Research on Nitrogen Containing Heterocyclic Compounds. XVII. Synthesis of 8*H*-Diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine, a Novel Tetracyclic Ring of Pharmaceutical Interest

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The synthesis of 8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine **6**, a novel nitrogen-containing tetracyclic ring, is reported starting from 5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **7**. Reaction of this compound with nitromethane and subsequent reduction of the obtained nitromethyl derivative **8** afforded 11-aminomethyl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **9**. Treatment of the latter compound with formaldehyde led to 1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine **10**, which was then oxidized to the title compound.

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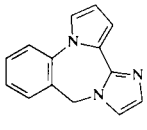
Tetracyclic benzodiazepines annelated with imidazole and pyrrole have received great attention in the last few years [1]. The syntheses of 5*H*-imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine **1** and 9*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine **2** have been described as chemical approaches to tetracyclic nitrogen heterocycles of medicinal interest [2,3].

Among derivatives with high biological activity bretazenil **3**, a derivative of 9*H*-imidazo[1,5-*a*]pyrrolo[2,1-*c*][1,4]-benzodiazepine, is characterized by clear-cut partial agonistic properties at benzodiazepine receptors [4] and actually is in ongoing pharmacological screening as an anxiolytic agent [5,6].



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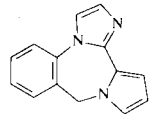

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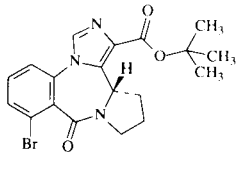

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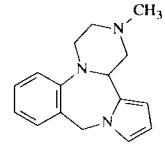
The importance of the tetracyclic moiety as a pharmacophoric support for displaying CNS activities is also documented by aptazepine **4**, a potent antidepressant agent with clinical application.

In pursuing our decennial engagement in the area of nitrogen-containing tetracyclic compounds we recently reported the synthesis of 10-methyl-10-azaaptazepine **5** as a new potential antidepressant agent [7] and we describe now the synthesis of some derivatives of 8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine **6**, a novel nitrogen heterocyclic ring, strictly related to the tetracyclic structures **1-5**.



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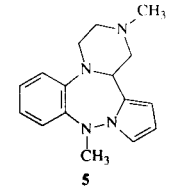

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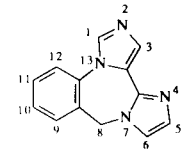


6

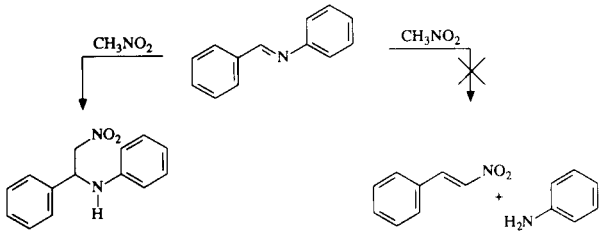
The key step for the synthesis of **6** was annelation at the 10,11 positions of 5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **7**. For this purpose we decided to follow the procedure described by Hurd and Strong, based on the addition of nitromethane to the azomethine double bond [8]. This reaction is well known as "synthesis with anils" and has been reviewed in 1978 as a general method for the preparation of olefins [9]. However, different results were obtained starting from different substrates.

When the Schiff base from *p*-chloroaniline and benzaldehyde reacted with various dichlorotoluenes different products were obtained depending on reaction conditions and molar ratios. 2,4-Dichlorotoluene yielded only the expected stilbene with loss of aniline. 2,5-Dichlorotoluene furnished stilbene or the related 1,2,3-triarylpropane. Only with 2,6-dichlorotoluene the anilino moiety was retained with formation of 1-phenyl-1-*p*-chlorophenylamino-2-(2,6-dichlorophenyl)ethane [10].

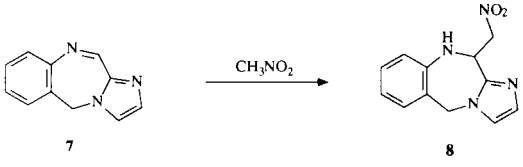
Although Hass and Riley state that formation of a nitro-

olefin might to be expected from reaction between anils and nitroalkanes, Hurd and Strong obtained *N*-(2-nitro-1-phenylethyl)aniline from reacting benzylideneaniline with nitromethane [8]. Also in this case the anilino moiety was retained according to the equation reported in Scheme 1.

Scheme 1



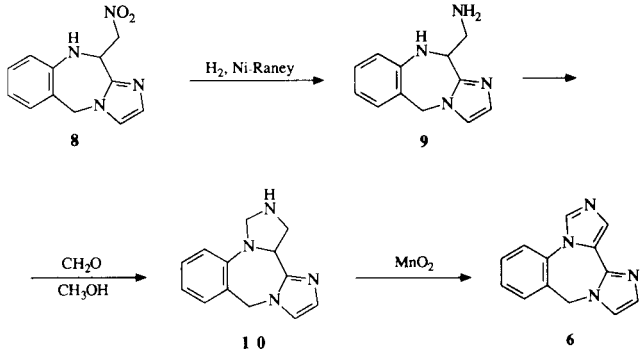
In our case the reaction between 5*H*-imidazo[2,1-*c*][1,4]-benzodiazepine **7** [11] and nitromethane led to 10,11-dihydro-11-nitromethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **8**, thus confirming the results obtained by Hurd and Strong.



This interesting result did permit us to obtain the key nitro intermediate useful for the synthesis of **6**. In fact, reduction of **8** with hydrogen in the presence of Raney-Ni as a catalyst led to amine **9**, which was cyclized intramolecularly by treatment with formaldehyde in methanol to give 1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine **10**. Oxidation of the latter compound with activated manganese dioxide led to the titled parent tetracycle **6** (Scheme 2).

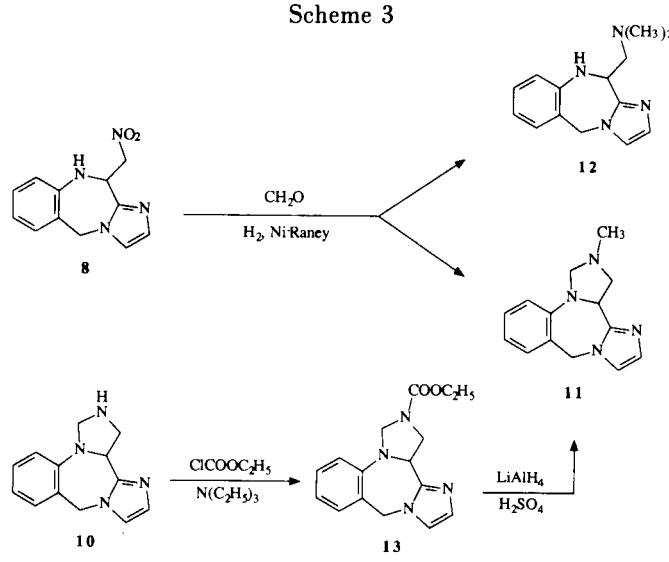
When the reduction of **8** was carried out in the presence of an excess of formaldehyde we obtained directly 2-methyl-1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine **11**, by a one-pot reaction involving reductive alkylation and intramolecular cyclization. In this reaction

Scheme 2



formation of 10,11-dihydro-11-dimethylaminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **12** was always observed (Scheme 3).

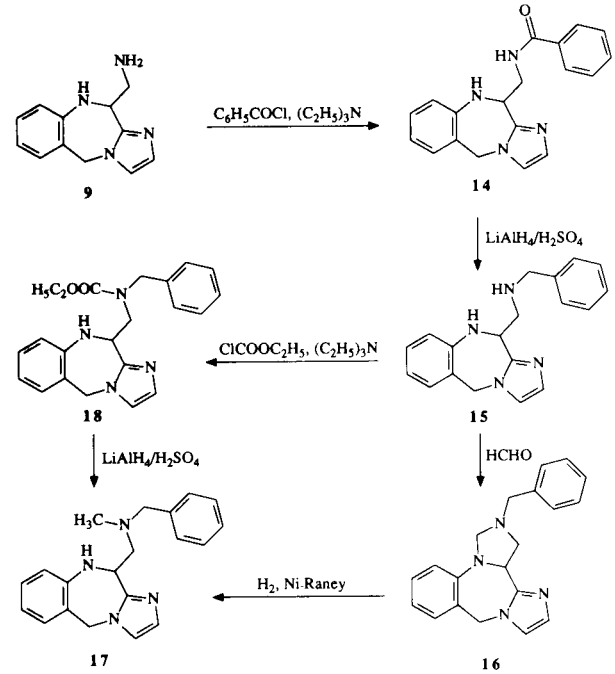
Scheme 3



Transformation of **10** into **11** was also achieved by treatment with ethyl chloroformate followed by reduction of **13** with a lithium aluminium hydride-sulfuric acid mixture.

Benzoylation of **9** and subsequent reduction of amide **14** led to benzylamine **15**. This compound cyclized to **16** by treatment with formaldehyde. Attempts to transform **16** into **10** by reduction was unsuccessful giving always 10,11-dihydro-11-(*N*-methyl-*N*-benzyl)aminomethyl-5*H*-imidazo-[2,1-*c*][1,4]benzodiazepine **17**. The last compound was also obtained from **15** *via* the intermediate **18** (Scheme 4).

Scheme 4



EXPERIMENTAL

Melting points were determined by an Electrothermal IA 6304 apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 1310 spectrophotometer. The pmr spectra were recorded on Varian EM-390 or Varian XL-300 spectrometers with TMS as internal standard. Merck alumina and Merck silica gel (70-230 mesh ASTM) were used for chromatographic purification. Carlo Erba Stratocrom SIF and Stratocrom ALF precoated plates were used for thin-layer chromatography. Microanalyses were performed by A. Pietrogrande, Padova, Italy. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvents involved the use of a rotary evaporator operating at reduced pressure.

10,11-Dihydro-11-nitromethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**8**).

A solution of 5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **7** (0.900 g, 0.0049 mole) and nitromethane (2.98 g, 0.049 mole) in ethanol (8.8 ml) was heated at 100° for 12 hours, then evaporated to dryness. The residue was purified on silica gel column, eluting with ethyl acetate. The central eluates were collected and evaporated to yield 1.0 g of compound **8** (84%) as an oil which solidified by trituration with carbon tetrachloride. An analytical sample could be obtained by recrystallization from cycloexane, mp 103-105°; pmr (deuteriochloroform): δ 7.38-7.20 (m, 2H, benzene), 7.12-6.98 (m, 2H, benzene), 6.97 (s, 1H, imidazole), 6.90 (s, 1H, imidazole), 5.40 (td, J = 3, J′ = 3 and J″ = 12 Hz, 1H, C_{11}-H), 5.28 and 4.90 (2d, J_{gem} = 15 Hz, 2H, C_5-H), 5.08 and 4.52 (2dd, J = 3 and J_{gem} = 16 Hz, 2H, C*H*-NO_2), 4.33 ppm (d, broad, disappears on treatment with deuterium oxide, J = 3 Hz, 1H, N-H).

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 58.96; H, 5.06; N, 22.88.

10,11-Dihydro-11-aminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**9**).

A suspension of 10,11-dihydro-11-nitromethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **8** (1.0 g, 0.0041 mole) in tetrahydrofuran (40 ml) and methanol (20 ml) was hydrogenated in presence of Raney-Ni (3 ml of Raney-Ni water suspension - Fluka catalogue 83440) as catalyst for 24 hours at an initial pressure of 155 psi. The catalyst was removed by filtration on Celite® 545 (Fluka catalogue 22140) and the filtrate was evaporated. Dissolution of the residue with dichloromethane followed by washing with water, drying and evaporation of the solvent gave 0.800 g of amine **9** (91%) as an oil. The 1:2 maleate salt melted at 156-159° after recrystallization from 2-propanol/isopropyl ether.

Anal. Calcd. for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.55. Found: C, 53.52; H, 4.86; N, 12.35.

1,2,3,3a-Tetrahydro-8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine (**10**).

A solution of 10,11-dihydro-11-aminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **9** (0.75 g, 0.0035 mole) and formaldehyde (0.26 ml of 40% solution in water, 0.0035 mole) in methanol (15 ml) was heated at 60° overnight, then concentrated. Dissolution of the residue with chloroform followed by washing with water, drying and evaporating of the solvent gave an oil which was chromatographed on an alumina column eluting with chloroform. The first eluated were collected and evaporated to give 0.550 g (68%) of compound **10**, mp 160-163° (after recrystallization from toluene/cyclohexane); pmr (deuteriochloroform): δ 7.38-6.95 (m, 4H, benzene), 6.80 (d, J = 9 Hz, 1H, imidazole), 6.57 (d, J = 9 Hz, 1H, imidazole), 5.55 and 4.93 (2d, J_{gem} = 15 Hz, 2H, C_8-H), 5.15 (t, J = 7 Hz, 1H, C_{3a}-H), 4.48 and 4.22 (2d, J_{gem} = 6 Hz, 2H, C_1-H), 3.92-3.45 (m, 2H, C_3-H), 2.75 ppm (s, broad, disappears on treatment with deuterium oxide, 1H, N-H).

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.29; H, 6.13; N, 24.50.

8*H*-Diimidazo[1,5-*a*:1′,2′-*c*][1,4]benzodiazepine (**6**).

Active manganese dioxide (3 g) was added to a solution of 1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine **10** (0.560 g, 0.0025 mole) in acetone (125 ml) and the mixture was stirred at room temperature overnight. After filtration, the solution was evaporated to give an oil which was subjected to chromatographic purification on alumina column eluting with chloroform. The first eluates were collected and evaporated to yield 0.190 g (34%) of compound **6**, mp 217-220° (after crystallization from ethyl acetate/*n*-hexane); pmr (deuteriochloroform): δ 8.06 (s, 1H), 7.88 (s, 1H), 7.45 (m, 4H), 7.08 (m, 2H), 4.98 ppm (s, 2H).

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.47; H, 4.67; N, 24.96.

2-Methyl-1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine (**11**).

Method A. Hydrogenation of 10,11-Dihydro-11-nitromethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **8** in the Presence of Formaldehyde.

A mixture of compound **8** (1.0 g, 0.0041 mole), formaldehyde (0.61 ml of 40% solution in water, 0.0082 mole), tetrahydrofuran (40 ml) and methanol (20 ml) was hydrogenated as reported for the preparation of compound **9**. Chromatographic separation on alumina column eluting with chloroform gave first 0.240 g (24%) of 10,11-dihydro-11-dimethylaminomethyl-5*H*-imidazo[2,1-*c*][1,4]-benzodiazepine **12**, mp 143-145° (after recrystallization from cyclohexane); pmr (deuteriochloroform): δ 7.38-7.08 (m, 2H), 7.01-6.74 (m, 4H), 5.20 and 5.04 (2d, AX/AB pattern, J_{gem} = 14 Hz, 2H, C_5-H), 4.91 (s, disappears on treatment with deuterium oxide, 1H, N-H), 4.60 (t, J = 7 Hz, 3H, C_{3a}-H), 2.94 [d, J = 7 Hz, 2H, CH_2-N(CH_3)$_2$], 2.36 ppm [s, 6H, CH_2-N(CH_3)$_2$]. The second fraction yield 0.480 g (50%) of **11**, mp 145-148° (after recrystallization from cyclohexane); pmr (deuteriochloroform): δ 7.37-6.87 (m, 4H, benzene), 6.73 (d, J = 9 Hz, 1H, imidazole), 6.45 (d, J = 9 Hz, 1H, imidazole), 5.55 and 4.75 (2d, J_{gem} = 15 Hz, 2H, C_5-H), 5.23 (t, J = 7 Hz, 1H, C_{3a}-H), 4.26 and 3.93 (2d, J_{gem} = 5 Hz, 1H, C_1-H), 3.80-3.37 (m, 2H, C_3-H), 2.53 ppm (s, 3H, N-CH_3).

Anal. Calcd. for $C_{14}H_{18}N_4$ (**11**): C, 69.39; H, 7.49; N, 23.12. Found: C, 69.63; H, 7.63; N, 22.92.

Anal. Calcd. for $C_{14}H_{16}N_4$ (**12**): C, 69.97; H, 6.71; N, 23.32. Found: C, 69.93; H, 6.75; N, 23.20.

Method B. Reduction of 2-Ethoxycarbonyl-1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2′,1′-*c*][1,4]benzodiazepine **13** with LAH.

Concentrated sulfuric acid (0.5 ml) was carefully added dropwise while stirring into an ice-cooled suspension of lithium aluminium hydride (0.740 g, 0.019 mole) in dry tetrahydrofuran (15 ml), then the mixture was stirred at room temperature for 30 minutes. After this time, a solution of compound **13** (0.90 g, 0.003 mole) in dry tetrahydrofuran (10 ml) was slowly added dropwise. One hour later a 2*N* sodium hydroxide solution (6 ml) was added dropwise to the cooled (-15°) reaction mixture. The solid was removed by filtration and washed with tetrahydrofuran, then the

combined filtrates were concentrated and extracted with chloroform. The organic solution was washed with water, dried and evaporated to give a reside which was purified on alumina column eluting with chloroform. Evaporation of the eluent yielded 0.420 g of 2-methyl-1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2',1'-*c*][1,4]benzodiazepine **11**, with properties agreeing with the analytical sample prepared as reported in method A.

2-Ethoxycarbonyl-1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:1',2'-*c*]-[1,4]benzodiazepine (**13**).

A solution of ethyl chloroformate (0.350 g, 0.0025 mole) in dry tetrahydrofuran (5 ml) was added dropwise to a cooled solution (0°) of 1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2',1'-*c*][1,4]benzodiazepine **10** (0.56 g, 0.0025 mole) and triethylamine (0.25 g, 0.0025 mole) in the same solvent (20 ml). After stirring for 1 hour at 0°, the mixture was filtered and the solvent was evaporated to give an oil which was purified on an alumina column eluting with chloroform. The first eluates after evaporation of the solvent yielded 0.450 g (59%) of 2-ethoxycarbonyl-1,2,3,3a-tetrahydro-8*H*-diimidazo[1,5-*a*:2',1'-*c*][1,4]benzodiazepine **13**, mp 189-192° (after recrystallization from toluene).

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.70; H, 6.31; N, 18.69.

10,11-Dihydro-11-benzoylaminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**14**).

The preparation of **14** was carried out starting from 10,11-dihydro-11-aminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **9** (0.53 g, 0.0025 mole) and benzoyl chloride (0.350 g, 0.0025 mole) as reported for the preparation of compound **13**. Evaporation of the solvent yielded 0.740 g (94%) of **14**, mp 103-106° (after recrystallization from cyclohexane).

Anal. Calcd. for $C_{19}H_{18}N_4O$: C, 71.67; H, 5.70; N, 17.60. Found: C, 71.88; H, 5.43; N, 17.75.

10,11-Dihydro-11-benzylaminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**15**).

The preparation of **15** was carried out as reported for the reduction of compound **13**, starting from 10,11-dihydro-11-benzoylaminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **14** (0.95 g, 0.003 mole). Purification on an alumina column eluting with chloroform yielded 0.850 g (98%) of compound **15** as an oil. The 1:2 maleate salt melted at 132-134° after recrystallization from 2-propanol/isopropyl ether.

1,2,3,3a-Tetrahydro-2-benzyl-8*H*-diimidazo[1,5-*a*:2',1'-*c*][1,4]benzodiazepine (**16**).

Cyclization was carried out as previously reported for compound **10**, starting from 10,11-dihydro-11-benzylaminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **15** (1.06 g, 0.0035 mole). Chromatographic purification yielded 0.980 g (90%) of compound **16**, mp 121-124° (after recrystallization from diethyl ether/petroleum ether 1:1); pmr (deuteriochloroform): δ 7.58-6.82 (m, 9H, benzene), 6.70 (d, J = 9 Hz, 1H, imidazole), 6.38 (d, J = 9 Hz, 1H, imidazole), 5.48 and 4.70 (2d, J_{gem} = 15 Hz, 2H, C_5-H), 5.20 (t, J = 7 Hz, 1H, C_{3a}-H), 4.27 and 3.93 (2d, J_{gem} = 5 Hz, 2H, C_1-H), 3.86 (s, 2H, N-C*H*$_2$-Bz), 3.62 (d, J = 7 Hz, 2H, C_3-H).

Anal. Calcd. for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.66; H, 6.28; N, 17.52.

10,11-Dihydro-11-(*N*-methyl-*N*-benzyl)aminomethyl-5*H*-imidazo-[2,1-*c*][1,4]benzodiazepine (**17**).

Method A. Hydrogenation of 1,2,3,3a-Tetrahydro-2-benzyl-8*H*-diimidazo[1,5-*a*:2',1'-*c*][1,4]benzodiazepine (**16**).

A suspension of compound **16** (1.29 g, 0.0041 mole) in tetrahydrofuran (40 ml) and methanol (20 ml) was hydrogenated in the presence of Raney-Ni as the catalyst for 6 hours at an initial pressure of 155 psi. The reaction was carried out as previously reported for the preparation of compound **9** and 1.16 g of **17** (89%) was obtained as an oil. The 1:2 maleate salt melted at 104-106° after recrystallization from 2-propanol/isopropyl ether; pmr (deuteriochloroform): δ 7.53-6.78 (m, 11H, aromatic), 5.15 and 5.02 (2d, AX/AB pattern, J_{gem} = 15 Hz, 2H, C_5-H), 4.97 (s, disappears on treatment with deuterium oxide, 1H, N-H), 4.74-4.54 (m, 1H, C_{11}-H), 3.78 and 3.54 (2d, J_{gem} = 14 Hz, 2H, N-C*H*$_2$-Bz), 3.31-2.91 (m, 2H, C_{11}-C*H*$_2$), 2.31 ppm (s, 3H, N-C*H*$_3$).

Anal. Calcd. for $C_{28}H_{30}N_4O_6$: C, 61.08; H, 5.49; N, 10.18. Found: C, 61.25; H, 5.56; N, 9.97.

Method B. Reduction of 10,11-Dihydro-11-(*N*-ethoxycarbonyl-*N*-benzyl)aminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **18** with LAH.

The reaction was carried out as previously reported for the reduction of compound **13**, starting from **18** (1.13 g, 0.003 mole). After purification on alumina column eluting with chloroform, 0.930 g (98%) of compound **17** was obtained as an oil. The 1:2 maleate salt had properties in agreement with the analytical sample prepared in method A.

10,11-Dihydro-11-(*N*-ethoxycarbonyl-*N*-benzyl)aminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**18**).

The reaction was carried out starting from 10,11-dihydro-11-benzylaminomethyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **15** (0.76 g, 0.0025 mole) as previously reported for the preparation of compound **13**; 0.940 g (98%) of **18** was obtained as a pure oil.

Anal. Calcd. for $C_{22}H_{24}N_4O_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.36; H, 6.55; N, 14.70.

Acknowledgements.

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REFERENCES AND NOTES

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