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FUNCTIONALIZED 2-AZABICYCLO[3.3.1]NONANES. IV.[1,2] SYNTHESIS OF THE INDOLO[3,2-*b*]MORPHAN SYSTEM.

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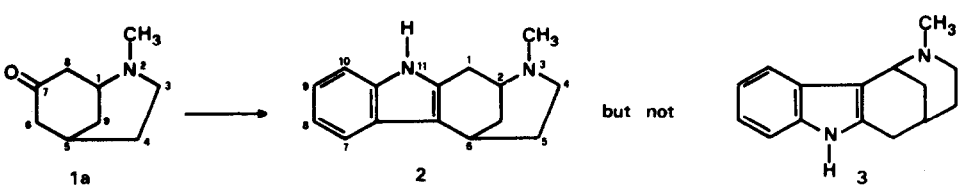
Abstract - A short route to the 2-azabicyclo[3.3.1]nonan-7-one system 1 is described. Condensation of 4-piperidones with diethyl 2-oxopropylphosphonate, followed by catalytic hydrogenation furnished the corresponding piperidylpropanones 6 which were cyclized with mercuric acetate in acetic acid to the target bicyclic ketones 1. The Fischer indole synthesis from 1a afforded regioselectively the indolo[3,2-*b*]morphan 2, a new heteromorphan type.

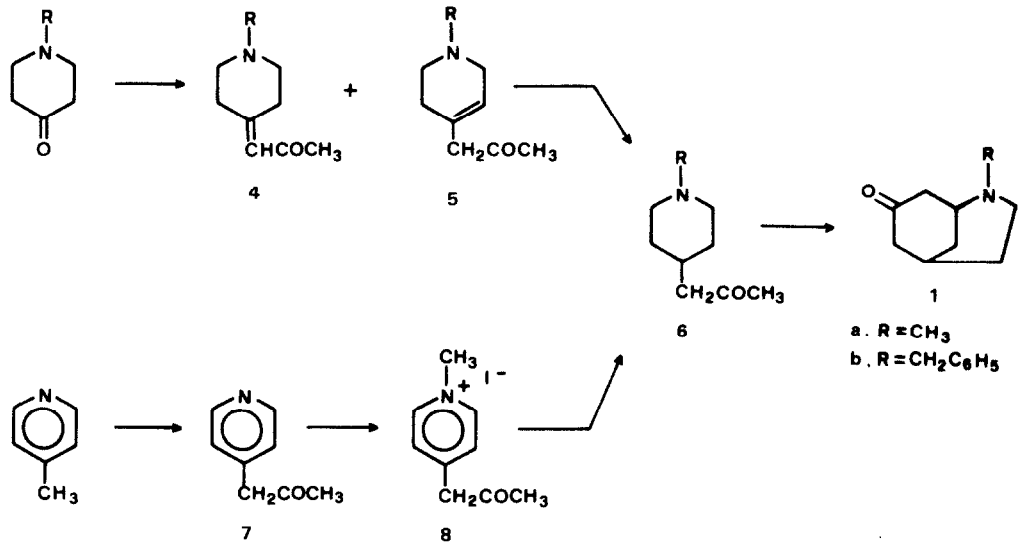
In the synthesis of indole alkaloids, the use of bridged azacyclic ketoderivatives in order to elaborate the indole nucleus in the last synthetic steps has been limited.[3] Functionalized 2-azabicyclo[3.3.1]nonanes possess synthetic interest in this context since the 2-azabicyclo[3.3.1]nonane[4] (morphan) moiety is present in *Strychnos* alkaloids. Furthermore, they can be utilized as intermediates in the synthesis of polycyclic systems related to morphine, such as heteromorphans.[5] The latter compounds come from isosteric substitution of the benzene ring in 6,7-benzomorphans[6] by an heteroaromatic system, and they are interesting because of their potential pharmacological activity as analgesics.[7]

This paper describes a successful synthetic route to the 2-azabicyclo[3.3.1]nonan-7-one system 1 and the synthesis of the indolo[3,2-*b*]morphan 2, a new heteromorphan type.

Heteromorphan synthesis generally involves the acid-induced cyclization of a 2-(heteroarylmethyl)tetrahydropyridine[8] (Grewe's method). Nevertheless, this procedure is not applicable to heterocyclic systems sensitive to the strong acid medium required in the cyclization step. This is the case of 2-(furylmethyl)-[9] and 2-(2-indolylmethyl)tetrahydropyridines[10] which would lead to furo- and indolo[3,2-*b*]morphans, respectively.

In order to overcome these limitations, we have recently developed[5] a new methodology for the synthesis of





heteromorphans consisting in the elaboration of the heterocyclic ring in the last stage of the synthesis from a conveniently functionalized 2-azabicyclo[3.3.1]nonane. By this procedure we have prepared pyrazolo[3,4-*b*]-, pyrido[2,3-*b*]-, and indolo[2,3-*b*]morphans[5] from a single 6-functionalized 2-azabicyclo[3.3.1]nonane.[11] According to the same planning we describe here the first synthesis of an indolo[3,2-*b*]morphan system.

The azabicyclononanones **1** were obtained by oxidative cyclization of an appropriate 1-(1-alkyl-4-piperidyl)-2-propanone, **6**. This ring closure implies the formation of the C_1-C_8 bond in the last synthetic step[12] by intramolecular cyclization between an iminium salt, generated by mercuric acetate oxidation, and the α-position of a ketone carbonyl group.[13]

We have obtained 4-piperidylpropanones **6** in good yields by Wadsworth-Emmons condensation[14] between the appropriate N-alkyl-4-piperidone and diethyl 2-oxopropylphosphonate,[15,16] followed by catalytic hydrogenation of the resulting mixture of enones **4** and **5**. The ratio of isomers[17] was determined from the integrated intensity of the signals due to the vinylic protons in the NMR spectra, at δ5.9 (W=3Hz) for **4a,b** and at δ5.4 (W=7Hz) for **5a,b**. The partial isomerization of the initially formed α,β-unsaturated ketones **4** to tetrahydropyridines **5** under the basic reaction conditions is a process similar to the one previously observed in related condensations.[18] Alternatively, **6a** was obtained by quaternization of 4-pyridylpropanone **7** with methyl iodide followed by catalytic hydrogenation of the resulting pyridinium salt. This last procedure is less convenient since preparation of ketone **7** by acylation of 4-picoline with ethyl acetate in the presence of lithium diisopropylamide takes place in low yield.[19]

Treatment of ketones **6a** or **6b** with mercuric acetate in refluxing aqueous acetic acid led, respectively, to the cyclized products **1a** or **1b**, as expected. In spite of the moderate yield for the cyclization step, the synthetic way that we have developed for **1a** and **1b** seems to be better than those previously described[20,21] (seven steps from diethyl 3-oxoglutarate), because of the simplicity of the method, the low number of steps, and the satisfactory overall yield.

Finally, the Fischer indole synthesis from **1a** took place regioselectively when working with ethanol saturated with hydrogen chloride,[22] to give the desired indolo[3,2-*b*]morphan **2** in 62% yield. On the contrary, when using

acetic or formic acid as catalyst we obtained complex reaction mixtures. The formation of indolo[2,3-*g*]morphan 3 was never detected.

The structural assignment of 2 was made from its spectroscopic data. Thus, in the ^{1}H NMR spectrum, the angular C_2-H methine proton resonates at a field higher than δ3.4, as in 6,7-benzomorphans and heteroaromatic analogues.[23] Instead, when the aromatic nucleus is condensed with the *g* side (C_7-C_8) of the morphan system, the methine proton α to the aromatic ring and to the piperidine nitrogen atom is characterized by a downfield signal below δ3.4.[24] Furthermore, the ^{13}C NMR chemical shifts of C-1 (δ20.56,t) and C-6 (δ24.38,d) confirm clearly this structure. Thus, the relatively low-field value of the former is due to the γ-effect of the N-methyl group,[25] whereas the chemical shift of the latter is the one expected from 1,2,3,4-tetrahydrocarbazole data.[26]

The regioselective formation of indolomorphan 2 can be interpreted by considering that the phenylhydrazone of the unsymmetrically substituted ketone 1a leads preferentially to the enehydrazine tautomer with a C_6-C_7 double bond, which undergoes the rearrangement process of the Fischer reaction.[27] However, this result could simply reflect the instability of the regioisomer indolo[2,3-*g*]morphan 3 under the acidic reaction conditions, as has been reported for deethyluleine.[28]

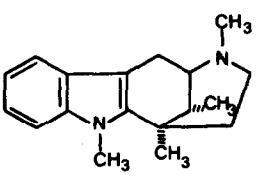
The preparation of the indolo[3,2-*f*]morphan 2 makes evident the synthetic usefulness of functionalized 2-azabicyclo[3.3.1]nonanes and completes the series of the four possible indolomorphans in which varies the mode of fusion of the morphan carbocyclic ring with the indole nucleus.[29-31]

The application of 2-azabicyclo[3.3.1]nonan-7-one systems to the synthesis of *Strychnos* indole alkaloids is in progress.

EXPERIMENTAL

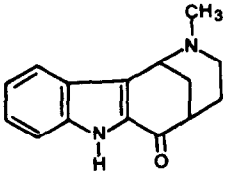
General. NMR spectra were recorded in $CDCl_3$ with TMS as internal standard (PMR: Perkin-Elmer R-24B; CMR: Varian XL-200). Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Distillations were carried out on a Fischer Spaltrohr MMS·152 microcolumn. Aluminium Oxide 90 (Merck) was used for column chromatography. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ powder. Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

1-(1-Methyl-4-piperidylidene)-2-propanone (4a). 1-Methyl-4-piperidone (5.45 ml, 46 mmol) was added to a stirred solution of diethyl 2-oxopropylphosphonate[15] (10 g, 50 mmol) and potassium hydroxide (2.88 g, 50 mmol) in 4:1 ethanol-water (37.5 ml) cooled at 5°C. The resulting mixture was stirred at room temperature for 3 hr. Ethanol was evaporated and the residue was extracted with ether. The ethereal extracts were evaporated to give a crude 4a and 5a mixture. After *vacuum* distillation (b.p. 42-43°C/0.1 mm Hg), 5.6 g (78% yield) of a mixture of 4a and 5a were obtained. Although the α,β-unsaturated ketone 4a partially isomerizes to the β,γ-unsaturated one 5a during its purification by column chromatography, a pure sample of 4a could be isolated on elution with benzene; NMR 2.01 (s,



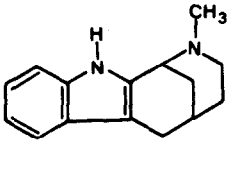
Indolo[2,3-f]morphan

ref. 29



Indolo[2,3-g]morphan
(Deethyldasycarpidone)

ref. 30



Indolo[3,2-g]morphan

ref. 31

3H,$COCH_3$), 2.11 (s,3H,NCH_3), 1.9-2.6 (m,6H), 2.65-3.00 (m,2H,NCH_{eq}), 5.95 (s,1H,C=CH); IR (NaCl) 1710 (ketone). The picrate melted at 138-139°C (ethanol). (Found: C, 47.36; H, 4.71; N, 14.33. Calcd.for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.78; N, 14.65).

1-Methyl-4-(2-oxopropyl)pyridinium iodide (8). A solution of 1-(4-pyridyl)-2-propanone (7)[19] (2.33 g, 17.25 mmol) in 5 ml of anhydrous acetone was added dropwise to a cooled (0°C) solution of methyl iodide (1.16 ml, 18.7 mmol) in 6 ml of anhydrous benzene. The resulting mixture was stirred overnight at room temperature. The precipitate was filtered, dried, and crystallized from anhydrous acetone to give 3.15 g (66% yield) of 8; NMR 2.34 (s,3H,$COCH_3$), 4.37 (s,2H,CH_2), 4.54 (s,3H,NCH_3), 7.99 (d,2H,H_β-pyr), 9.12 (d,2H,H_α-pyr). (Found: C, 38.72; H, 4.33; I, 45.91; N, 5.37. Calcd.for $C_9H_{12}INO$: C, 38.98; H, 4.33; I, 45.84; N, 5.05).

1-(1-Methyl-4-piperidyl)-2-propanone (6a).

Method A. A mixture of 4a and 5a (4.3 g, 28 mmol) in 100 ml of ethanol was hydrogenated at room temperature and atmospheric pressure over 10% palladium on charcoal (215 mg). When the absorption ceased, the catalyst was filtered off and the filtrate was evaporated to give piperidylpropanone 6a (4.27 g, 98%). An analytical sample was obtained by column chromatography using benzene as eluent; NMR 1.0-2.4 (m,9H), 2.08 (s,3H,$COCH_3$), 2.20 (s,3H,NCH_3), 2.60-2.95 (m,2H,NCH_{eq}); IR ($CHCl_3$) 1710 (ketone). The picrate melted at 166-167°C (ethanol). (Found: C, 46.79; H, 5.22; N, 14.22. Calcd.for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.20; N, 14.58).

Method B. A solution of pyridinium iodide 8 (2.78 g, 10 mmol) in 40 ml of methanol was hydrogenated at room temperature and atmospheric pressure over platinum oxide (278 mg). When the absorption ceased, the catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in water, basified with 4N sodium hydroxide, and extracted with ether to give 1.48 g (96%) of amino ketone 6a.

2-Methyl-2-azabicyclo[3.3.1]nonan-7-one (1a). A mixture of 6a (3 g, 19.35 mmol), yellow mercuric oxide (42 g, 193 mmol), and 40% acetic acid (185 ml) was refluxed for 5 hr 30 min. The precipitate of mercurous acetate formed during the reaction was filtered off and washed with 40% acetic acid. The combined filtrates were saturated with hydrogen sulfide for 45 min. Mercuric sulfide was removed by filtration through "Hyflo Super-Cel" and washed with 40% acetic acid. The resulting solution was refluxed overnight. After cooling, the reaction mixture was basified with 20% sodium hydroxide and extracted with methylene chloride. Evaporation of the dried organic extracts gave a reddish oil which, by *vacuum* distillation, afforded morphan 1a (0.95 g, 32%) as a yellow oil, b.p. 100-110°C/0.1 mm Hg; ^1H NMR 1.4-3.0 (m, 11H), 2.30 (s,3H,NCH_3), 3.05-3.35 (m, 1H,C_1-H); IR ($CHCl_3$) 1700 (ketone); ^{13}C NMR 212.2 (s,C-7), 55.88 (d,C-1), 47.00 (t,C-6), 46.47 (t,C-3), 43.10 (q,NCH_3), 39.18 (t,C-8), 33.09 (t,C-9), 31.12 (t,C-4), 28.02 (d,C-5). The picrate melted at 220-222°C dec. (Lit.[20] 224-226°C dec.). (Found: C, 47.08; H, 4.74; N, 14.37. Calcd.for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.71; N, 14.65).

1-(1-Benzyl-4-piperidyl)-2-propanone (6b). 1-Benzyl-4-piperidone (8 ml, 46 mmol) was added to a stirred solution of diethyl 2-oxopropylphosphonate[15] (10 g, 50 mmol) and potassium hydroxide (2.88 g, 50 mmol) in 4:1 ethanol-water (37.5 ml) cooled at 5°C. The resulting mixture was stirred at room temperature for 2 hr. Ethanol was evaporated and the residue was extracted with benzene. The organic extracts were dried and evaporated to give a mixture of ketones 4b and 5b (10.4 g). This mixture was dissolved in 150 ml of ethanol and hydrogenated at room temperature and atmospheric pressure over 10% palladium on charcoal (520 mg). When the absorption ceased, the catalyst was filtered off and the filtrate was evaporated to give piperidylpropanone 6b (9.44 g, 90% overall yield); NMR 1.0-2.4 (m,9H), 2.05 (s,3H,$COCH_3$), 2.5-3.0 (m,2H,NCH_{eq}), 3.40 (s,2H,CH_2Ar), 7.15 (s,5H,ArH); IR ($CHCl_3$) 1710 (ketone). The picrate melted at 137-138°C (ethanol). (Found: C, 54.69; H, 5.26; N, 11.98. Calc.for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.21; N, 12.17).

2-Benzyl-2-azabicyclo[3.3.1]nonan-7-one (1b). A mixture of amine 6b (4 g, 17.3 mmol), mercuric acetate (55.1 g, 173.1 mmol) and 5% acetic acid (200 ml) was refluxed for 5 hr. After removal of mercurial derivatives as above, the resulting solution was refluxed overnight. The oily residue obtained after usual work-up was filtered through Aluminium Oxide (benzene as eluent) to give morphan 1b (0.79 g, 20%). When the reaction times were shortened (45 min and 6 hr, respectively) the yield of morphan 1b increases (32.5%) but it is accompanied by the starting piperidine 6b. This mixture proved to be difficult to separate by column chromatography or by *vacuum* distillation; ^1H NMR 1.4-3.0 (m,11H), 3.05-3.35 (m,1H,C_1-H), 3.50 (s,2H,CH_2Ar), 7.15 (s,5H,ArH); IR ($CHCl_3$) 1690 (ketone); ^{13}C NMR 128.80 (d), 128.34 (d), 127.17 (s), 59.41 (t, CH_2Ar), 53.81 (d,C-1), 47.08 (t,C-6), 44.82 (t,C-3), 40.02 (t,C-8), 32.82 (t,C-9), 30.94 (t,C-4), 28.58 (d,C-5). The picrate melted at 179-180°C (ethanol). (Found: C, 55.07; H, 4.80; N, 12.22. Calc.for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.80; N, 12.22).

3-Methyl-1,2,3,4,5,6-hexahydro-2,6-methanoazocino[4,5-b]indole (2). Phenylhydrazine hydrochloride (930 mg, 6.49 mmol) and anhydrous sodium carbonate (350 mg) were added to a stirred solution of ketone 1a (910 mg, 5.9 mmol) in 70 ml of absolute ethanol. The resulting mixture was refluxed under nitrogen for 8 hr. After cooling,

the solvent was evaporated and the resulting residue was diluted with water and extracted with methylene chloride. Drying and evaporation of the organic extracts followed by distillation of excess phenylhydrazine afforded 1.3 g of the corresponding phenylhydrazone. A solution of this hydrazone in 10 ml of absolute ethanol saturated with dry hydrogen chloride was refluxed for 3 hr. The resulting solution was cooled overnight and evaporated. The residue was dissolved in aqueous ammonia and extracted with ether. The ethereal extracts were dried and evaporated to give 770 mg of 2 (overall yield 58%). A sample recrystallized from anhydrous ether melted at 156-157°C; ^{1}H NMR 1.55-3.40 (m,10H), 2.38 (s,3H,NCH_3), 6.8-7.5 (m,4H,ArH), 7.88 (br s,1H,NH); ^{13}C NMR 20.56 (t,C-1), 24.38 (d,C-6), 30.16 (t,C-5), 33.24 (t,C-12), 43.11 (q,NCH_3), 46.49 (t,C-4), 53.50 (d,C-2), 110.54 (d,C-10), 112.94 (s,C-6a), 117.44 (d, C-7), 119.12 (d,C-8), 120.86 (d,C-9), 126.33 (s,C-6b), 133.93 (s,C-11a), 135.96 (s,C-10a). (Found: C, 77.81; H, 8.44; N, 11.32. Calcd.for $C_{15}H_{18}N_2$.1/3 $C_4H_{10}O$: C, 78.15; H, 8.56; N, 11.15).

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