5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetic Acid Diethyl Ester, an Useful Synthon for the Synthesis of New Polycyclic Nitrogen Systems of Pharmacological Interest

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This report describes the synthesis of derivatives of two nitrogen tetracyclic ring systems, respectively 9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine and spiro[piperidine-4,4'-[4*H*]pyrrolo[1,2-*a*][1,4]-benzodiazepine], by the use of the diethyl ester of 5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetic acid as a synthon. This compound was obtained by condensation of 1-(2-aminomethylphenyl)-1*H*-pyrrole with diethyl 1,3-acetonedicarboxylate in acid medium. Pyrimidopyrrolobenzodiazepine derivatives were obtained by treating either the pyrrolobenzodiazepine 4,4-diacetate or the related 4-methyl-4-acetate with phenylisocyanate in boiling diethyl ether in the presence of sodium metal. The structure of 12,13-dihydro-11,13-dioxo-12-phenyl-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine, a product formed by loss of an acetate unit when 5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetate, sodium metal and phenylisocyanate reacted in boiling xylene, was proved by catalytic reduction to 11,13-dioxo-12-phenyl-12,13,14,14a-tetrahydro-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine, which was synthesized by unambiguous pathway *via* 5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-acetate. The 2,6-dioxospiro[piperidine-4,4'-[4*H*]pyrrolo[1,2-*a*][1,4]benzodiazepine] derivatives were synthesized from the *N*-BOC derivative of 5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetic acid diethyl ester, by hydrolysis followed by treatment with 2 equivalents of 1,1'-carbonyldiimidazole (CDI) and then with aniline or benzylamine. Removal of BOC from the *N*-phenyl-2,6-dioxopiperidine derivative was obtained by heating the related spiroderivative in toluene in the presence of *p*-toluenesulphonic acid. Similar reaction failed when the *N*-benzyl-2,6-dioxopiperidine analog was used as substrate.

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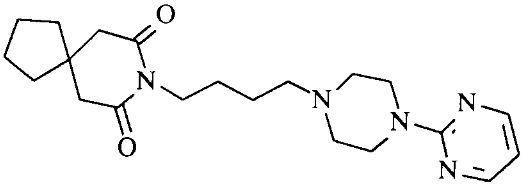
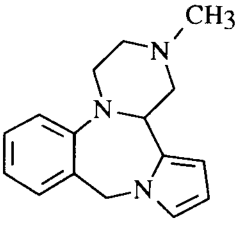
Although all currently marketed anxiolytic agents are very effective in ameliorating the anxiety syndrome, they all possess unwanted side-effects with exception of buspirone **1**, a new original agent active on the 5HT-1A receptors [1-5]. Buspirone and its analogues (ipsapirone, gepirone) showed also antidepressant properties like aptazepine **2** [6] and related products, *i.e.* mianserin and isoaptazepine **3** [7,8]. Consequently, the syntheses of new ring systems related to buspirone and pyrrolobenzodiazepine moieties are greatly warrantable.

Pursuing our studies on buspirone-like spiroderivatives [9,10] we decided to explore the usefulness of 5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetic acid diethyl ester **4** as a synthon to build new polycyclic nitrogen systems of pharmacological interest.

We prepared the diacetic ester **4** by condensation between diethyl 1,3-acetonedicarboxylate and 1-(2-aminomethylphenyl)-1*H*-pyrrole [11] in acid medium. However,



1



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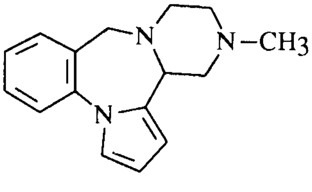

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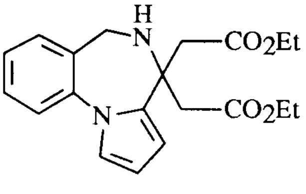
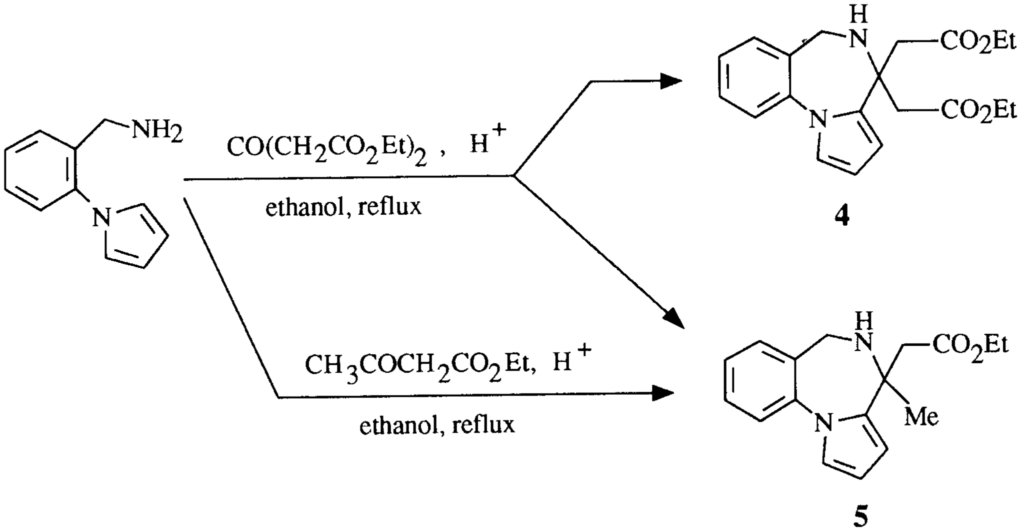


4

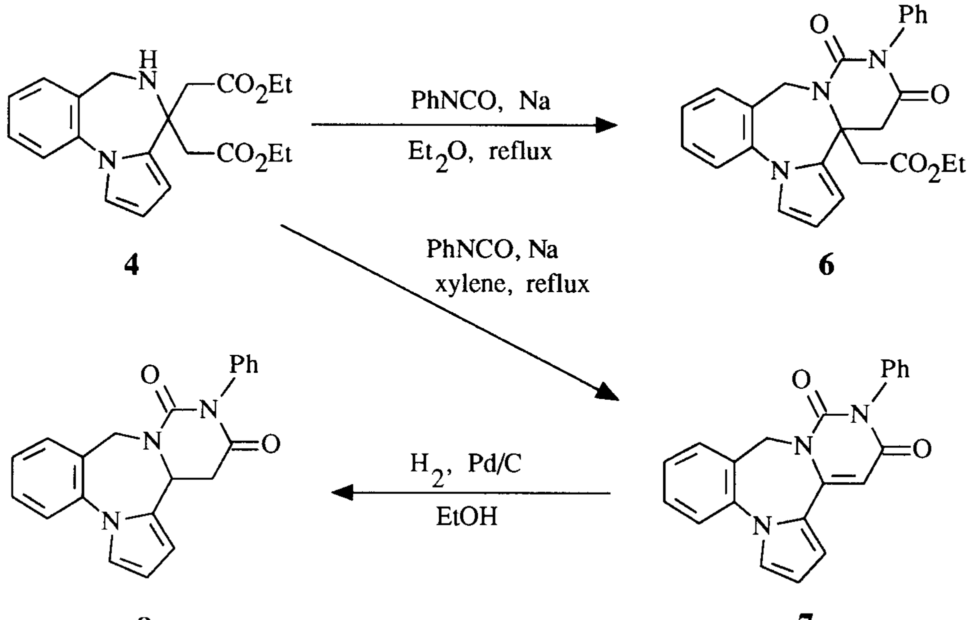
Scheme 1



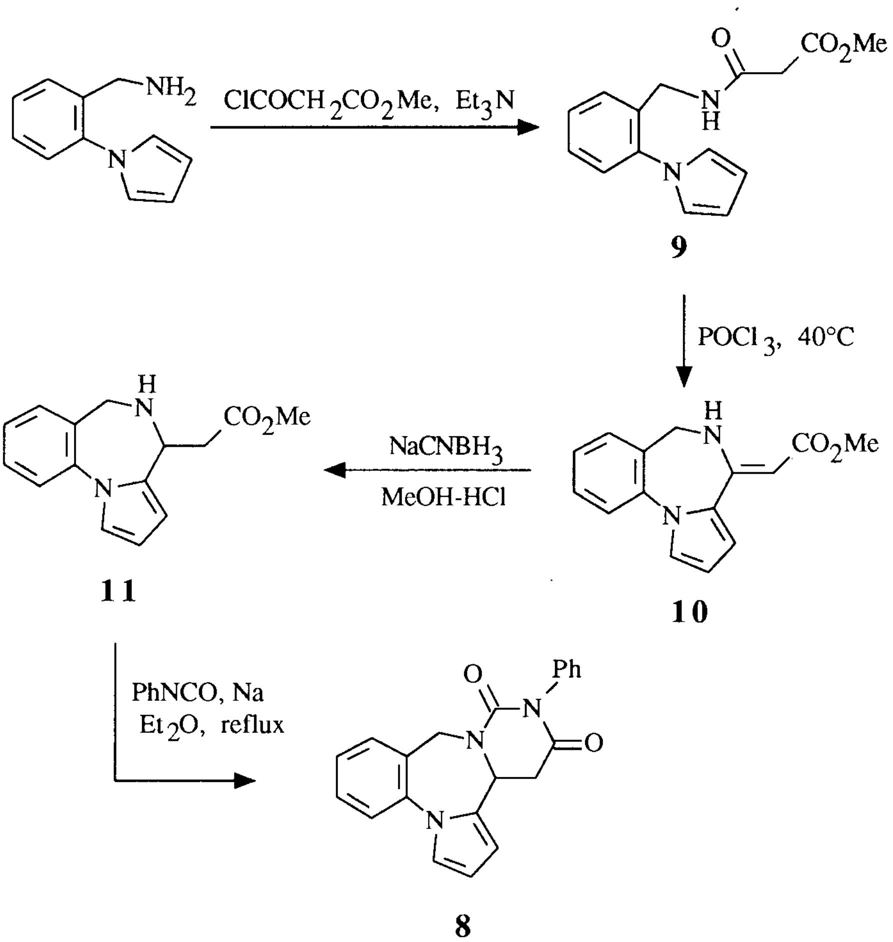
the formation of **4** was always accompanied by the presence of the ethyl ester of 5,6-dihydro-4*H*-pyrrolo[1,2-*a*]-[1,4]benzodiazepine-4-methyl-4-acetic acid **5**, which was obtained as the sole product by reacting ethyl acetylacetate with 1-(2-aminomethylphenyl)-1*H*-pyrrole (Scheme 1).

Attempts to transform compound **4** into the corresponding dioxopiperidino spiroderivative by treating the diester with ammonia, urea or aniline under different conditions were unsuccessful. Then, we tried to build the 2,6-dioxopiperidine moiety by the reaction of **4** with phenylisocyanate according to the literature [12]. However, our efforts in this direction failed, the reaction leading exclusively to the dioxopyrimidopyrrolobenzodiazepine **6**, a novel tetracyclic nitrogen ring strictly related to the aptazepine skeleton (Scheme 2). Furthermore, we found that reaction between **4**, sodium metal and phenylisocyanate is strongly affected by the experimental conditions employed. In fact, formation of **6** took place when the reaction was carried out in boiling diethyl ether for 4 hours, whereas a different product was obtained when the same reaction was purchased in boiling xylene for 12 hours. The new product was identified as **7** on the grounds of nmr and elemental analytical data. Probably **7** was formed from **4** *via* **6** owing to the loss of an acetate unit. Catalytic reduction of **7** with hydrogen in the presence of Pd/C as a catalyst afforded the saturated dioxopyrimidine **8**, the structure of which

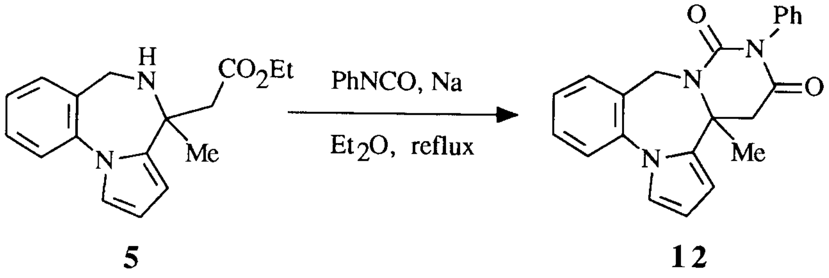
Scheme 2



Scheme 3



Scheme 4

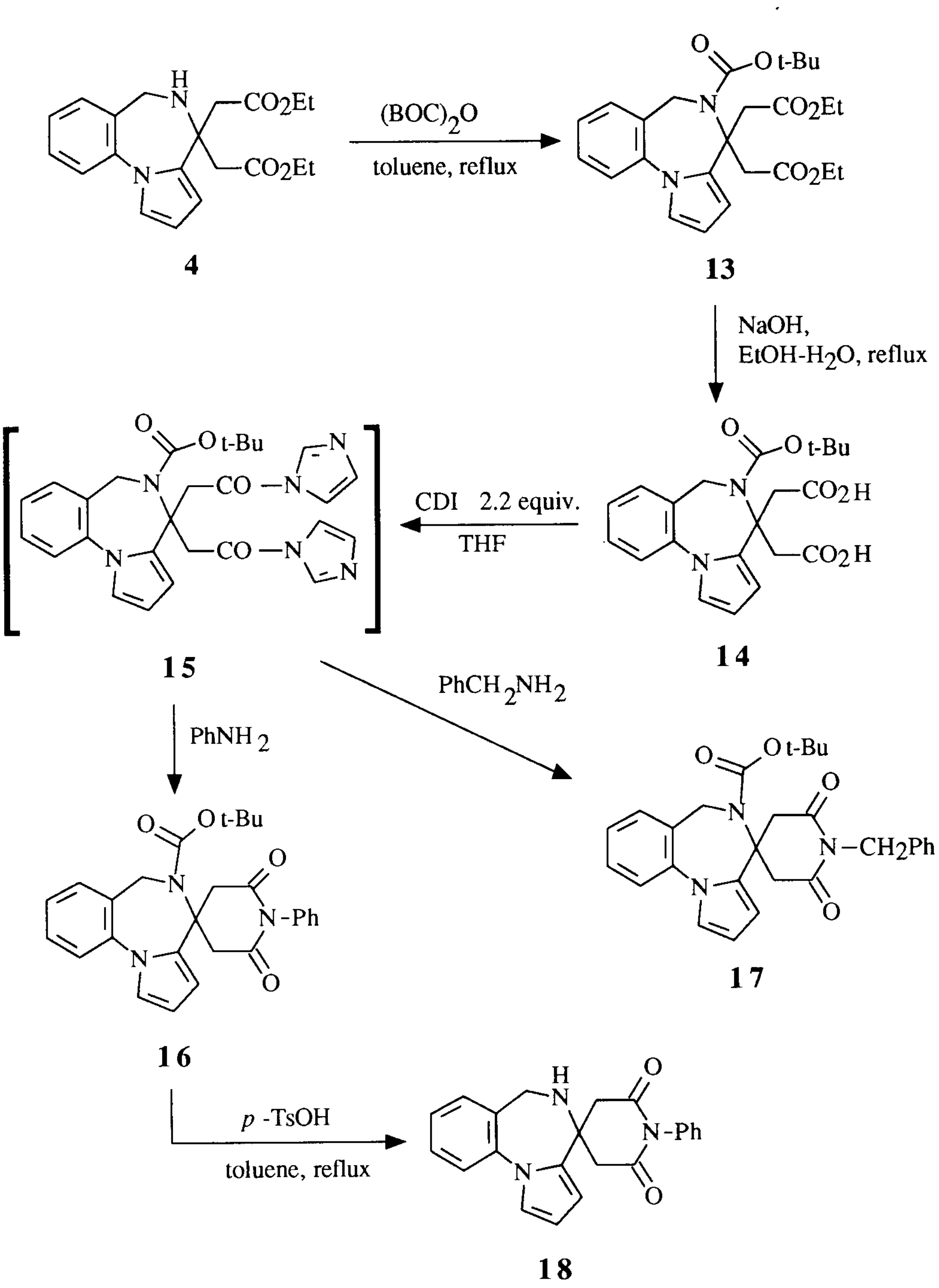


was confirmed by an unambiguous synthetic procedure starting from 1-(2-aminomethylphenyl)-1*H*-pyrrole (Scheme 3). Reaction of the last compound with methyl malonyl chloride in the presence of triethylamine afforded 1-(2-methoxycarbonylacetamidomethyl)phenyl-1*H*-pyrrole **9**, which was cyclized to **10** by treatment with phosphorus oxychloride. Reduction of **10** with sodium cyanoborohydride gave **11**, which on treatment with phenylisocyanate furnished the tetracyclic derivative **8**. This compound was identical with that obtained by catalytic reduction of **7**.

Also derivative **5** when treated with sodium metal and phenylisocyanate afforded the corresponding pyrimidopyrrolobenzodiazepine **12** (Scheme 4).

To avoid the formation of the pyrimidopyrrolobenzodiazepine ring we protected the *NH* group of compound **4** with the introduction of the *t*-butoxycarbonyl (BOC) group. The new derivative **13**, however, did not interact with phenylisocyanate in the presence of strong bases (NaH or BuLi in THF) and none tetracyclic material was formed. A further approach to spiroderivatives by reacting

Scheme 5



1-(2-aminomethylphenyl)1*H*-pyrrole with 1-phenyl-2,4,6-trioxopiperidine was also unsuccessful.

However, we were able to obtain the buspirone-like spiro derivatives through the single-step conversion of the diacetic acid **14**, obtained from **13** by alkaline hydrolysis, into the required 2,6-dioxopiperidines according to the procedure proposed by Kruse *et al.* [13]. Reaction of **14** with 2.2 equivalents of 1,1'-carbonyldiimidazole (CDI) and treatment of the *in situ* formed intermediate **15** with aniline afforded the dioxopiperidine **16**.

Similar reaction with benzylamine gave the spiro derivative **17**. Removal of BOC group from **16** by heating in toluene at reflux in the presence of *p*-toluenesulphonic acid furnished the spiro derivative **18** (Scheme 5). Deprotection of **17** by this and other procedures failed.

EXPERIMENTAL

Melting points were taken on a Büchi 530 apparatus and are uncorrected. The ir spectra (nujol mulls) were run on a Perkin Elmer spectrophotometer. The ^{1}H nmr spectra were recorded at 90 MHz (Varian EM 390) and 200 MHz (Varian XL 200) as specified. The ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane as internal reference. Merck Kieselgel 60 (70-230 mesh) and alumina 90 were used for chromatographic purifications. All compounds were routinely checked by tlc and ^{1}H nmr. Tlc was carried out on Merck Kieselgel 60 GF 254 plates and on Carlo Erba Stratocrom ALF aluminum oxide plates. Developed plates were visualized by uv light. Solvents were reagent grade and were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved use of rotary evaporator operating at reduced pressure of approximately 20 torr. Organic solutions were dried over anhydrous sodium sulphate. Elemental analyses were performed by Professor A. Pietrogrande, Padova, Italy.

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetic Acid Diethyl Ester (**4**) and 5,6-Dihydro-4-methyl-4*H*-pyrrolo-[1,2-*a*][1,4]benzodiazepine-4-acetic Acid Ethyl Ester (**5**).

A solution of diethyl 1,3-acetonedicarboxylate (1.45 g, 7.2 mmoles) in absolute ethanol (100 ml) was gradually added in a period of 2 hours to a pre-heated (80°, oil bath) solution of 1-(2-aminomethylphenyl)-1*H*-pyrrole hydrochloride (1.00 g, 4.8 mmoles) and maleic acid (55 mg, 0.48 mmole) in the same solvent (100 ml), and the resulting mixture was refluxed for 6 hours. After cooling, the alcohol was evaporated and the residue was diluted with water (100 ml), made basic with sodium carbonate and extracted with chloroform (3 x 50 ml). The organic layer was washed with brine (100 ml), dried and evaporated to afford a brown oily residue which was chromatographed over silica gel (chloroform-ethyl acetate, 1:1). The first eluates were discarded, while central fractions were collected and evaporated to give **4** as a pure yellow oil (0.73 g, 43%); ir: 3340 (NH), 1730 cm^{-1} (CO, ester); ^{1}H nmr (90 MHz, carbon tetrachloride): δ 1.10 (t, J = 7 Hz, 6H, CH_3), 2.73 (d, 4H, CH_2CO), 2.93 (br s, 1H, NH), 3.75 (s, 2H, CH_2N), 3.93 (q, J = 7 Hz, 4H, OCH_2), 6.08-6.17 (m, 2H, pyrrole β-H), 6.87-6.93 (m, 1H, pyrrole α-H), 7.23-7.30 (m, 4H, Ph).

Anal. Calcd. for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 62.12; H, 6.50; N, 7.03.

Further elution afforded **5** (0.35 g, 26%) as a pure solid, mp 106-108° (cyclohexane); ir: 3340 (NH), 1725 cm^{-1} (CO, ester); ^{1}H nmr (90 MHz, carbon tetrachloride): δ 1.10 (t, J = 7 Hz, 3H, CH_2CH_3), 1.38 (s, 3H, 4-CH_3), 2.25 (d, 2H, CH_2CO), 2.50 (s, 1H, NH), 3.70 (d, 2H, CH_2N), 3.93 (q, J = 7 Hz, 2H, OCH_2), 6.07-6.15 (m, 2H, pyrrole β-H), 6.83-6.90 (m, 1H, pyrrole α-H), 7.25-7.35 (m, 4H, Ph).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.77; H, 7.10; N, 9.95.

Compound **5** was obtained as the sole product when 1-(2-aminomethylphenyl)-1*H*-pyrrole was allowed to react with ethyl acetylacetate according to the above procedure (32% yield).

General Procedure for the Preparation of 11,13-Dioxo-12,13,14,14a-tetrahydro-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine Derivatives **6**, **8** and **12**.

To a stirred solution of the appropriate aminoester **4**, **11** or **5** (3.5 mmoles) in anhydrous diethyl ether (100 ml) sodium metal (0.10 g, 0.0042 g-atoms) was added and the mixture was heated until the metal disappeared. After cooling, phenylisocyanate (0.50 g, 4.2 mmoles) was very carefully added and the resulting solution was refluxed for 4 hours, cooled, diluted with water (200 ml) and acidified with 0.5 *N* hydrogen chloride. Ethyl acetate (100 ml) was added, then the organic layer was separated, washed with brine (100 ml) and dried. Removal of the solvent gave a residue which was purified by crystallization for **8** or by column chromatography for **6** and **12** over silica gel (ethyl acetate-hexane 2:1).

11,13-Dioxo-12-phenyl-12,13,14,14a-tetrahydro-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine-14a-acetic Acid Ethyl Ester (**6**).

This compound was obtained in a yield of 0.63 g, 42%, mp 199-200° (ethanol); ir: 1725, 1670 cm^{-1} (CO, imide); ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.02 (t, J = 4 Hz, 3H, CH_3), 2.34 (d, J = 9 Hz, 1H, CH_2CO_2Et half of AB quartet), 2.82 (d, J = 9 Hz, 1H, CH_2CO_2Et half of AB quartet), 3.48 (d, J = 9 Hz, 1H, CH_2CON half of AB quartet), 3.73 (d, J = 9 Hz, 1H, CH_2CON half of AB quartet), 3.83 (q, J = 4 Hz, 2H, OCH_2), 4.15 (d, J = 8.5 Hz, 1H, CH_2N half of AB quartet), 5.43 (d, J = 8.5, 1H, CH_2N half of AB quartet), 6.30-6.34 (m, 2H, pyrrole β-H), 7.07-7.10 (m, 1H, pyrrole α-H), 7.17-7.48 (m, 9H, Ph).

Anal. Calcd. for $C_{25}H_{23}N_3O_4$: C, 69.91; H, 5.40; N, 9.79. Found: C, 69.82; H, 5.38; N, 9.88.

11,13-Dioxo-12-phenyl-12,13,14,14a-tetrahydro-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**8**).

This compound was obtained in a yield of 1.08 g, 90%, mp 230.0-230.5° (benzene); ir: 1710, 1660 cm^{-1} (CO, imide); ^{1}H nmr (90 MHz, deuteriochloroform): δ 3.17-3.27 (m, 2H, CH_2CO), 3.97 (d, J = 13.5 Hz, 1H, CH_2N half of AB quartet), 4.53-4.70 (m, 1H, CH), 5.37 (d, J = 13.5 Hz, 1H, CH_2N half of AB quartet), 6.30-6.42 (m, 2H, pyrrole β-H), 7.10-7.43 (m, 10H, pyrrole α-H and Ph).

Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.20; H, 4.82; N, 12.39.

11,13-Dioxo-14a-methyl-12-phenyl-12,13,14,14a-tetrahydro-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**12**).

This compound was obtained in a yield of 0.76 g, 61%, mp 200-202° (ethyl acetate); ir: 1710, 1665 cm^{-1} (CO, imide); ^{1}H nmr (90 MHz, deuteriochloroform): δ 1.32 (s, 3H, CH_3), 3.07 (d, J = 16 Hz, 1H, CH_2CO half of AB quartet), 3.52 (d, J = 16 Hz, 1H, CH_2CO half of AB quartet), 4.08 (d, J = 14 Hz, 1H, CH_2N half of AB quartet), 5.33 (d, J = 14 Hz, 1H, CH_2N half of AB quartet), 6.28-6.37 (m, 2H, pyrrole β-H), 7.10-7.53 (m, 10H, pyrrole α-H and Ph).

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.82; H, 5.33; N, 11.87.

12,13-Dihydro-11,13-dioxo-12-phenyl-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**7**).

To a stirred solution of **4** (1.20 g, 3.5 mmoles) in anhydrous xylene (100 ml) sodium metal (0.1 g, 0.0042 g-atoms) was added and the mixture was heated at 70° until the metal had disappeared. After cooling, phenylisocyanate (0.50 g, 4.2 mmoles) was carefully added and the resulting solution was refluxed overnight. Successively the mixture was cooled, diluted with water (200 ml) and acidified with 0.5 *N* hydrogen chloride. Ethyl acetate (100 ml) was added, the organic layer was separated, washed with brine (100 ml) and dried. Removal of the solvent gave a residue which was chromatographed over silica gel (chloroform) to furnish 0.43 g (36%) of the product, mp 254-256° (benzene); ir: 1695, 1650 cm^{-1} (CO, imide); ^{1}H nmr (90 MHz, deuteriochloroform): δ 4.43 (d, J = 15 Hz, 1H, CH_2N half of AB quartet), 5.62 (d, J = 15 Hz, 1H, CH_2N half of AB quartet), 6.00 (s, 1H, CH), 6.49-6.58 (m, 1H, pyrrole β-H), 7.00-7.08 (m, 1H, pyrrole β-H), 7.22-7.67 (m, 10H, pyrrole α-H and Ph).

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.70; H, 4.36; N, 12.42.

11,13-Dioxo-12-phenyl-12,13,14,14a-tetrahydro-9*H*,11*H*-pyrimido[4,3-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**8**) from Compound **7**.

A stirred solution of **7** (1.00 g, 2.9 mmoles) and palladium on charcoal (10%, 300 mg) in ethanol (100 ml) was hydrogenated in a Parr apparatus for 6 hours at 50° (*ca.* 50 psi). After filtration of the catalyst the ethanolic solution was evaporated to yield compound **8** (0.90 g, 92%) as a solid, identical (mp, spectral data) to the product obtained from the aminoester **11**.

1-(2-Methoxycarbonylacetamidomethyl)phenyl-1*H*-pyrrole (**9**).

A solution of methyl malonyl chloride (6.50 g, 48.0 mmoles) in anhydrous dichloromethane (50 ml) was gradually added to an ice-cooled solution of 1-(2-aminomethylphenyl)-1*H*-pyrrole hydrochloride (10.00 g, 48.0 mmoles) and triethylamine (13.4 ml, 96.0 mmoles) in the same solvent (100 ml). After stirring for 2 hours at room temperature the solution was washed with 10% hydrogen chloride (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml) and finally dried. The organic layer evaporated under reduced pressure gave a white solid (12.81 g, 98%), which was purified by crystallization, mp 91-92° (benzene); ir: 3300 (NH), 1745 (CO, ester), 1645 cm^{-1} (CO, amide).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.07; H, 6.05; N, 10.39.

5,6-Dihydro-4-methoxycarbonylmethylene-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**10**).

A stirred mixture of **9** (12.81 g, 47.0 mmoles) with phosphorus oxychloride (20 ml) was heated at 40° for 2 hours. After cooling the mixture was treated with crushed ice (200 ml) and made basic by adding concentrated ammonium hydroxide. The red oil which separated was extracted with chloroform (2 x 100 ml) and the combined extracts were washed with brine (2 x 100 ml), dried and evaporated. The residue was chromatographed over silica gel (ethyl acetate) to afford a pure oil (8.90 g, 73%), which solidified on standing, mp 133-134° (benzene); ir: 3320 (NH), 1635 cm^{-1} (CO ester); ^{1}H nmr (90 MHz, deuteriochloroform): δ 3.63 (s, 3H, CH_3), 4.23-4.30 (m, 2H, CH_2N), 4.90 (s, 1H, CH), 6.37-6.43 (m, 1H, pyrrole β-H), 6.77-6.80 (m, 1H, pyrrole β-H), 7.17-7.23 (m, 1H, pyrrole α-H), 7.30-7.43 (m, 4H, Ph).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.47; H, 5.38; N, 11.37.

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-acetic Acid Methyl Ester (**11**).

To a stirred solution of **10** (2.00 g, 7.9 mmoles) in a mixture of methanol (50 ml) and tetrahydrofuran (15 ml) sodium cyanoborohydride (0.49 g, 7.9 mmoles) and then a saturated methanolic solution of hydrogen chloride (4.5 ml) were added. The reaction mixture was stirred at room temperature for 20 hours, then evaporated under reduced pressure. The residue was treated with ice-cooled 10% potassium hydroxide (40 ml) and stirred for 5 minutes. Ethyl acetate (50 ml) was added, the organic layer was separated, washed with brine (100 ml) and dried. Removal of the solvent gave **11** (1.47 g, 73%) as a pure oil, which crystallized on standing mp 81-82° (benzene); ir: 3300 (NH), 1720 cm^{-1} (CO, ester); ^{1}H nmr (90 MHz, deuteriochloroform): δ 2.55 (s, 1H, NH), 2.87 (d, 2H, CH_2CO), 3.67 (s, 3H, CH_3), 3.68 (s, 2H, CH_2N overlapped signal), 4.18 (t, 1H, CH), 6.13-6.22 (m, 1H, pyrrole β-H), 6.27-6.33 (m, 1H, pyrrole β-H), 6.97-7.03 (m, 1H, pyrrole α-H), 7.35-7.36 (m, 4H, Ph).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.30; H, 6.30; N, 10.88.

5-*t*-Butoxycarbonyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetic Acid Diethyl Ester (**13**).

To a stirred solution of **4** (6.80 g, 19.0 mmoles) in toluene (200 ml) di-*t*-butyl dicarbonate (6.30 g, 28.0 mmoles) was added and the mixture was refluxed for 12 hours. After cooling the solvent was evaporated, the residue was taken up in ethyl acetate (200 ml) and washed with 2 *N* hydrogen chloride (100 ml), saturated aqueous sodium carbonate (100 ml) and brine (2 x 100 ml). The organic layer, dried and evaporated afforded a residue which was chromatographed over silica gel (chloroform-ethyl acetate, 1:1) to furnish **13** (8.67 g, quantitative) as a pure solid, mp 110-111° (ethyl acetate); ir: 1700-1630 cm^{-1} (CO, ester, amide); ^{1}H nmr (90 MHz, carbon tetrachloride): δ 1.10 (t, 6H, CH_2CH_3), 1.47 [s, 9H, $(CH_3)_3$], 3.37-3.53 (m, 4H, CH_2CO), 3.83-3.97 (m, 4H, OCH_2), 4.50-4.60 (m, 2H, CH_2N), 6.10-6.20 (m, 2H, pyrrole β-H), 6.78-6.83 (m, 1H, pyrrole α-H), 7.27-7.43 (m, 4H, Ph).

Anal. Calcd. for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 65.80; H, 7.07; N, 6.12.

5-*t*-Butoxycarbonyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,4-diacetic Acid (**14**).

To a stirred solution of **13** (8.70 g, 19.0 mmoles) in ethanol (200 ml) an ice-cooled solution of sodium hydroxide (7.60 g, 190.0 mmoles) in water (100 ml) was added, and the resulting mixture was heated at 90° for 2.5 hours. After cooling the solution was diluted with water (300 ml), acidified with 1 *N* hydrogen chloride and extracted with ethyl acetate (3 x 100 ml). The organic layer, dried and evaporated afforded **14** (4.64 g, 61%) as a solid, mp 175-176° (ethyl acetate); ir: 3330 (OH), 1700-1640 cm^{-1} (CO, acid, amide); ^{1}H nmr (90 MHz, DMF-d_7): δ 1.47 [s, 9H, $(CH_3)_3$], 3.53-3.67 (m, 4H, CH_2CO), 4.57-4.63 (m, 2H, CH_2N), 6.20-6.33 (m, 2H, pyrrole β-H), 7.13-7.20 (m, 1H, pyrrole α-H), 7.47-7.63 (m, 4H, Ph), 12.03 (br s, 2H, OH).

Anal. Calcd. for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 63.37; H, 6.18; N, 6.77.

General Procedure for the Preparation of 5′-*t*-Butoxycarbonyl-5′,6′-dihydro-2,6-dioxospiro[piperidine-4,4′-[4*H*]pyrrolo[1,2-*a*]-[1,4]benzodiazepine] Derivatives **16** and **17**.

To a stirred suspension of **14** (3.00 g, 7.5 mmoles) in dry tetrahydrofuran (30 ml) 1,1′-carbonyldiimidazole (2.67 g, 16.5 mmoles) was added and the reaction mixture was stirred at room temperature for 18 hours. The appropriate amine (7.5 mmoles) was successively added to the clear solution, and the resulting mixture was stirred at room temperature for 3 hours and at reflux for a further 4 hours. After cooling the mixture was concentrated *in vacuo* and the residue was taken up in ethyl acetate (100 ml). The organic layer was washed with 0.5 *N* hydrogen chloride (2 x 100 ml), saturated aqueous sodium carbonate (100 ml) and brine (100 ml). After drying the solvent was evaporated and the residue was chromatographed over silica gel (chloroform) to give the imides as pure solids.

5′-*t*-Butoxycarbonyl-5′,6′-dihydro-2,6-dioxo-1-phenylspiro[piperidine-4,4′-[4*H*]pyrrolo[1,2-*a*][1,4]benzodiazepine] **(16)**.

This compound was obtained in a yield of 1.10 g, 32%, mp 208-209° (benzene-cyclohexane, 1:1); ir: 1725, 1670 cm^{-1} (CO, carbamate, imide); ^{1}H nmr (90 MHz, deuteriochloroform): δ 1.47 [s, 9H, $(CH_3)_3$], 2.97 (d, J = 17 Hz, 2H, CH_2CO half of AB quartet), 4.47 (d, J = 17 Hz, 2H, CH_2CO half of AB quartet), 4.43 (s, 2H, CH_2N overlapped signal), 6.28-6.38 (m, 1H, pyrrole β-H), 6.48-6.57 (m, 1H, pyrrole β-H), 6.90-7.53 (m, 10H, pyrrole α-H and Ph).

Anal. Calcd. for $C_{27}H_{27}N_3O_4$: C, 70.88; H, 5.95; N, 9.19. Found: C, 70.95; H, 6.02; N, 9.02.

1-Benzyl-5′-*t*-butoxycarbonyl-5′,6′-dihydro-2,6-dioxospiro[piperidine-4,4′-[4*H*]pyrrolo[1,2-*a*][1,4]benzodiazepine] **(17)**.

This compound was obtained in a yield of 2.48 g, 70%, mp 176-178° (aqueous ethanol); ir: 1710-1665 cm^{-1} (CO, carbamate, imide); ^{1}H nmr (90 MHz, deuteriochloroform): δ 1.47 [s, 9H, $(CH_3)_3$], 2.85 (d, J = 17 Hz, 2H, CH_2CO half of AB quartet), 4.23 (d, J = 17 Hz, 2H, CH_2CO half of AB quartet), 4.33 (s, 2H, CH_2N overlapped signal), 4.80 (s, 2H, CH_2Ph), 6.07-6.17 (m, 2H, pyrrole β-H), 6.87-6.97 (m, 1H, pyrrole α-H), 7.17-7.50 (m, 9H, Ph).

Anal. Calcd. for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.40; H, 6.21; N, 8.82.

5′,6′-Dihydro-2,6-dioxo-1-phenylspiro[piperidine-4,4′-[4*H*]pyrrolo-[1,2-*a*][1,4]benzodiazepine] **(18)**.

A stirred solution of **16** (0.80 g, 1.8 mmoles) in toluene (200 ml) was treated with finely tritured *p*-toluenesulfonic acid monohydrate (200 mg) and was refluxed for 24 hours while water was removed azeotropically. After cooling the solvent was evaporated, the residue was taken up in water (100 ml) and ethyl acetate (100 ml) and the mixture was made basic with sodium hydrogen carbonate. The organic layer was washed with brine (100 ml), dried and evaporated to afford a residue successively purified by column chromatography (alumina, chloroform): the imide **18** was obtained (0.21 g, 33%) as a pure solid, mp 191-193° (diethyl ether); ir: 3300 (NH), 1700, 1690 cm^{-1} (CO, imide); ^{1}H nmr (90 MHz, deuteriochloroform): δ 2.37 (br s, 1H, NH), 2.75 (d, J = 16 Hz, 2H, CH_2CO half of AB quartet), 3.07 (d, J = 16 Hz, 2H, CH_2CO half of AB quartet), 3.80 (s, 2H, CH_2N), 6.27-6.33 (m, 2H, pyrrole β-H), 7.00-7.43 (m, 10H, pyrrole α-H and Ph).

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.80; H, 5.40; N, 11.90.

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