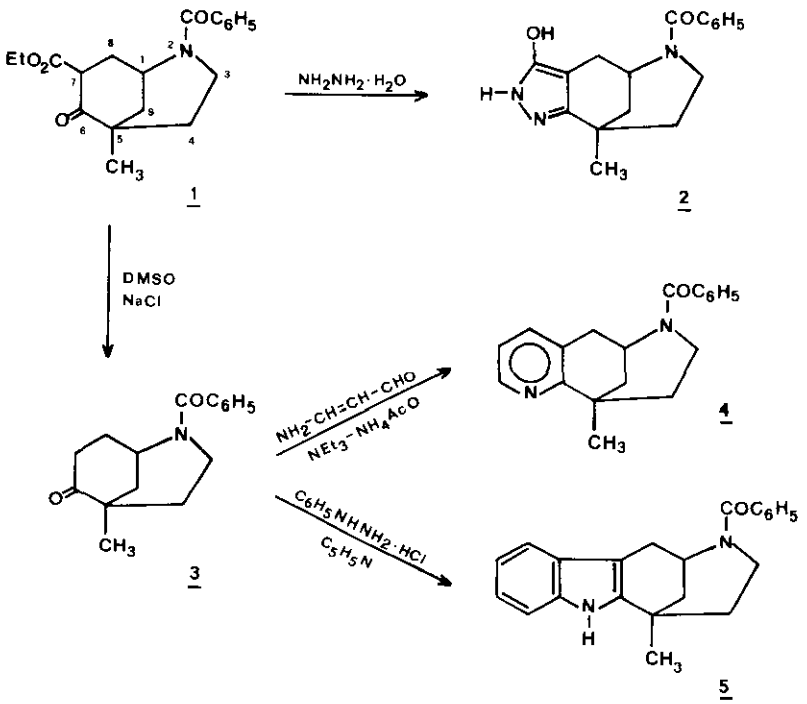
Heteromorphan synthesis has also been achieved by other ways. Thus, a pyrido[2,3-f]morphan synthesis whose last stage consists in the piperidine ring formation by lactamization from a 5,6,7,8-tetrahydroquinoline amino ester has been developed[16].

In this work we deal with a different approach to the synthesis of heteromorphans as far as we start from functionalized 2-azabicyclo[3.3.1]nonanes[17]. It implies that the heteroaromatic ring fused to the morphan nucleus is formed in the last stage of the synthesis. This procedure constitutes a general and versatile synthetic route to heteromorphans since, from a single functionalized morphan as intermediate, heteromorphans with different heteroaromatic rings can be prepared, even those inaccessible by the conventional cyclization of 2-(heteroarylmethyl)tetrahydropyridines.

Some precedents exist of heteromorphan synthesis starting from functionalized 2-azabicyclo[3.3.1]nonanes. However, by this procedure, systems whose heteroaromatic ring is fused between 6 and 7 positions of the morphan nucleus are never unequivocally obtained. Instead of this, 7,8-fused systems[18,19] or isomeric mixtures of both[20] are formed as a consequence of the morphan functionalized position. In this context, we wish to report the synthesis of 5-alkylsubstituted heteromorphans, in which the heteroaromatic ring is unambigously fused between 6 and 7 positions of the morphan nucleus, as in morphine and related synthetic analgesics[21].

The treatment of ethyl 2-benzoyl-5-methyl-6-oxo-2-azabicyclo[3.3.1]nonane-7-carboxylate (1), the first C-6 functionalized morphan described[17,22], with 80% hydrazine hydrate in ethanol-water afforded 5-methylpyrazolo[3,4-f]morphan 2. Its NMR spectrum shows, as more characteristic signals, singlets at δ7.40 and δ1.24 due to the aromatic protons[23] and the quaternary methyl group, respectively. Equatorial α-piperidine protons appear at low fields (δ5.05, methine; δ4.10, methylene) due to the amide carbonyl deshielding effect[24], their integration being smaller than the expected from the aromatic protons. This fact, together with the appearance of signals at δ4.4 and δ3.4 whose integration complements the preceding indicates that

compound 2 consisted of a mixture of two rotamers due to the presence of the N-benzoyl group, which is an unusual phenomenon in tertiary benzamides[25].



On the other hand, from 2-azabicyclo[3.3.1]nonan-6-one 3 obtained[17,22] by decarbethoxylation of the β-keto ester 1 with sodium chloride in wet DMSO, we have synthesized two other heteromorphan systems where the heteroaromatic nuclei formed in the last step of the synthesis are pyridine and indole, respectively. Thus, treatment of 3 with 3-aminoacrolein[26] in the presence of triethylamine and catalytic amount of ammonium acetate[27] led to pyrido[2,3-f]morphan 4 in moderate yields, ketone 3 being partially recovered as described in related condensations[16,20,28]. In the NMR spectrum of pyridomorphan 4 the characteristic coupling constants ($J_{\alpha\beta}$= 5Hz, $J_{\beta\gamma}$=7.5Hz and $J_{\alpha\gamma}$=2Hz) of pyridine protons are observed, the γ proton being masked under the N-benzoyl signal. The methyl signal appears as a singlet at δ1.50 and again the presence of rotamers is observed. This synthesis constitutes the first one for a pyrido[2,3-f]morphan with an alkyl substituent on 5-position of the morphan nucleus, which is a fundamental condition in synthetic opiate analgesics[21].

Finally, Fischer indole synthesis from azabicyclononanone 3 and phenylhydrazine employing pyridinium hydrochloride as catalyst[29] afforded the 5-methylindolo

[2,3-f]morphan 5. The most characteristic features in the NMR spectrum of indolomorphan 5 are again the singlet due to the quaternary methyl group and the presence of rotamers with different chemical shifts for the equatorial α-piperidine protons. This suggests that in heteromorphans 2, 4, and 5 the steric interactions between the phenyl ring and the α-alkyl substituent of the piperidine ring are lower than in simple piperidines, probably because of the conformational effects[30] on 2-azabicyclo[3.3.1]nonane systems.

Further removal of the benzoyl group in the heteromorphan systems 2, 4, and 5, could allow the introduction of pharmacologically more suitable radicals upon the nitrogen atom of the piperidine ring.

EXPERIMENTAL

Melting points were determined on a Büchi capillary apparatus and are uncorrected. NMR spectra were obtained with a Perkin-Elmer R-24B (60MHz) spectrometer. A Perkin-Elmer 577 spectrophotometer was used to obtain infrarred spectra. Elemental analyses were perfomed by Instituto de Química Bio-Orgánica, Barcelona.

6-Benzoyl-3-hydroxy-9-methyl-4,5,6,7,8,9-hexahydro-2H-5,9-methanopyrazolo[4,3-d]azocine (2). A mixture of 1 (300 mg, 0.9 mmol), 80% $NH_2NH_2.H_2O$ (630 mg, 10 mmol) and water (0.9 ml) was refluxed for 1 h. The mixture was concentrated in vacuo to dryness. Recrystallization of the residue from ethanol gave 210 mg (77%) of pyrazolone 2, mp 210°C with decomposition. NMR (DMSO-d_6), δ1.24 (s,3H,CH_3), 1.6 (br peak,4H,8- and 10-CH_2), 2.4 (complex m,2H,4-CH_2), 2.8-5.2 (complex m,3H,NCH_2 and CH), 7.4 (s,5H,C_6H_5); IR (KBr), 2500-3500 (OH) and 1600 cm^{-1} (benzamide). Anal. Calcd for $C_{17}H_{19}N_3O_2$: C,67.75; H,6.35; N,13.94. Found: C,67.89; H,6.52; N,13.87.

7-Benzoyl-10-methyl-5,6,7,8,9,10-hexahydro-6,10-methanopyrido[3,2-d]azocine(4). A mixture of 3 (450 mg, 1.75 mmol), 3-aminoacrolein[26] (246 mg, 3.5 mmol), Et_3N (5 ml) and a catalytic amount of NH_4OAc was heated on an oil bath at 100-110°C for 72 h. After concentration in vacuo the residue was dissolved in ether and extracted with 3% HCl. From the ethereal solution 125 mg (24%) of unchanged ketone 3 was recovered. The aqueous extract was basified with NH_4OH and extracted with ether. The ethereal solution was washed with brine, dried over $MgSO_4$ and concentrated to afford an oil which on chromatography (SiO_2, benzene) gave 60 mg (12%) of pyridomorphan 4. NMR ($CDCl_3$), δ1.50 (s,3H,CH_3), 1.6-2.1 (complex m,4H,9- and 11-CH_2), 2.5-3.2 (com-

plex m,2H,5-CH_2), 3.4 (m,1H,C_8-H_{ax}), 3.7 (br peak,0.4H,C_8-H_{eq}), 4.25 (br peak,0.6H, C_8-H_{eq}), 4.8 (br peak,0.4H,C_6-H), 5.3 (br peak,0.6H,C_6-H), 7.0 (dd,1H,H_β-pyr), 7.2-7.5 (masked peak,1H,H_γ-pyr), 7.3 (s,5H,C_6H_5), 8.3-8.5 (m,1H,H_α-pyr); IR ($CHCl_3$), 1615 cm^{-1} (benzamide). The picrate recrystallized from ethanol melted at 198-199°C. Anal. Calcd for $C_{19}H_{20}N_2O.C_6H_3N_3O_7$: C,57.58; N,4.44; N,13.42. Found: C,57.62; H, 4.46; N,13.33.

8-Benzoyl-11-methyl-6,7,8,9,10,11-hexahydro-7,11-methanoazocino[5,4-b]indol (5). A solution of ketone 3 (500 mg, 1.94 mmol) and phenylhydrazine hydrochloride (281 mg, 1.94 mmol) in dry pyridine (1.5 ml) was heated at 110-115°C with stirring under a nitrogen atmosphere for 18 h. The reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with 1N HCl, dried and evaporated to yield 480 mg (74%) of indolomorphan 5. An analytical sample was obtained by crystallization from ethanol, mp 211-213°C. NMR ($CDCl_3$), δ1.38 (s,3H,CH_3), 1.5-2.0 (br peak,4H,10- and 12-CH_2), 2.4-3.1 (br peak,2H,6-CH_2), 3.35 (m,1H,C_9-H_{ax}), 3.65 (br peak,0.3H,C_9-H_{eq}), 4.35 (br peak,0.7H,C_9-H_{eq}), 4.6 (br peak,0.3H,C_7-H), 5.4 (br peak, 0.7H,C_7-H), 7.0-7.6 (m,9H,ArH), 8.3 (br peak,1H,NH); IR ($CHCl_3$), 3480 (NH) and 1610 cm^{-1} (benzamide). Anal. Calcd for $C_{22}H_{22}N_2O.1/4C_2H_5OH$: C,79.03; H,6.92; N,8.18. Found: C,78.94; H,7.23; N,8.23.

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