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Two alternative syntheses of 2,6-methanopyrrolo[1,2-*d*][1,4]diazocines (I) based in the acidic cyclization of 2-(1-pyrrolylmethyl)tetrahydropyridines are described. In the first synthetic route, lithium aluminum hydride reduction of 2-cyano-1,4-dimethyl-1,2,3,6-tetrahydropyridine (IIa) followed by reaction of the resulting primary amine with 2,5-diethoxytetrahydrofuran affords the requisite tetrahydropyridine IVa. An analogous sequence from 2-cyano-4,6-dimethylpyridine (V) leads to the corresponding 2-(1-pyrrolylmethyl)pyridine VII which by quaternization and borohydride reduction yields a mixture of isomeric tetrahydropyridines, precursors of the pyrrolodiazocine systems Ib and Ic. Structural and stereochemical assignment of the synthesized compounds are discussed.

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One of the attempted modifications in 6,7-benzomorphans (1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines) (3) has been the introduction of an additional nitrogen atom in the benzazocine system, aiming to obtain new structures with potential analgesic activity. Thus, the six methanobenzodiazocines resulting from replacement of each of the alicyclic carbon atoms in the 6,7-benzomorphan system have been obtained (4).

In connection with our studies about heteromorphans (compounds coming from isosteric substitution by an heterocyclic ring of the benzene ring in 6,7-benzomorphans) (5-11) we now wish to report the synthesis of 2,6-methanopyrrolo[1,2-*d*][1,4]diazocines (I). These compounds contain an additional nitrogen atom in a condensation position, which implies an heterocyclic character for the aromatic ring. We have obtained such compounds by two synthetic routes, both leading to 2-(1-pyrrolylmethyl)tetrahydropyridines which are used as pyrrolodiazocines precursors (Scheme I).

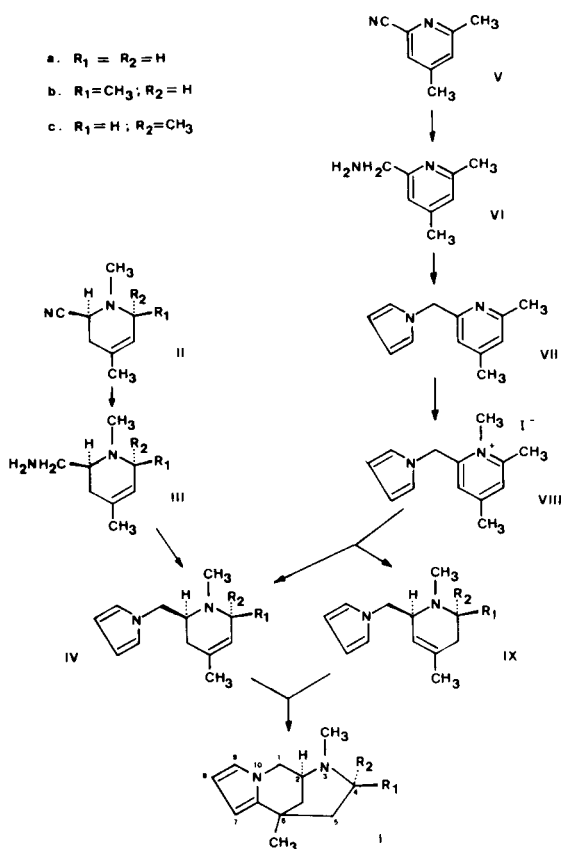
The first synthetic route, which is the most direct one, starts with 2-cyano-1,4-dimethyl-1,2,3,6-tetrahydropyridine (IIa), obtained by reaction of 1,4-dimethylpyridinium iodide with sodium borohydride in the presence of cyanide ions (12). Reduction of α -aminonitrile IIa with lithium aluminum hydride (13) afforded the aminomethyltetrahydropyridine IIIa in excellent yield, being undetected the 1,4-dimethyltetrahydropyridine which would result from substitution (14) of the hydride for the cyano group. Elaboration of the pyrrole ring was carried out by the Clauson-Kaas reaction (15) between the primary amine IIIa and 2,5-diethoxytetrahydrofuran in glacial acetic acid under reflux. The nmr spectrum of the resulting pyrrolylmethyltetrahydropyridine IVa showed as characteristic signals two singlets at

δ 1.62 and 2.37 due to the methyl groups, a multiplet (AB part of an ABX pattern) at δ 3.44-4.26 due to the C-2-methylene group, a broad singlet at δ 5.32 for the olefinic proton and two triplets at δ 6.08 and 6.53 arising from the β - and α -pyrrole hydrogens, respectively.

Polyposphoric acid treatment of IVa promoted cyclization of the double bond upon the 2-position of the pyrrole ring affording the pyrrolodiazocine Ia, whose nmr spectrum showed: i) three signals in the aromatic region at δ 5.85, 6.15 and 6.53 due to the protons on 3, 4 and 5 positions in the pyrrole ring, respectively, thus indicating that Ia is a cyclization product, ii) two singlets at δ 1.34 and 2.43 due to the methyl groups, and iii) one multiplet (AB part of an ABX pattern) at δ 3.60-4.46 due to the methylene group on the pyrrole nitrogen atom.

The second synthetic route allows the introduction of substituents on positions not accessible by the former one. Thus, the pyrrolodiazocines Ib and Ic have an additional methyl group in the 4-position arising from the C-6 methyl group of the cyanopyridine V. Substitution at the 3 or 5 positions in the starting cyanopyridines would lead to substituted pyrrolodiazocines either in the methano bridge or in 5-position, respectively. Reduction of 2-cyano-4,6-dimethylpyridine (V) (16) was carried out with lithium aluminum hydride in ether at 0-5° for 2-3 minutes. Under these conditions, aminomethylpyridine VI was obtained in almost quantitative yield, while with longer times of reaction by-products resulting from partial reduction of pyridine ring were formed (17). The nmr spectrum of VI shows six singlets, two of which (δ 3.69 and 1.78) due to the methylene and amino groups, respectively.

Condensation of amine VI with 2,5-diethoxytetrahydrofuran in glacial acetic acid (15) afforded the desired



pyrrolylmethylpyridine VII. Its nmr spectrum showed two triplets in the aromatic region due to the pyrrole protons. Disappearance of the signal due to the amino group as well as a downfield shift of the methylene group signal at δ 4.91 was observed. The best yields (51%) were obtained with 3-5 minutes reflux (18). Increasing times of reaction to 30 minutes, as usual in these reactions, resulted in a mixture of pyrrolylmethylpyridine VII (14%)

and 1-(4,6-dimethyl-2-pyrrolylmethyl)indole (5%) which arises from the attack of 2,5-diethoxytetrahydrofuran upon the pyrrole nucleus of the compound VII initially formed. Methiodide VIII was obtained in good yield by quaternization of pyridine VII with methyl iodide. Its nmr spectrum showed a singlet at δ 4.24 due to the *N*-methyl group. Sodium borohydride reduction in methanolic solution of *N*-methyl quaternary pyridine salt VIII afforded a mixture of four isomeric tetrahydropyridines IXb, IXc, IVb and IVc, in the ratio 3.6:1:1:1, respectively (based on gas chromatography). From this mixture the major isomer IXb was separated by column chromatography. The main differences of nmr spectra of tetrahydropyridines IXb and IVa were the doublet ($J = 6.5$ Hz) at δ 1.05 due to the C-6 methyl group of IXb and the upfield shift of the olefinic signal in IXb (δ 4.92 against 5.32 in IVa), which indicated the Δ^3 -position of the double bond in tetrahydropyridine IXb (19). This assignment was confirmed by spin-decoupling experiments. Thus, irradiation at δ 2.9 (C-2-H signal) simplifies interannular methylene signal, while irradiation at δ 2.25 (C-6 H signal) simplifies C-6 methyl and C-5 methylene signals simultaneously. The *cis*-assignment for this tetrahydropyridine was deduced from the stereochemistry of C-4 methyl group in the major cyclization product Ib. The observed selectivity in the reduction of methiodide VIII could be interpreted by considering the initial formation of a metastable π -complex (20) between the pyrrole ring and borane formed from the sodium borohydride. The initial hydride ion attack occurs then intramolecularly in a preferent way at the nearest 2-position of the pyridinium salt. Protonation at the central double bond (5-position) of the resulting dieneamine system (21) and subsequent hydride attack upon the most accessible side of the iminium salt thus formed leads to the *cis*- Δ^3 -tetrahydropyridine IXb.

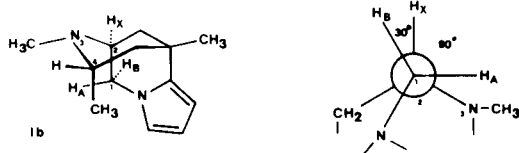
Table I

Analyses

Compound No.	M.p. (°C) (solvent) (a)	Yield	Formula	Carbon %		Hydrogen %		Nitrogen %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
Ia (picrate)	162-163 (E)	43%	$C_{18}H_{21}N_5O_7$	51.55	51.60	5.05	5.11	16.70	16.66
Ib (picrate)	145-146 (E)	48% (b)	$C_{19}H_{23}N_5O_7$	52.65	52.59	5.35	5.36	16.16	16.40
III (benzoyl derivative)	— (c)	94%	$C_{15}H_{20}N_2O$	73.74	73.57	8.25	8.41	11.46	11.52
IVa (picrate)	134-135 (E)	38%	$C_{18}H_{21}N_5O_7$	51.55	51.62	5.05	4.99	16.70	16.75
VI (dipicrate)	179-181 (E)	98%	$C_{20}H_{18}N_8O_{14}$	40.41	40.23	3.05	2.87	18.85	18.87
VII (picrate)	150-151 (E)	51%	$C_{18}H_{17}N_5O_7$	52.05	51.86	4.13	4.00	16.86	16.84
VIII	118-121 (A-E)	90%	$C_{13}H_{17}N_2I$ (d)	49.75	49.45	6.00	5.70	7.25	7.50
IXb (picrate)	128-130 (E)	70% (E)	$C_{19}H_{23}N_5O_7$	52.65	52.52	5.35	5.34	16.16	16.40

(a) Solvents: A = acetone, E = ethanol. (b) Yield from a mixture of *cis*- and *trans*-isomers. (c) The benzoyl derivative of amine III is a liquid, b.p. 140-150° (0.5 mm Hg). (d) Iodine: Calcd.: 32.85. Found: 32.93. (e) Yield from a mixture of the four isomers IVb, IVc, IXb and IXc.

Treatment of the above tetrahydropyridine mixture with polyphosphoric acid led to two diastereomeric pyrrolidiazocines, Ib and Ic, in the ratio 2.2:1 (based on nmr). The major isomer Ib was isolated by column chromatography. Its nmr spectrum showed a doublet ($J = 7$ Hz) at δ 0.18 due to the axial C-4 methyl group, strongly shielded by the aromatic ring (Scheme II). In the nmr spectrum of the minor isomer Ic the C-4 methyl group was observed as a doublet ($J = 6$ Hz) at δ 0.91. This chemical shift is identical to the described for the equatorial C-3 methyl group of 2,3,5-trimethylbenzomorphan (22). The C-1 and C-2 position protons appeared as an ABX system in pyrrolidiazocines Ia, Ib and Ic. The vicinal coupling constants ($J_{AX} = 0.5$ Hz and $J_{BX} = 4.2$ Hz) reflected dihedral angles of $85-90^\circ$ and $35-30^\circ$, respectively (23), accordingly to the measured angles in Dreiding stereomodels (Scheme II).



EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer model R-24B (60 MHz, tetramethylsilane at δ 0.00 as internal standard) with carbon tetrachloride as a solvent unless otherwise indicated. Chemical shifts are reported in δ values in parts per million (ppm). The glc were run isothermally on a Perkin-Elmer F-11 chromatograph with a flame ionization detector. A 2 m glass column, 6.4 mm in diameter was used, packed with 2.5% OV-225 on 100-120 mesh chromosorb WHP. Elemental analyses (Table I) were performed by Instituto de Química Orgánica Aplicada de Cataluña, Barcelona.

2-Aminomethyl-1,4-dimethyl-1,2,3,6-tetrahydropyridine (IIIa).

A solution of 3.40 g. (25 mmoles) of IIa in 40 ml. of anhydrous ether was added to a stirred and ice-bath cooled suspension of 2.66 g. (70 mmoles) of lithium aluminum hydride in anhydrous ether (100 ml.). The resulting mixture was refluxed for 1 hour and then 200 ml. of 1 N aqueous sodium hydroxide were added dropwise. The ethereal layer was removed and the aqueous one extracted with ether. The whole ethereal extracts were dried and the solvent removed at reduced pressure obtaining 3.29 g. (94% yield) of IIIa; nmr: 1.22 (s, 2, NH_2), 1.64 (s, 3, $=\text{C}-\text{CH}_3$), 1.73-2.05 (broad signal, 2, C-3 H_2), 2.24 (s, 3, $\text{N}-\text{CH}_3$), 2.20-2.50 (m, 1, C-2 H), 2.68 (d, $J = 5$ Hz, 2, CH_2-NH_2), 2.80-3.10 (m, 2, C-6 H_2), 5.24 (broad singlet, 1, $=\text{CH}$).

1,4-Dimethyl-2-(1-pyrrolylmethyl)-1,2,3,6-tetrahydropyridine (IVa).

A solution of 4.2 g. (30 mmoles) of IIIa, 4.8 g. (30 mmoles) of 2,5-diethoxytetrahydrofuran and 50 ml. of glacial acetic acid was refluxed for 30 minutes. After the solvent was removed at reduced pressure, the residue was dissolved in excess 15% aqueous sodium carbonate and extracted with ether. The dried ethereal extracts were evaporated to give an oil which was filtered through

a silica gel column. On elution with chloroform-methanol (98:2), 2.17 g. (38% yield) of IVa were obtained; nmr (deuteriochloroform): 1.62 (s, 3, $=\text{C}-\text{CH}_3$), 1.70 (broad signal, 2, C-3 H_2), 2.37 (s, 3, $\text{N}-\text{CH}_3$), 2.65-3.20 (m, 3, C-6 $\text{H}_2 + \text{C}-2$ H), 3.44-4.26 (AB part of an ABX, $J_{AB} = 13$ Hz, $J_{AX} = 5$ Hz, $J_{BX} = 8.5$ Hz, 2, interannular CH_2), 5.32 (broad singlet, 1, $=\text{CH}$), 6.08 (t, $J = 1.5$ Hz, 2, pyrrole- H_β), 6.53 (t, $J = 1.5$ Hz, 2, pyrrole- H_α).

1,2,3,4,5,6-Hexahydro-3,6-dimethyl-2,6-methanopyrrolo[1,2-d]-[1,4]diazocine (Ia).

Polyphosphoric acid (60 g.) and 7.6 g. (40 mmoles) of IVa were stirred at $125-130^\circ$ for 3 hours under nitrogen. The cooled solution was poured into concentrated ammonia-ice and extracted with ether. Solvent was removed from the dried extract leaving an oily residue which was purified by chromatography through a silica gel column. On elution with chloroform-methanol (98:2), 3.27 g. (43% yield) of the pyrrolidiazocine Ia were obtained; nmr (deuteriochloroform): 1.34 (s, 3, C-6 CH_3), 1.45-2.75 (m, 6, C-4 $\text{H}_2 + \text{C}-5$ $\text{H}_2 + \text{CH}_2$ bridge), 2.43 (s, 3, $\text{N}-\text{CH}_3$), 3.12-3.35 (m, 1, C-2 H), 3.60-4.46 (AB part of an ABX, $J_{AB} = 13.5$ Hz, $J_{AX} = 0.5$ Hz, $J_{BX} = 5$ Hz, 2, $\text{N}-\text{CH}_2$), 5.85 (dd, $J = 1.7$ Hz and $J = 3.8$ Hz, 1, C-7 H), 6.15 (dd, $J = 3.8$ Hz, $J = 2.4$ Hz, 1, C-8 H), 6.53 (dd, $J = 1.7$ Hz, $J = 2.4$ Hz, 1, C-9 H).

2-Aminomethyl-4,6-dimethylpyridine (VI).

To a stirred and ice-bath cooled suspension of 6.8 g. (177 mmoles) of lithium aluminum hydride in 280 ml. of anhydrous ether, a solution of 11.3 g. (85 mmoles) of V in 170 ml. of dry ether was added over a 3 minute period. Aqueous sodium hydroxide (1N, 100 ml.) was added dropwise (temperature between 0 and 5°), the ethereal layer was removed, 400 ml. of water were added and the basic solution was extracted with ether. The dried ethereal extracts were evaporated to give 11.4 g. (98% yield) of the amine VI; nmr: 1.78 (s, 2, NH_2), 2.22 (s, 3, C-4 CH_3), 2.39 (s, 3, C-6 CH_3), 3.69 (s, 2, CH_2-NH_2), 6.68 (s, 1, pyridine- H_β), 6.76 (s, 1, pyridine- H_α).

4,6-Dimethyl-2-(1-pyrrolylmethyl)pyridine (VII).

A solution of 12.0 g. (90 mmoles) of VI and 22 g. (148 mmoles) of 2,5-diethoxytetrahydrofuran in 87 ml. of glacial acetic acid was kept at 120° (oil bath) for 5 minutes. After cooling in an ice-bath, the solution was poured into ice-water, rendered basic with 2N sodium hydroxide solution and extracted with ether. The ethereal layer was extracted with 0.5N hydrochloric acid solution, the aqueous solution was basified with 2N sodium hydroxide solution and extracted with ether. The dried ethereal extract was evaporated to give 8.54 g. (51% yield) of VII (b.p. $90-95^\circ$, 0.5 mm Hg); nmr: 2.10 (s, 3, C-4 CH_3), 2.39 (s, 3, C-6 CH_3), 4.91 (s, 2, CH_2N), 6.00 (t, $J = 1.5$ Hz, 2 pyrrole- H_β), 6.20 (s, 1, pyridine C-3 H), 6.52 (t, $J = 1.5$ Hz, 2, pyrrole- H_α), 6.67 (s, 1, pyridine C-5 H).

1,4,6-Trimethyl-2-(1-pyrrolylmethyl)pyridinium Iodide (VIII).

A solution of 1.86 g. (10 mmoles) of VII and 9.12 g. (65 mmoles) of methyl iodide in 20 ml. of anhydrous acetone and 4 ml. of dry benzene was gently refluxed for 54 hours. The mixture was allowed to stand at 5° for 24 hours and the methiodide VIII (2.95 g., 90% yield) was obtained by filtration; nmr (deuteriochloroform): 2.36 (s, 3, C-4 CH_3), 2.80 (s, 3, C-6 CH_3), 4.24 (s, 3, $\text{N}-\text{CH}_3$), 5.93 (s, 2, CH_2), 6.15-6.35 (m, 3, pyrrole- $\text{H}_\beta +$ pyridine C-3 H), 6.95 (t, 2, pyrrole- H_α), 7.60 (s, 1, pyridine C-5 H).

Tetrahydropyridines IXb, IXc, IVb and IVc.

To an ice-bath cooled solution of 6.56 g. (20 mmoles) of

VIII in 60 ml. of methanol, 2.0 g. (53 mmoles) of sodium borohydride were added portionwise. The resulting solution was refluxed for 3 hours, the solvent was removed at reduced pressure, 150 ml. of water were added and the aqueous basic solution was extracted with ether. Evaporation of dried ethereal layers afforded 2.86 g. (70% yield) of an oil which on gas chromatography shows four peaks of relative areas 3.6:1:1:1. The *cis*-1,4,6-trimethyl-2-(1-pyrrolylmethyl)-1,2,5,6-tetrahydropyridine (IXb) was obtained from the mixture by silica gel column chromatography on elution with chloroform-methanol (99:1); nmr: 1.05 (d, $J = 6.5$ Hz, 3, C-6 -CH₃), 1.58 (s, 3, =C-CH₃), 1.60-1.90 (broad signal, 2, C-5 H₂), 2.00-2.50 (m, 1, C-6 H), 2.20 (s, 3, N-CH₃), 2.80-3.05 (m, 1, C-2 H), 3.35-4.15 (AB part of an ABX, $J_{AB} = 13$ Hz, $J_{AX} = 4.7$ Hz, $J_{BX} = 7.2$ Hz, 2 interannular CH₂), 4.92 (s, 1, =CH), 5.89 (t, $J = 1.7$ Hz, 2, pyrrole-H_β), 6.44 (t, $J = 1.7$ Hz, 2, pyrrole-H_α). On elution with chloroform-methanol (98:2), mixtures of the tetrahydropyridines IXb,c and IVb,c at different ratios were obtained.

cis- and *trans*-1,2,3,4,5,6-Hexahydro-3,4,6-trimethyl-2,6-methanopyrrolo[1,2-*d*][1,4]diazocines (Ib and Ic).

Polyphosphoric acid (40 g.) and 1.2 g. (5.9 mmoles) of the tetrahydropyridine mixture IXb,c and IVb,c were heated at 125-130° for 6 hours. The cooled solution is poured into an excess of concentrated ammonium hydroxide-ice and extracted with ether. Solvent was removed from the dried extract leaving 0.50 g. (48% yield) of an oil, mixture of the pyrroliodiazocines Ib and Ic in the ratio 2.2:1, respectively. The major isomer Ib was isolated by column chromatography on silica gel (chloroform-methanol 99:1 as eluent); nmr: (Ib) 0.18 (d, $J = 7$ Hz, 3, C-4 -CH₃), 1.28 (s, 3, C-6 -CH₃), 1.20-2.05 (m, 4, C-5 H₂ + CH₂ bridge), 2.38 (s, 3, N-CH₃), 2.70-3.25 (m, 2, C-4 H + C-2 H), 3.48-4.14 (AB part of an ABX, $J_{AB} = 12.5$ Hz, $J_{AX} = 0.5$ Hz, $J_{BX} = 4.2$ Hz, 2, C-1 H₂), 5.64 (dd, $J = 1.7$ Hz, $J = 3.7$ Hz, 1, C-7 H), 5.88 (dd, $J = 2.5$ Hz, $J = 3.7$ Hz, 1, C-8 H), 6.28 (dd, $J = 1.7$ Hz, $J = 2.5$ Hz, 1, C-9 H). On elution with chloroform-methanol (98:2) a mixture of Ic and Ib in the ratio 6:4 was obtained. The nmr spectrum of this mixture allowed the assignment of the signals of compound Ic; nmr: (Ic) 0.91 (d, $J = 6$ Hz, 3, C-4 -CH₃), 1.28 (s, 3, C-6 -CH₃), 1.20-2.10 (m, 5, C-5 H₂ + CH₂ bridge + C-4 H), 2.31 (s, 3, N-CH₃), 3.00-3.25 (m, 1, C-2 H), 3.48-4.35 (AB part of an ABX, $J_{AB} = 12.5$ Hz, $J_{AX} = 0.5$ Hz, $J_{BX} = 4.2$ Hz, 2, C-1 H₂), 5.64 (dd, $J = 1.7$ Hz, $J = 3.7$ Hz, 1, C-7 H), 5.88 (dd, $J = 2.5$ Hz, $J = 3.7$ Hz, 1, C-8 H), 6.28 (dd, $J = 1.7$ Hz, $J = 2.5$ Hz, 1, C-9 H).

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REFERENCES AND NOTES

- (1) Paper XII, J. Bosch, M. Alvarez and R. Granados, *J. Heterocyclic Chem.*, in press.
- (2) This work was presented in a preliminary form at the First European Symposium on Organic Chemistry, Cologne (FRG) (August 1979).
- (3) D. C. Palmer and M. J. Strauss, *Chem. Rev.*, **77**, 1 (1977).
- (4) T. Kametani, K. Kigasawa, M. Hiiragi and K. Wakisaka, *Heterocycles*, **2**, 349 (1974).
- (5) M. Alvarez, J. Bosch and J. Canals, *An. Quim.*, **71**, 807 (1975).
- (6) J. Bosch, R. Granados and F. López, *J. Heterocyclic Chem.*, **12**, 651 (1975).
- (7) M. Alvarez, J. Bosch, R. Granados and F. López, *ibid.*, **15**, 193 (1978).
- (8) M. Alvarez, J. Bosch and M. Feliz, *ibid.*, **15**, 1089 (1978).
- (9) J. Bosch and F. Boncompte, *An. Quim.*, **75**, 357 (1979).
- (10) J. Bosch, R. Granados and R. Llobera, *ibid.*, **75**, 360 (1979).
- (11) J. Bosch, M. Alvarez, R. Llobera and M. Feliz, *ibid.*, **75**, 712 (1979).
- (12) E. M. Fry, *J. Org. Chem.*, **29**, 1647 (1964).
- (13a) Z. Welvart, *Compt. Rend.*, **238**, 2536 (1954); (b) Z. Welvart and M. Delepine, *ibid.*, **239**, 1299 (1954); (c) R. F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955).
- (14) In a former work (11) we described that reaction of 2-cyano-1,4-dimethyl-1,2,3,6-tetrahydropyridine (IIa) with Grignard reagents took place with substitution of the cyano group by the organometallic radical. However, when organolithium derivatives were used, only ketones resulting from the addition to the cyano group and subsequent hydrolysis of the resulting imines were obtained.
- (15a) N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952); (b) N. Elming and N. Clauson-Kaas, *ibid.*, **6**, 867 (1952).
- (16) W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959).
- (17) Catalytic hydrogenation (palladium on charcoal) in methanol-dry hydrochloric acid led to a mixture of VI (54% yield) and 2-hydroxymethyl-4,6-dimethylpyridine.
- (18) A Clauson-Kaas reaction with a reaction time shortened to one minute has been described lately: A. Nudelman, F. Braun and E. Karoly, *J. Org. Chem.*, **43**, 3788 (1978).
- (19) M. Takeda, A. E. Jacobson and E. L. May, *J. Org. Chem.*, **34**, 4158 and 4161 (1969).
- (20) N. W. Gabel, *J. Heterocyclic Chem.*, **4**, 627 (1967).
- (21) R. E. Lyle and P. S. Anderson, *Adv. Heterocyclic Chem.*, **6**, 45 (1966).
- (22) R. T. Parfitt and S. M. Walters, *J. Med. Chem.*, **14**, 565 (1971).
- (23) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).