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# SYNTHESIS AND PROPERTIES OF 1,4,9-TRIAZASPIRO[5,5]UNDECANE AND 3,7,11-TRIAZASPIRO[5,6]DODECANE

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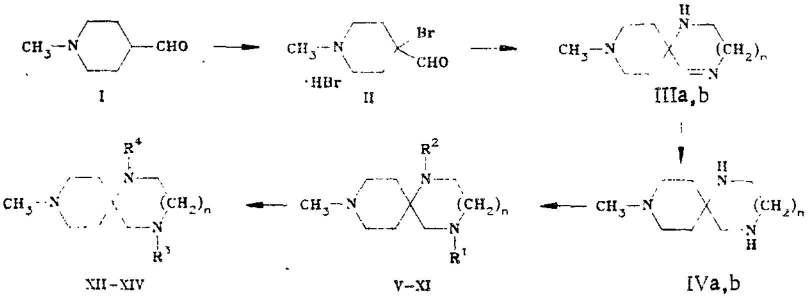
Bromination of 1-methylpiperidine-4-carboxaldehyde gave 4-bromo-1-methylpiperidine-4-carboxaldehyde hydrobromide which was used to synthesize 1,4,9-triazaspiro[5,5]undecane and 3,7,11-triazaspiro[5,6]dodecane. Cyanoethylation and alkylation with various alkyl halides gave their mono- and di-substituted derivatives. The side chain nitrile group was reduced and the hydrazide was obtained from the ester analog.

The synthesis has recently been reported of new spiroheterocycles combining different nitrogen-containing rings with tetrahydropyran and tetrahydrothiopyran systems [1-4]. Continuing this work, we have developed a synthetic method for new spiroheterocycles in which a piperidine ring is spiro joined to piperazines or perhydrodiazepines:



III, IV a n=1, b n=2; V, VII—XII, XIV n=1, VI, XIII n=2; R¹—R⁴ see Table 1

Aldehyde I [5] was brominated in glacial acetic acid to give the α-bromoaldehyde hydrobromide (II) in almost quantitative yield. Treatment of II with ethylenediamine gave the spiroimine IIIa which was hydrogenated under pressure using Raney nickel to the spiro-amine IVa. A similar reaction of II with 1,3-diaminopropane led to IIIb, reduction of which with lithium aluminum hydride gave IVb. The nitrogen atom in IVa, b, situated α to the spiro carbon atom, was found to be relatively inert. Thus, treatment of IVa, b with excess acrylonitrile gave only the products of mono-addition V, VI occurring at the β position to the spiro carbon (in agreement with the inertness of the spiroimines IIIa, b under the same conditions). Mono-substituted derivatives of IVa were also obtained with excess of chloroacetonitrile (VII), chloroacetamide (VIII), ethyl acrylate (IX), and acrylamide (X). When ethyl bromoacetate was used to alkylate IVa, the production of di-substitution XI was obtained exclusively. Reduction of nitriles V, VI with lithium aluminum hydride gave the amines XII, XIII and the dihydrazide XIV was obtained from diester XI. The structures of the compounds obtained were proved by IR, PMR, and mass spectroscopic methods (Tables 1 and 2).

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TABLE 1. Mono- and Di-Substituted 1,4,9-Triazaspiro[5,5]undecanes and 3,7,11-Triazaspiro[5,6]dodecanes (V-XIV)

| Compound | $R_1$ or $R_3$ | $R_2$ or $R_4$ | bp [mp], °C (mm) | $n_D^{20}$ ($d_4^{20}$) | IR spectrum, cm$^{-1}$ | PMR spectrum, δ, ppm | $t_R$, min (°C) or $R_f$ | Found, % |  |  | Empirical formula | Calculated, % |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  |  |  | C | H | N |  | C | H | N |  |
| V | $CH_2CH_2CN$ | H | 159—161 (2) | 1,5040 (1,0225) | 2265 (C≡N) |  | 3,2 (214) | 64,7 | 10,0 | 25,3 | $C_{12}H_{22}N_4$ | 64,8 | 9,9 | 25,2 | 60 |
| VI | $CH_2CH_2CN$ | H | 178—180 (5) | Viscous mass | 2260 (C≡N) |  | 0,75 (a) | 66,2 | 10,0 | 23,8 | $C_{13}H_{24}N_4$ | 66,0 | 10,2 | 23,7 | 70 |
| VII | $CH_2CN$ | H | [65—67] |  | 2250 (C≡N) | 3,43 (2H, s, 4-$CH_2$) | 5,7 (186) | 63,6 | 9,8 | 26,9 | $C_{11}H_{20}N_4$ | 63,4 | 9,6 | 26,8 | 65 |
| VIII | $CH_2CONH_2$ | H | [117—118] |  | 1690 (C=O) | 2,91 (2H, s, 4-$CH_2$) | 0,54 (c) | 58,2 | 9,8 | 24,9 | $C_{11}H_{22}N_4O$ | 58,3 | 9,7 | 24,7 | 70 |
| IX | $CH_2CH_2COOC_2H_5$ | H | 164—166 (3) | 1,4910 (1,0340) | 1750 (C=O) | 4,12 (2H, q, $OCH_2$) | 4 (214) | 62,6 | 10,3 | 15,5 | $C_{14}H_{27}N_3O_2$ | 62,4 | 10,1 | 15,6 | 75 |
| X | $CH_2CH_2CONH_2$ | H | 225—227 (6,5) | Viscous mass | 1680 (C=O) | 2,32 (3H, s, 9-$CH_3$) | 0,47 (c) | 60,1 | 10,1 | 23,4 | $C_{12}H_{24}N_4O$ | 59,9 | 10,0 | 23,3 | 52 |
| XI | $CH_2COOC_2H_5$ | $CH_2COOC_2H_5$ | [44—45] |  | 1760 (C=O) | 1,23 [6H, t, $(CH_2CH_3)_2$] | 0,48 (c) | 59,9 | 9,2 | 12,4 | $C_{17}H_{31}N_3O_4$ | 59,7 | 9,1 | 12,3 | 65 |
| XII | $CH_2CH_2NH_2$ | H | 147—150 (4) | 1,5050 | 3250—3400 ($NH_2$, NH) | 2,08 (3H, s, 9-$CH_3$) | 0,90 (c) | 62,4 | 11,1 | 26,5 | $C_{11}H_{24}N_4$ | 62,2 | 11,3 | 26,3 | 50 |
| XIII | $CH_2CH_2CH_2NH_2$ | H | 162—165 (4) | 1,5060 | 3250—3400 ($NH_2$, NH) |  | 0,82 (b) | 64,8 | 11,5 | 23,5 | $C_{13}H_{28}N_4$ | 64,9 | 11,7 | 23,3 | 60 |
| XIV | $CH_2CONHNH_2$ | $CH_2CONHNH_2$ | [133—134] |  | 1630 (C=O) |  | 0,65 (b) | 49,9 | 8,5 | 31,3 | $C_{13}H_{27}N_7O_2$ | 49,8 | 8,6 | 31,2 | 75 |

TABLE 2. Mass Spectra of IIIa, IVa, b

| Compound | m/z* (relative to most intense peak, %) |
|---|---|
| IIIa | 167 (100), 139 (77), 111 (24), 96 (45), 94 (37), 82 (14), 71 (21), 70 (26), 58 (18), 44 (37) |
| IVa | 169 (100), 139 (36), 125 (36), 111 (90), 97 (26), 96 (72), 70 (30), 58 (80), 57 (20), 44 (40) |
| IVb | 183 (63), 153 (22), 139 (32), 126 (35), 125 (60), 111 (60), 97 (28), 96 (69), 70 (73), 58 (100) |

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*Ten most intense peaks given for each compound.

## EXPERIMENTAL

GLC was carried out on a Chrom-4 instrument with flame-ionization detector, stationary phase methylsilicone elastomer E-301 (6%) on chromaton NAW (0.20-0.25 mm) treated with HMDS, 120 × 0.3 cm column, and $N_2$ gas carrier (0.9 liter/h). TLC for VI, VIII, X-XIV was performed on Silufol UV-254 in water:dioxan:formic acid 3:2:1 (a) or 3:1:2 (b) or water:dioxan:acetic acid 3:3:1 (c) with visualization by iodine vapor. IR spectra were recorded as a thin layer on a UR-20 instrument (II, VII, VIII, XI, and XIV in Vaseline mull). PMR spectra were taken on a T-60 instrument with $CCl_4$ solvent and TMS internal standard while mass spectra were measured on an MX-1320 with direct introduction of the sample into the ion source.

The parameters for V-XIV are given in Table 1.

1-Methyl-4-bromopiperidine-4-carboxaldehyde Hydrobromide (II). Freshly distilled 1-methylpiperidine-4-carboxaldehyde (7.65 g, 60 mmole) was added to glacial acetic acid (25 ml) cooled in ice water. Then, with stirring and decolorization, there was added fromine (13 g, 80 mmole) dropwise while the temperature was held at 18-20°C. Stirring was continued for a further 1 h 30 min at 20°C and the hydrobromide II precipitated. Ether (100 ml) was added, the precipitate filtered off, washed with ether, and dried in a vacuum desiccator to give 16.5 g (96%). Recrystallization from a mixture of acetone:water (4:1) was necessary to give mp 155-156°C. IR spectrum: 2735 (OC—H), 1710 $cm^{-1}$ (C═O). Found, %: C 29.4, H 4.3, $Br^-$ 28.0, Br 55.5, N 4.8. $C_7H_{13}Br_2NO$. Calculated, %: C 29.2, H 4.5, $Br^-$ 27.8, Br 55.6, N 4.8.

9-Methyl-1,4,9-triazaspiro[5,5]undec-4-ene (IIIa). A solution of II (17.2 g, 60 mmole) in acetonitrile (25 ml) and methanol (15 ml) was added dropwise with stirring over 10 min to a mixture of potassium carbonate (14 g, 100 mmole), water (5 ml), acetonitrile (30 ml), and ethylenediamine solution (70%, 5.1 g, 60 mmole). The reaction temperature was kept below 20°C. Stirring was continued for 5-6 h and the product left for 2 days. Methanol (20-25 ml) was added and the solution filtered. The residue was washed with ether, the solvent removed, and the product distilled in vacuo to give 4.7 g (47%) with bp 105°C (3 mm); $n_D^{20}$ 1.5180, $d_4^{20}$ 1.0190. Retention time 1.95 min (188°C). IR spectrum: 1670 (C═N); 3280 $cm^{-1}$ (NH). PMR spectrum: 2.11 (3H, s, 9-$CH_3$); 2.7 (2H, t, 2.2-H); 3.06-3.66 (2H, M, 3.3-H); 7.26 ppm (1H, t, 5-H). Found, %: C 64.5, H 10.3, N 25.3; $M^+$ 167. $C_9H_{17}N_3$. Calculated, %: C 64.6, H 10.2, N 25.1; M 167.

3-Methyl-3,7,11-triazaspiro[5,6]dodec-11-ene (IIIb), obtained similarly to IIIa in 34% yield with bp 113-115°C (5 mm); $n_D^{20}$ 1.5090; $d_4^{20}$ 0.9990. Retention time 2.1 min (185°C). IR spectrum: 1685 (C═N); 3290 $cm^{-1}$ (N—H). PMR spectrum: 2.16 (3H, s, 3-$CH_3$); 7.26 ppm (1H, t, 6-H). Found, %: C 66.4, H 10.6, N 22.8. $C_{10}H_{19}N_3$. Calculated, %: C 66.2, H 10.5, N 23.1.

9-Methyl-1,4,9-triazaspiro[5,5]undecane (IVa). A mixture of spiroimine IIIa (10 g, 59 mmole) in tert-butyl alcohol (100 ml) and Raney nickel (4 g) were hydrogenated in an autoclave under a hydrogen pressure of 11 MPa for 9 h at 90°C. The catalyst was removed by filtration and the tert-butyl alcohol was removed on a water pump. The residue was distilled in vacuo to give 8 g (80%), bp 110°C (3 mm); $n_D^{20}$ 1.5015, $d_4^{20}$ 0.9875. The retention time was 1.9 min (186°C). IR spectrum: 3280 $cm^{-1}$ (NH). PMR spectrum: 2.13 (3H, s, 9-$CH_3$); 2.46 (2H, s, 6.6-H), 2.60 ppm (4H, s, 2,2,3,3-H). Found, %: C 63.6, H 11.3, N 24.6; $M^+$ 169. $C_9H_{19}N_3$. Calculated, %: C 63.8, H 11.3, N 24.8; M 169.

3-Methyl-3,7,11-triazaspiro[5,6]dodecane (IVb). Spiroimine IIIb (2.5 g, 14 mmole) in THF (5 ml) was added dropwise with stirring at −5°C to a suspension of lithium aluminum hydride (0.76 g, 20 mmole) in THF (35 ml). The product was stirred for 5 h at 55°C, water (3 ml) added dropwise to the solution cooled in ice, stirring continued for 1 h at 20°C and the solution filtered. THF was removed and the residue distilled in vacuo to give 1.5 g (60%) with bp 110-112°C (4 mm); $n_D^{20}$ 1.5005, $d_4^{20}$ 0.9790. Retention time 2.3 min (185°C). IR spectrum: 3280 $cm^{-1}$ (NH). Found, %: C 65.7, H 11.5, N 23.0; $M^+$ 183. $C_{10}H_{21}N_3$. Calculated, %: C 65.5, H 11.5, N 22.9; M 183.

4-R-9-Methyl-1,4,9-triazaspiro[5,5]undecane (V, IX, X). A mixture of spiroamine IVa (10 mmole) and 40 mmole of acrylontrile, ethyl acrylate, or acrylamide were heated for 12 h at 80°C and then distilled in vacuo.

11-Cyanoethyl-3-methyl-3,7,11-triazaspiro[5,6]dodecane (VI) was obtained similarly to V from spiroamine IVb and acrylonitrile.

4-Cyanomethyl-9-methyl-1,4,9-triazaspiro[5,5]undecane (VII). A mixture of spiroamine IVa (1.6 g, 10 mmole), acetonitrile (10 ml), $K_2CO_3$ (1.5 g, 11 mmole), water (1 ml), and chloroacetonitrile (0.8 g, 11 mmole) were heated at 70°C for 12 h, extracted with ether and dried ($MgSO_4$). After removal of solvent the residue was distilled in vacuo.

4-Carbamoylmethyl-9-methyl-1,4,9-triazaspiro[5,5]undecane (VIII). A mixture of spiroamine IVa (1.6 g, 10 mmole) and chloroacetamide (0.9 g, 10 mmole) were heated at 60°C until solidifying. Ethanol (10 ml) was added and the product was heated on a water bath for 10 h, treated with concentrated $K_2CO_3$ solution, extracted with ether, and dried ($MgSO_4$). After removal of the solvent, the residue was crystallized by trituration with dry ether.

1,4-Di(carbethoxymethyl)-9-methyl-1,4,9-triazaspiro[5,5]undecane (XI). A mixture of spiroamine IVa (1.6 g, 10 mmole), acetonitrile (10 ml), $K_2CO_3$ (3.5 g, 25 mmole), water (1 ml), and ethyl bromoacetate (3.3 g, 20 mmole) was heated for 12 h at 70°C, extracted with ether, and dried ($MgSO_4$). Removal of solvent and distillation of the residue in vacuo gave the crystalline diester (after recrystallization from ether).

4-(γ-Aminoethyl)-9-methyl-1,4,9-triazaspiro[5,5]undecane (XII). A solution of nitrile VII (1 g, 5 mmole) in THF (10 ml) was added dropwise with cooling to a suspension of lithium aluminum hydride (0.38 g, 10 mmole) in dry THF (30 ml), stirred at 20°C for 2 h, and then at 60°C for 6 h. After cooling with ice, water (2 ml) was added dropwise, stirring continued for 1 h at 20°C, filtered, and the precipitate washed with ether. Solvent was removed and the residue was distilled in vacuo.

11-(γ-Aminopropyl)-3-methyl-3,7,11-triazaspiro[5,6]dodecane (XIII). A solution of nitrile VI (0.95 g, 4 mmole) in ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (0.38 g, 10 mmole) in ether (40 ml). After stirring for 12 h at 20°C, the product was cooled in ice and water (2 ml) was added dropwise. After stirring for 1 h and filtering, the solid was washed with ether. Removal of solvent and distillation in vacuo gave the product.

1,4-Di hydrazidocarbonylmethyl)-9-methyl-1,4,9-triazinospiro-[5,5]undecane (XIV). A mixture of diester XI (1.3 g, 4 mmole), methanol (10 ml), and hydrazine hydrate (1 g, 20 mmole) was fitted with a reflux condenser and heated at 100°C for 20 h. After removal of methanol the residue was crystallized.

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