Polycondensed Nitrogen Heterocycles. IX. 5,6-Dihydro-7*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-one

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The reaction of amino derivative I with bromoacetyl bromide led to the formation of a complex mixture from which, in addition to the title compound, which was formed in low yield, compounds III, IV and VI were separated. Pyrrolo[1,2-*d*][1,4]benzodiazepine V was obtained in 85% yield when the bromoamide III was treated with an equimolar amount of potassium *t*-butoxide.

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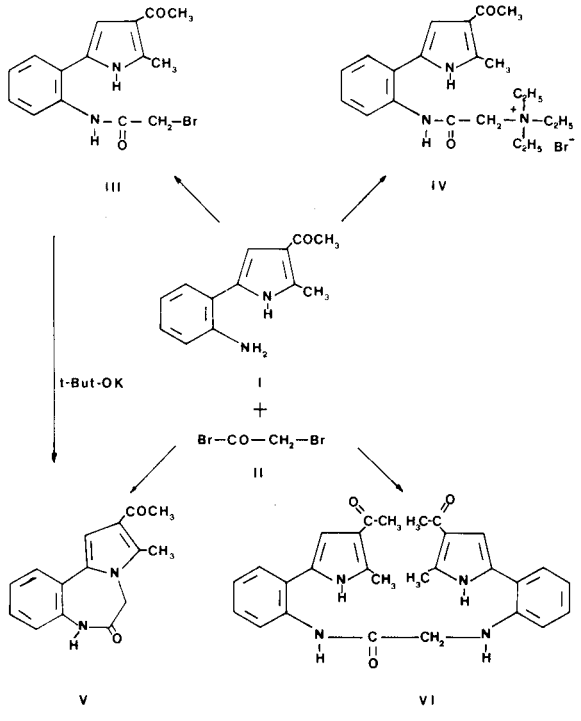
In the preceding paper in this series (1) we described the preparation of a novel class of annelated 1,4-benzodiazepines, namely, 5,6-dihydro-7*H*-pyrrolo[1,2-*d*][1,4]-benzodiazepin-6-ones (V), *via* two alternative synthetic routes. The first synthetic procedure consisted of the catalytic reduction of 2-methyl-3-*R*-5-(2-nitrophenyl)pyrrol-1-yl-acetic acids, prepared by the condensation of 1,4-diketones and appropriate α-aminoacids. However, the least satisfactory step of this procedure is the synthesis of the pyrrol-1-yl-acetic acids, which were obtained in yields which varied considerably depending on the α-aminoacid employed. The yields were 93%, 65%, 7% and 4%, when glycine, alanine, valine and serine, respectively, were used. When the second synthetic procedure was used, the reaction of aminoderivatives of type I with bromoacetyl bromide II and triethylamine as the base, in addition to a complex mixture, the title compounds were obtained in very low yield.

Owing to the relationship of derivatives of V to the known 1,4-benzodiazepines which have shown pharmacological and clinical activities, we considered the possibility of developing the synthesis of V on a scale sufficient to permit the preparation of several derivatives. In this paper we describe the products that we were able to separate and identify from the mixture obtained in the reaction of I with bromoacetyl bromide, and report the possibility of obtaining title compounds in good yield.

When the reaction was carried out in dichloromethane using triethylamine as the base, a precipitate was formed after four days, which was filtered and recrystallized from benzene/ethanol. This product was brominated and water soluble, and was identified as 2-methyl-3-acetyl-5-(2-triethylammoniumacetanilido)pyrrole bromide (IV) by elemental analysis, ir and nmr data. The ir spectrum for this product shows two NH bands at 3250 and 3100 cm^{-1} and two carbonyl stretchings at 1675 and 1650 cm^{-1}. The nmr spectrum shows, in addition to the signals due to the acetyl, methyl, C4-H, and NH groups, a multiplet for four aromatic protons and a triplet for nine protons at δ 1.27, a quartet for six protons at δ 3.52 due to three ethyl groups, a singlet at δ 4.25 for two protons attributable to the methylene group, and an amidic NH at δ 9.77 exchangeable with deuterium oxide.

SCHEME



Column chromatography of the worked-up dichloromethane solution resulted in the formation of, besides unreacted amine I and the pyrrolobenzodiazepine V, two principal components.

The first component, which eluted rapidly from the column, was easily identified as 2-methyl-3-acetyl-5-(2-bromoacetanilido)pyrrole (III). The ir spectrum for this product exhibits two bands at 3220 and 3140 cm^{-1}, due to the pyrrole and amidic NH, and two carbonyl bands at 1660 and 1630 cm^{-1}, attributable to the acetyl and amidic CO. The nmr spectrum for this product shows, beside other signals for substituent protons, a singlet at δ 6.57 for two protons due to the methylene group and a singlet at δ 9.60 due to the amidic NH.

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A second component was isolated from the column, for which the elemental composition ($C_{28}H_{28}N_4O_3$) and mass spectral molecular weight (468) correspond to the reaction product mixture of I and III. The nmr spectrum showed, besides a multiplet for eight aromatic protons, four singlets at δ 2.07, 2.27, 2.37 and 2.45 for three protons each (4 × CH_3), a broad singlet at δ 6.60 for two protons (2 × CH) which splits into two sharp singlets at δ 6.53 and 6.62 upon exchange with deuterium oxide, a broad signal at δ 11.20 for two exchangeable protons (2 × pyrrole NH), a triplet at δ 5.70 for one proton (CH_2-N*H*), a doublet at δ 3.95 for two protons (CH_2) which becomes a singlet at δ 3.90 upon exchange with deuterium oxide, and a singlet at δ 9.30 for one exchangeable proton (*NH*-CO). These signals, together with analytical data, led us to characterize VI as the 1,2-*bis*anilino-2-(4-acetyl-5-methyl-pyrrol-2-yl)ethanone.

Attempts were made to improve the yield of the pyrrolobenzodiazepine V using potassium carbonate instead of triethylamine as the base. However, comparable results were obtained and the reaction pathway was not appreciably influenced by either the reactant ratios, by the nature of solvent (dichloromethane, dioxane) or by the temperature (25, 40 or 100°). Under the condition employed, it was quite possible, owing to the presence of several nucleophiles in the reaction, that the actual isolated products were formed as the result of secondary reactions occurring after the primary product III had been formed.

These findings suggested to divide the reaction into two steps, the first consisting of isolating the bromoamide III. This product was obtained in 85% yield from the reaction of I with bromoacetyl bromide and triethylamine as the base in a ratio of 1:1:1, respectively. The bromoamide III, on reaction with an equimolar amount of potassium *t*-butoxide at room temperature, afforded the pyrrolobenzodiazepine V in 85% yield.

This method of cyclizing the benzodiazepine is of interest to synthetize C-5 substituted derivatives of V in good yield, which can only be made with great difficulty by previously described routes.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected; ir spectra were determined in nujol mull with a Perkin-Elmer infracord 137 spectrophotometer; nmr spectra were obtained with a Jeol C-60 spectrometer (TMS as internal reference). Mass spectra were run on a Jeol JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 KW accelerating voltage. Exact mass measurements were performed at 20,000 resolving power and were carried out to an accuracy of ± 10 ppm of the theoretical values.

Reactions of 2-Methyl-3-acetyl-5-(2-aminophenyl)pyrrole (I) with Bromoacetylbromide (II) and Triethylamine as the Base.

Ratio of I:II:Base, Respectively, of 1:1:2.

To a stirred and cooled (ice/water bath) solution of 2.1 g. of amine I (10 mmoles) and 2.2 g. of triethylamine (20 mmoles) in dichloromethane (40 ml.), 2 g. of bromoacetyl bromide (10 mmoles) in dichloromethane (20 ml.) were added dropwise. After 30 minutes the mixture was allowed to warm to room temperature and was stirred for 4 days. The residue, 2-methyl-3-acetyl-5-(2-triethylammoniumacetanilido)pyrrole bromide (IV), was filtered and recrystallized from benzene/ethanol, m.p. 149-151° (30% yield); ir: 3250 (NH), 3100 (NH), 1675 (CO), 1650 cm^{-1} (CO); nmr (DMSO-d_6): δ 1.27 (9H, t, 3 × CH_2-C*H*$_3$), 2.30 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.52 (6H, q, 3 × C*H*$_2$-CH_3), 4.25 (2H, s, CH_2), 6.77 (1H, d, CH, J = 2 Hz; a singlet appeared upon exchange with deuterium oxide), 7.10-7.60 (4H, m, C_6H_4), 9.77 (1H, s, exchangeable amide NH), 11.20 (1H, broad, exchangeable pyrrole NH); ms: m/e (relative intensities) 327 (7), 254 (10), 239 (13), 86 (100), 43 (5).

Anal. Calcd. for $C_{21}H_{30}BrN_3O_2$: C, 57.80; H, 6.93; N, 9.63. Found: C, 57.87; H, 7.01; N, 9.57.

The filtered dichloromethane solution was washed with water, aqueous sodium bicarbonate (5%), and again with water, dried (sodium sulphate) and evaporated to dryness under reduced pressure. The residue was chromatographed on a dry column of silica gel (340 g.) deactivated with water (15%), and eluted with light petroleum ether (b.p. 50-70°)-ethyl acetate (8:2) fractions of 30 ml. each. The combined fractions 10-17 gave 2-methyl-3-acetyl-5-(2-bromoacetanilido)pyrrole (III), which was recrystallized from ethanol, m.p. 210° (yield 5%); ir: 3220 (NH), 3140 (NH), 1660 (CO), 1630 cm^{-1} (CO); nmr (DMSO-d_6): δ 2.30 (3H, s, CH_3), 2.47 (3H, s, CH_3), 6.57 (2H, s, CH_2), 6.74 (1H, d, CH, J = 1.5 Hz; a singlet appeared upon exchange with deuterium oxide), 7.10-7.70 (4H, m, C_6H_4), 9.60 (1H, s, exchangeable amide NH), 11.22 (1H, broad, exchangeable pyrrole NH); ms: m/e (relative intensities) 334 (M^+ 78), 319 (26), 255 (25), 241 (34), 213 (64), 199 (100), 43 (55); M^+ = 334.0324, $C_{15}H_{15}BrN_2O_2$ requires 334.0317.

Anal. Calcd. for $C_{15}H_{15}BrN_2O_2$: C, 53.74; H, 4.51; N, 8.36. Found: C, 53.80; H, 4.46; N, 8.40.

Further elution (300 ml.) gave 4% of unreacted amine I (m.p., mixed m.p., ir).

Elution with light petroleum ether (b.p. 50-70°)-ethyl acetate (1:1) (fraction 32-46) gave 5,6-dihydro-7-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-one (V) (yield 3%) and (fraction 111-139(1,2-*bis*anilino-2-(4-acetyl-5-methyl-2-yl)-ethanone (VI), recrystallized from ethanol, m.p. 261-263° (yield 4%); ir: 3360 (NH), 3250 (broad NH), 1700 (CO), 1650 cm^{-1} (CO); nmr (DMSO-d_6): δ 2.07 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.95 (2H, d, CH_2, J = 4.5 Hz; a singlet appeared at 3.90 upon exchange with deuterium oxide), 5.70 (1H, t, NH, J = 4.5 Hz exchangeable amine NH), 6.60 (2H, broad singlet, two singlets appeared at 6.53 and 6.62 upon exchange with deuterium oxide, 2 × pyrrole CH), 7.00-8.10 (8H, m, 2 × C_6H_4), 9.30 (1H, s, exchangeable amide NH), 11.20 (2H, broad, 2 × exchangeable pyrrole NH); ms: m/e (relative intensities): 468 (M^+ 89), 254 (21), 241 (43), 228 (49), 227 (52), 226 (56), 225 (95), 214 (53), 211 (44), 199 (39), 185 (100), 171 (70), 43 (48); M^+ = 468.2170, $C_{28}H_{28}N_4O_3$ requires 468.2161.

Anal. Calcd. for $C_{28}H_{28}N_4O_3$: C, 71.77; H, 6.02; N, 11.96. Found: C, 71.80; H, 5.98; N, 12.01.

No changes in the yields were observed when the mixture was refluxed for 24 hours.

Ratio of I:II:Base, Respectively, of 1:1:1.

To a cooled (ice/water bath) solution of amine (10 mmoles) and triethylamine (10 mmoles) in dichloromethane (40 ml.), bromoacetyl bromide II (10 mmoles) in dichloromethane (20 ml.) was added. After standing at room temperature overnight the solvent was evaporated under reduced pressure. The residue, washed with water, filtered, air dried and recrystallized from ethanol gave 2-methyl-3-acetyl-5-(2-bromoacetanilido)-pyrrolo (III) in 88% yield.

Reactions of 2-Methyl-3-acetyl-5-(2-aminophenyl)pyrrole (I) with Bromoacetyl Bromide II), using Potassium Carbonate as the Base.

Ratio of I:II:Potassium Carbonate, Respectively, of 1:1:2.

To a stirred and cooled (ice/water bath) mixture of fine powdered potassium carbonate (10 mmoles) and amine I (10 mmoles) in dioxane (40 ml.), a solution of bromoacetyl bromide (10 mmoles) in dioxane (20 ml.) was added. After standing at room temperature overnight, the mixture was evaporated to dryness under reduced pressure, and shaken with water for 30 minutes. The residue was filtered, air dried and chromatographed on a dry column of silica gel (300 g.) deactivated with water (15%). Elution with light petroleum ether (b.p. 50-70°)-ethyl acetate (8:2) (300 ml.) gave 2-methyl-3-acetyl-5-(2-bromoacetanilido)pyrrole (III) in 9% yield.

Further elution (300 ml.) gave the unreacted amine I (5%). Elution with light petroleum ether (b.p. 50-70°)-ethyl acetate (1:1) gave, in the first 600 ml., the 5,6-dihydro-7*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-one (V) (yield 2%); further elution (1000 ml.) gave 1,2-*bis*anilino-2-(4-acetyl-5-methyl-2-yl)ethanone (VI) (yield 20%).

Ratio of I:II:Potassium Carbonate, Respectively, of 1:1:1.

The reaction and the chromatography were performed in the same manner as described previously. 2-Methyl-3-acetyl-5-(2-bromoacetanilido)-pyrrole (III) was obtained in 20% yield, 5,6-dihydro-7*H*-pyrrolo[1,2-*d*]-[1,4]benzodiazepin-6-one (V) in 1% yield, and 1,2-*bis*anilino-2-(4-acetyl-5-methyl-pyrrol-2-yl)ethanone (VI) in 20% yield.

5,6-Dihydro-7*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-one (V).

To a solution of III (5 mmoles) in absolute ethanol (50 ml.), potassium *t*-butoxide (5 mmoles) in absolute ethanol (20 ml.) was added. After standing for 24 hours at room temperature the solvent was evaporated under reduced pressure. A residue was obtained which was shaken with slightly acidic water, filtered, dried and recrystallized from ethanol, giving 5,6-dihydro-7*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-one (V) in 85% yield.

REFERENCES AND NOTES

(1) E. Aiello, G. Dattolo, G. Cirrincione, S. Plescia and G. Daidone, *J. Heterocyclic Chem.*, **16**, 209 (1979).