Benzomorphan Related Compounds. II (1). New Synthesis Route to Thienomorphans

J. Bosch, R. Granados, and F. López

Department of Organic Chemistry, Faculty of Chemistry, Barcelona University, Barcelona, Spain

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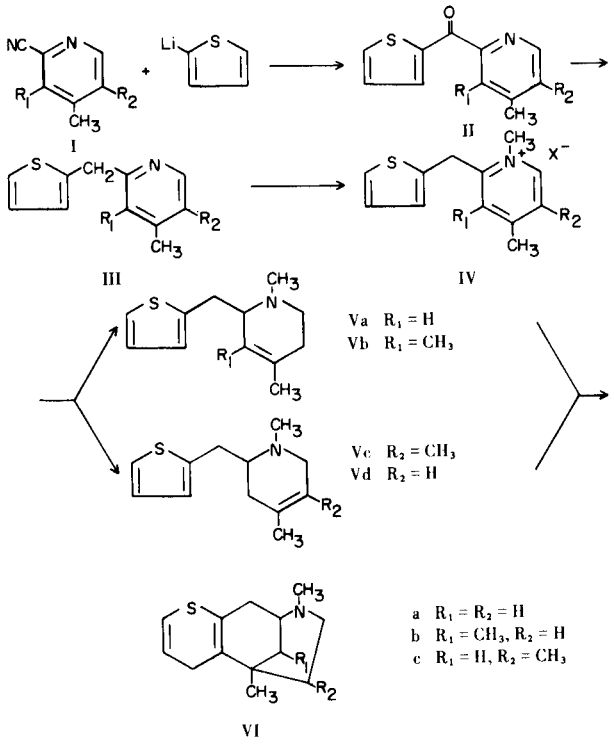
A new synthesis route to α-2,5,9-trimethylthieno[3,2-*f*]morphan and two analogous compounds from cyanopyridines and 2-thienyllithium is described. Spectroscopic data of these substances and their intermediates are included.

It is well known that interest in benzomorphans is due to their pharmacological action as strong analgesics and to the possibility of isolating, in some degree, their analgesic activity from addiction (physical dependence). More recently attention has been fixed on compounds analogous to benzomorphans in which the benzene ring has been substituted by a heteroaromatic ring (2) and which can be designated by the general name of heterocondensed morphans or simply "heteromorphans".

Recently, some thieno[2,3-*f*]morphans have been described (3), and in a previous paper (1) we have reported the preparation of a compound of this type, α-2,5,9-trimethylthieno[3,2-*f*]morphan, by a sequence of reactions similar to those used by Grewe (4) in the synthesis of morphinan and widely employed in the preparation of benzomorphans. In the present work an alternative route for the preparation of this compound and two analogous ones, 2,4,5-trimethylthieno[3,2-*f*]morphan and 2,5-dimethylthieno[3,2-*f*]morphan, is described. Synthesis of these compounds may give a better understanding of the structure-activity relationship in benzomorphans, especially the role of the aromatic ring and the effect of deleting a methyl group in the 9-position and incorporating it in the 4-position.

The new method described for the synthesis of these substances (Fig. 1) which can be extended to that of benzomorphans involves condensation of a cyanopyridine with 2-thienyllithium. Reduction of the resulting ketones to thenylpyridines, quaternization and borohydride reduction of the resulting *N*-methyl quaternary pyridine salts yields tetrahydropyridines equivalent to those obtained (5) by condensation of the lithium derivative of a bromopyridine with an aromatic aldehyde. In this last procedure some inconveniences appear during the reduction of the carbinol initially formed (as we have reported (6) with several 3,4,5-trimethoxyphenyl-(2-pyridyl)carbinols) and low yields are obtained in other occasions (as for example with 2-furyl-(2-pyridyl)carbinols (7).

(Figure 1)



The requisite cyanopyridines (I) were prepared by reaction between 1-methoxy-3,4-dimethylpyridinium methosulphate and an alkali cyanide (8). From the resulting mixture, 2-cyano-4,5-dimethylpyridine was obtained by crystallization and easily identified by its nmr spectrum in which two singlets appeared at δ 7.45 and δ 8.41 due to protons in positions 3 and 6, respectively. The other isomer, 2-cyano-3,4-dimethylpyridine, was obtained by crys-

tallization of its hydrochloride from the mother liquors. Its nmr spectrum showed two doublets at δ 7.32 and δ 8.43 due to protons in positions 5 and 6 of the ring.

Condensation of cyanopyridines (I) with 2-thienyllithium led to ketones (II), whose Wolff-Kishner reduction by the Huang-Minlon modification, afforded thenylpyridines (III) in 50-55% yield. The nmr spectra of III showed, in all cases, a singlet at δ 4.1-4.3 which must be assigned to the methylene group between the two rings. Reaction of IIIb and IIIc with methyl iodide yielded the corresponding methiodides (IV). The methiodide of IIIa was unstable in air and therefore IIIa was transformed in its methobromide. Sodium borohydride reduction in methanolic solution of *N*-methyl quaternary pyridine salts IVb and IVc afforded in good yields tetrahydropyridine bases Vb and Vc, respectively. Compound Vb was identical to the one obtained by the Grewe synthesis (1). Similar treatment of 2-thenyl-1,4-dimethylpyridinium bromide (IVa) gave a mixture of two compounds in the ratio 7:3 (by glc). They correspond respectively to the isomeric 1,2,3,6- and 1,2,5,6-tetrahydropyridines (V), also identical to the ones obtained by the Grewe method (9). Their separation and purification was achieved by fractional crystallization of their hydrochlorides. The position of the double bond in Va and Vd was determined by nmr spectral data. Thus, Δ^4-tetrahydropyridine (Vd) (longest glc retention time) showed a broad signal at δ 5.37 due to the olefinic proton, whereas in the Δ^3 isomer (Va) (lowest glc retention time) this signal appears at δ 5.27, in accordance with the results reported by May (10) for analogous compounds. Furthermore a Δ^4 structure for the major compound is consistent with the general results obtained in the borohydride reduction of *N*-methyl quaternary pyridine salts (11).

Cyclization of crude V effected by heating with 48% hydrobromic acid (bath temperature 135°) for 3-4 hours afforded the corresponding thieno[3,2-*f*]morphans (VI). In the nmr spectra of all thienomorphans two doublets appeared in the aromatic region indicating an AX system formed by protons of the thiophene ring and a singlet at δ 1.3 due to the methyl group in the 5-position. In addition, the nmr spectrum of the thienomorphan VIb showed a doublet at δ 0.83 due to the methyl group in the 9-position. These data showed evidence for the α diastereomer in which methyl groups in position 5 and 9 were in a *cis* orientation. Similarly, in the thienomorphan VIc spectrum, the 4-methyl group appears as a doublet, but is diamagnetically shifted at δ 0.64, indicating a diastereomer with equatorial conformation. Both results are similar to the ones obtained by hydrogen bromide cyclization in the benzomorphan series (12,13).

The accessibility of cyanopyridines and lithium derivatives of benzene or heteroaromatic systems, and the easy transformation of the resulting ketones to tetrahydropyridines, precursors of benzo and heteromorphans make the described method a valuable procedure for the synthesis of these substances. Presently we are studying the extension of this procedure to prepare thieno[2,3-*f*]morphans and furomorphans.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer model R-12 (60 MHz, TMS at δ 0,0 ppm as internal standard) with deuteriochloroform as solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). The glc were run isothermally at 140° on a Carlo Erba (Fractovap. Mol. GT) chromatograph with a flame ionization detector. A 2 m glass column, 4 mm in diameter was used, packed with 6% XE-60 on 80-100 mesh Chromorsorb P silanized.

2-Cyano-3,4-dimethylpyridine (Ib) and 2-Cyano-4,5-dimethylpyridine (Ic).

Dimethyl sulfate (126 g., 0.1 mole) was added dropwise to 123 g. (1.0 mole) of 3,4-lutidine *N*-oxide with vigorous stirring, keeping the temperature between 80° and 90°. When the addition was complete the mixture was heated for 2 hours at 100°. 1-Methoxy-3,4-dimethylpyridinium methosulphate thus obtained was dissolved in 250 ml. of water and added slowly to a solution of 120 g. (3.5 mole) of sodium cyanide in 570 ml. of water, previously cooled to 0-5° and stirred under nitrogen for 1 hour. The resulting mixture was stirred 24 hours under nitrogen at room temperature and extracted with chloroform. The extracts were dried and the solvent removed giving a liquid which was filtered with benzene through a silica-gel column yielding a mixture of 2-cyano-3,4-dimethylpyridine (Ib) and 2-cyano-4,5-dimethylpyridine (Ic). On cooling in methanol 2-cyano-4,5-dimethylpyridine (Ic) was separated.

An analytical sample of Ic melted at 77-78° (acetone); nmr: 2.32 (s, 6, C_3-CH_3 and C_4-CH_3), 7.45 (s, 1, C_3-H), 8.41 (s, 1, C_6-H).

Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.61; H, 6.17; N, 20.93.

The resulting mixture enriched in 2-cyano-3,4-dimethylpyridine was converted to the hydrochloride. Crystallization from acetone afforded 2-cyano-3,4-dimethylpyridine hydrochloride, m.p. 160-162°.

An analytical sample of 2-cyano-3,4-dimethylpyridine (Ib) sublimed at 40°/0.1 mm Hg, m.p. 46-47°; nmr: 2.37 (s, 3, C_4-CH_3), 2.50 (s, 3, C_3-CH_3), 7.32 (d, 1, C_5-H), 8.43 (d, 1, C_6-H).

Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.99; H, 6.20; N, 21.15.

The procedure was repeated and 22.5 g. of Ic, 26 g. of Ib and 9 g. of a mixture of both isomers was obtained.

2-Thienyl Pyridyl Ketones (II).

An ethereal butyllithium solution (460 ml., 0.83 *N*) was added dropwise to 0.38 mole of thiophene in 85 ml. of dry ether (temperature between -5 and -10°). The mixture was allowed to warm at room temperature, stirred for 1 hour and refluxed for 30 minutes. Then, 0.26 mole of cyanopyridine I in dry benzene was added dropwise (temperature between -10 and -20°). The resulting solution was refluxed for 30 minutes, hydrolized by boiling with 250 ml. of 30% hydrochloric acid and distilled to remove substances boiling below 100°.

The resulting solution was refluxed for 1 hour, rendered basic

with 40% sodium hydroxide solution and extracted with an organic solvent. The organic layer was dried and the solvent removed, giving a residue which corresponded to ketone II.

2-Thienyl 4-Methyl-2-pyridyl Ketone (IIa).

This compound was obtained by distillation (b.p. 107-115°/0.7 mm Hg) in 70% yield from Ia. An analytical sample recrystallized from methanol melted at 61-61.5°; nmr: 2.41 (s, 3, CH_3), 7.10-7.33 (m, 2, C_4-H thiophene and C_5-H pyridine), 7.72 (d, 1, C_5-H thiophene), 7.99 (s, 1, C_3-H pyridine), 8.37 (d, 1, C_3-H thiophene), 8.58 (d, 1, C_6-H pyridine).

Anal. Calcd. for $C_{11}H_9NOS$: C, 65.02; H, 4.46; N, 6.89; S, 15.74. Found: C, 65.01; H, 4.48; N, 6.91; S, 15.76.

2-Thienyl 3,4-Dimethyl-2-pyridyl Ketone (IIb).

This compound was obtained by distillation (b.p. 125-140°/0.8 mm Hg) in 73% yield from Ib; nmr: 2.33 (s, 6, C_3-CH_3 and C_4-CH_3), 7.0-7.32 (m, 2, C_5-H pyridine and C_4-H thiophene), 7.67 (d, 2, C_3-H and C_5-H thiophene), 8.35 (d, 1, C_6-H). Recrystallization of the hydrochloride from acetone gave a product of m.p. 162-164°.

Anal. Calcd. for $C_{12}H_{12}ClNOS$: C, 56.80; H, 4.76; N, 5.51; S, 12.63; Cl, 13.97. Found: C, 56.72; H, 4.78; N, 5.52; S, 12.69; Cl, 14.27.

2-Thienyl 4,5-Dimethyl-2-pyridyl Ketone (IIc).

This compound obtained in a 90% yield was purified by crystallization from acetone, m.p. 101-103° (b.p. 150-162°/0.6 mm Hg); nmr: 2.32 (s, 6, C_4-CH_3 and C_5-CH_3), 7.08 (dd, 1, C_4-H), 7.60 (dd, 1, C_3-H), 7.90 (s, 1, C_3-H pyridine), 8.29-8.42 (m, 2, C_6-H and C_3-H).

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.35; H, 5.10; N, 6.45; S, 14.75. Found: C, 66.31; H, 5.11; N, 6.24; S, 14.31.

2-Thenylpyridines (III).

To a solution of 34.8 g. of potassium hydroxide in 250 ml. of diethylene glycol, 0.17 mole of II and 27.8 g. of 85% hydrazine hydrate were added. The resulting mixture was refluxed for 1 hour and then enough water and excess hydrazine hydrate was distilled to raise the temperature to 220°, and the remaining solution was refluxed for 4 hours. The reaction mixture was poured over 200 g. of ice and extracted several times with ether. The ethereal layer was washed with water, dried and the solvent removed. Distillation of the oily residue gave thenylpyridines (50-55% yields), which were characterized as the hydrochlorides.

2-(2-Thenyl)-4-methylpyridine (IIIa) Hydrochloride.

This compound had m.p. 140-141° (acetone); nmr (base) (carbon tetrachloride): 2.11 (s, 3, CH_3), 4.14 (s, 2, CH_2), 6.69-7.01 (m, 5, C_3-H, C_5-H and thiophene), 8.22 (d, 1, C_6-H).

Anal. Calcd. for $C_{11}H_{12}ClNS$: C, 58.53; H, 5.36; N, 6.20; S, 14.20; Cl, 15.70. Found: C, 58.61; H, 5.42; N, 6.21; S, 13.86; Cl, 15.60.

2-(2-Thenyl)-3,4-dimethylpyridine (IIIb) Hydrochloride.

This compound had m.p. 181-183° (acetone); nmr (base) (carbon tetrachloride): 2.16 (s, 6, C_3-CH_3 and C_4-CH_3), 4.22 (s, 2, CH_2), 6.61-7.00 (m, 4, thiophene and C_5-H), 8.11 (d, 1, C_6-H).

Anal. Calcd. for $C_{12}H_{14}ClNS$: C, 60.11; H, 5.89; N, 5.85; S, 13.37; Cl, 14.79. Found: C, 59.90; H, 6.00; N, 6.13; S, 13.40; Cl, 14.81.

2-(2-Thenyl)-4,5-dimethylpyridine (IIIc) Hydrochloride.

This compound had m.p. 142-144° (acetone-methanol); nmr (base) (carbon tetrachloride): 2.12 (s, 6, C_3-CH_3 and C_4-CH_3), 4.14 (s, 2, CH_2), 6.77-7.07 (m, 4, thiophene and C_3-H), 8.14 (s, 1, C_6-H).

Anal. Calcd. for $C_{12}H_{14}ClNS$: C, 60.11; H, 5.89; N, 5.85; S, 13.37; Cl, 14.79. Found: C, 60.22; H, 5.95; N, 5.90; S, 13.46; Cl, 14.80.

2-(2-Thenyl)-1,4-dimethylpyridinium Bromide (IVa).

Excess methyl bromide was passed through a cool stirred solution of IIIa in acetone-benzene (3:1). The mixture was stirred for 1 hour at room temperature and then refluxed for 4 hours affording IVa in 66% yield, m.p. 214-215° (acetone-methanol); nmr: 2.55 (s, 3, C-CH_3), 4.57 (s, 3, N-CH_3), 4.92 (s, 2, CH_2), 6.90-7.38 (m, 3, thiophene), 7.58-7.74 (m, C_3-H and C_5-H), 9.45 (d, 2, C_6-H).

Anal. Calcd. for $C_{12}H_{14}BrNS$: C, 50.70; H, 4.96; N, 4.92; Br, 28.11. Found: C, 50.59; H, 5.12; N, 4.89; Br, 28.22.

2-(2-Thenyl)-1,3,4-trimethylpyridinium Iodide (IVb).

A solution of 2.1 ml. of methyl iodide in 10 ml. of benzene was added portionwise to a stirred solution of 7 g. of the thenylpyridine (III) in 10 ml. of acetone. The mixture was stirred at room temperature for 1 hour, and then refluxed for 4 hours. By cooling, the methiodide (IVb) was obtained in 65% yield. An analytical sample was crystallized from acetone, m.p. 149-150°; nmr: 2.50 (s, 3, CH_3), 2.59 (s, 3, CH_3), 4.48 (s, 3, N-CH_3), 4.81 (s, 2, CH_2), 6.73-7.32 (m, 3, thiophene), 7.79 (d, 1, C_5-H), 9.18 (d, 1, C_6-H).

Anal. Calcd. for $C_{13}H_{16}INS$: C, 45.23; H, 4.67; N, 4.06; S, 9.28; I, 36.76. Found: C, 45.24; H, 4.91; N, 4.14; S, 9.36; I, 36.81.

2-(2-Thenyl)-1,4,5-trimethylpyridinium Iodide (IVc).

This compound was obtained in 90% yield by the same procedure of IVb, m.p. 159-161°. Its unstability in air made impossible a further purification and characterization; nmr: 2.45 (s, 6, C_4-CH_3 and C_5-CH_3), 4.49 (s, 3, N-CH_3), 4.85 (s, 2, CH_2), 6.96-7.34 (m, 3, thiophene), 7.61 (s, 1, C_3-H), 9.34 (s, 1, C_6-H).

2-Thenyltetrahydropyridines (V).

Sodium borohydride (0.12 mole) was added portionwise in the cold to a stirred solution of 0.06 mole of *N*-methyl quaternary pyridine salt (IV) in 120 ml. of methanol. The mixture was gently refluxed for 6 hours, cooled, diluted with cold water and extracted with ether. Solvent was removed from the dried extract leaving the crude tetrahydropyridines (V) as an oil which was purified by distillation *in vacuo*.

2-(2-Thenyl)-1,4-dimethyl-1,2,3,6-tetrahydropyridine (Vd) Hydrochloride.

Reduction of 2-(2-thenyl)-1,4-dimethylpyridinium bromide (IVa) as above gave (b.p. 110-135°/0.5 mm Hg) a two component mixture of 2-(2-thenyl)-1,4-dimethyl-1,2,3,6-tetrahydropyridine (Vd) and 2-(2-thenyl)-1,4-dimethyl-1,2,5,6-tetrahydropyridine (Va) in the ratio (glc) of 7:3, which was converted to its hydrochloride. Crystallization from acetone gave Vd hydrochloride, m.p. 137-139°; nmr (base): 1.64 (s, 3, C-CH_3), 2.41 (s, 3, N-CH_3), 5.37 (broad, 1, =C-H), 6.74-7.22 (m, 3, thiophene).

Anal. Calcd. for $C_{12}H_{18}ClNS$: C, 59.11; H, 7.44; N, 5.74. Found: C, 58.90; H, 7.57; N, 5.50.

2-(2-Thenyl)-1,4-dimethyl-1,2,5,6-tetrahydropyridine (Va) Hydrochloride.

The filtrate was concentrated yielding a small amount of Va hydrochloride m.p. 108-109° (acetone); nmr (base): 1.66 (s, 3,

C-CH_3), 2.42 (s, 3, N-CH_3), 5.27 (broad, 1,=C-H), 6.83-7.20 (m, 3, thiophene).

Anal. Calcd. for $C_{12}H_{18}ClNS \cdot 1/2H_2O$: C, 57.24; H, 7.57; N, 5.54; Cl, 14.04. Found: C, 57.34; H, 7.57; N, 5.56; Cl, 14.05.

2-(2-Thenyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (Vb).

This compound was obtained (b.p. 80-87°/0.07 mm Hg) in 35% yield from IVb and was characterized as the hydrochloride, m.p. 120-122° (acetone-ether); nmr (base): 1.59 (s, 6, C_3-CH_3 and C_4-CH_3), 2.39 (s, 3, N-CH_3), 6.78-7.10 (m, 3, thiophene).

Anal. Calcd. for $C_{13}H_{20}ClNS$: C, 60.57; H, 7.81; N, 5.43; S, 12.45; Cl, 13.75. Found: C, 60.93; H, 8.04; N, 5.51; S, 12.05; Cl, 14.12.

2-(2-Thenyl)-1,4,5-trimethyl-1,2,3,6-tetrahydropyridine (Vc).

This compound was obtained (b.p. 100-104°/0.15 mm Hg) in 50% yield from IVc, and was characterized as the hydrochloride, m.p. 134-135° (acetone-ethanol absolute); nmr (base): 1.58 (s, 6, C_4-CH_3 and C_5-CH_3), 2.41 (s, 3, N-CH_3), 6.73-7.26 (m, 3, thiophene).

Anal. Calcd. for $C_{13}H_{20}ClNS$: C, 60.57; H, 7.81; N, 5.43; S, 12.45; Cl, 13.75. Found: C, 60.28; H, 7.78; N, 5.41; S, 12.27; Cl, 13.78.

Thieno[3,2-*f*]morphans (VI).

Tetrahydropyridine (V) (5 g.) and 60 ml. of 48% hydrobromic acid were kept at 130-135° (oil-bath temperature) for 3 hours, cooled, poured into ice water, basified with concentrated ammonium hydroxide, and extracted with ether. The dried ethereal extracts were evaporated at reduced pressure to give an oily material which was distilled *in vacuo*.

2,5-Dimethylthieno[3,2-*f*]morphan (VIa).

This compound obtained in 49% yield from a mixture of 1,2,3,6- and 1,2,5,6-tetrahydropyridines (V) was characterized as the hydrochloride, m.p. 203-204° (acetone); nmr (carbon tetrachloride): 1.30 (s, 3, C-CH_3), 2.27 (s, 3, N-CH_3), 6.70 (d, 1, H_β), 6.92 (d, 1, H_α).

Anal. Calcd. for $C_{12}H_{18}ClNS$: C, 59.11; H, 7.44; N, 5.74; S, 13.15; Cl, 14.54. Found: C, 58.87; H, 7.68; N, 5.57; S, 12.86; Cl, 14.86.

α-2,5,9-Trimethylthieno[3,2-*f*]morphan (VIb).

This compound obtained in 45% yield from Vb was crystallized from acetone and purified by sublimation (55-60°/0.3 mm Hg), m.p. 78-79°; nmr: 0.84 (d, 3, C_9-CH_3), 1.32 (s, 3, C_5-CH_3), 2.36 (s, 3, N-CH_3), 6.79 (d, 1, H_β), 7.06 (d, 1, H_α).

Anal. Calcd. for $C_{13}H_{19}NS$: C, 70.55; H, 8.65; N, 6.33; S, 14.46. Found: C, 70.42; H, 8.71; N, 6.45; S, 14.35.

Hydrochloride: m.p. 210-211° (acetone-ether).

2,4,5-Trimethylthieno[3,2-*f*]morphan (VIc).

This compound (b.p. 100-102°/0.04 mm Hg) obtained in 67% yield from Vc was characterized as the hydrochloride, m.p. 192-194° (acetone-ether); nmr (base): 0.64 (d, 3, C_4-CH_3), 1.3 (s, 3, C_5-CH_3), 2.36 (s, 3, N-CH_3), 6.79 (d, 1, H_β), 7.00 (d, 1, H_α).

Anal. Calcd. for $C_{13}H_{20}ClNS \cdot H_2O$: C, 56.61; H, 8.04; N, 5.08; S, 11.62. Found: C, 56.57; H, 8.06; N, 4.61; S, 11.78.

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REFERENCES

(1) Paper I. M. Alvarez, J. Bosch and J. Canals, *Ann. Quim.*, (in press).

(2) G. C. Morrison, R. O. Waite, A. N. Caro and J. Shavel Jr., *J. Org. Chem.*, 32, 3691 (1967).

(3) T. A. Montzka and J. D. Matiskella, *J. Heterocyclic Chem.*, 11, 853 (1974).

(4) R. Grewe, *Angew. Chem.*, 59, 194 (1947).

(5) G. Thyagarajan and E. L. May, *J. Heterocyclic Chem.*, 8, 465 (1971).

(6) J. Bosch, J. Canals and R. Granados, *Ann. Quim.*, (in press).

(7) J. Bosch and R. Llobera, Unpublished data.

(8) W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, 81, 4004 (1959).

(9) M. Alvarez, J. Bosch, J. Canals and F. López, to be published.

(10) M. Takeda, A. E. Jacobson and E. L. May, *J. Org. Chem.*, 34, 4161 (1969).

(11a) R. E. Lyle and P. S. Anderson, *Advan. Heterocyclic Chem.*, 6, 45 (1966); (b) M. Ferles and J. Plim, *ibid.*, 12, 43 (1970).

(12) S. E. Fullerton, E. L. May and E. D. Becker, *ibid.*, 27, 2144 (1962).

(13) R. T. Parfitt and S. M. Walters, *J. Med. Chem.*, 14, 565 (1971).