Polycondensed Nitrogen Heterocycles. VII. 5,6-Dihydro-7-H-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-ones. A Novel Series of Annelated 1,4-Benzodiazepines

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Received June 22, 1978

The synthesis of a novel class of annelated 1,4-benzodiazepines, the 2-R-3-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-ones (Vc-e), is described. The reaction of 2-(*o*-aminophenyl)-3-R-5-methylpyrroles (IIIa,b) with bromoacetyl bromide in the presence of triethylamine produced the title compounds. An alternative synthetic route was achieved by means of the reactions of Ia,b with the appropriated α-aminoacids. The catalytic reduction of IVc-e over 10% palladium on charcoal led in good to excellent yields directly to the formation of pyrrolo[1,2-*d*][1,4]benzodiazepines (Vc-e).

J. Heterocyclic Chem., **16**, 209 (1979).

The large number of reviews and books which have been published, attest to the pharmacological and clinical eminence of 1,4-benzodiazepines, a remarkable class of compounds with potent minor tranquillizer, muscle-relaxant, anticonvulsant and sedative-hypnotic activity (1a).

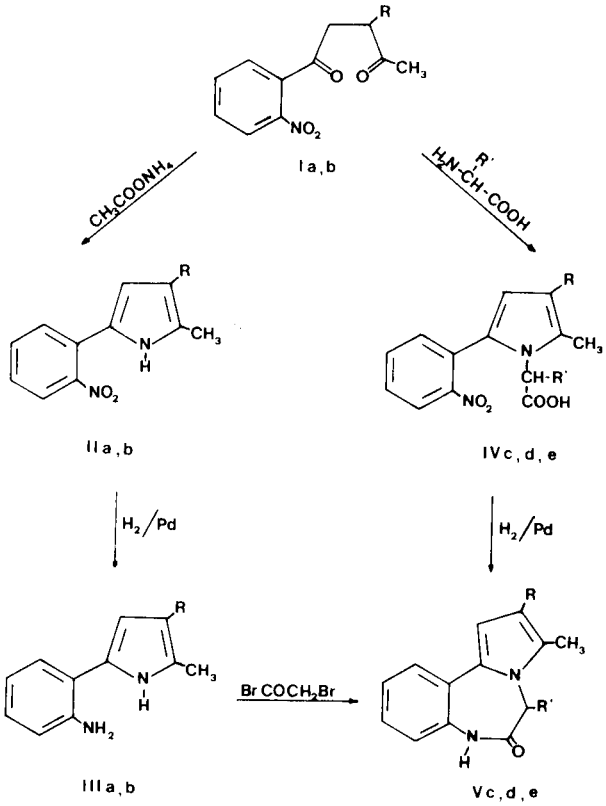
The intense work carried out on the 1,4-benzodiazepine system concerns mainly the development of the chemistry, structure-activity relationships and clinical properties. A great deal of this work, however, has been devoted to the synthesis of annelated 1,4-benzodiazepines, which show similar pharmacological profiles to the benzodiazepines from which they are derived, but which are an order of magnitude more potent (1a-f). Moreover, the discovery of Anthamicin, an antitumor antibiotic (2) and the structure elucidation of this antibiotic, 5,10,11,11a-tetrahydro-9,11-dihydroxy-8-methyl-5-oxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (3), produced a number of scientific publications (4) dealing with the synthesis of some pyrrolo[2,1-*c*][1,4]- and [1,5]benzodiazepine derivatives, and the study of their cytostatic and cytotoxic activities.

In connection with our investigation on polycondensed heterocycles with potential pharmaceutical and microbiological properties (5), it was of interest to us to extend our work to the synthesis of a novel series of annelated 1,4-benzodiazepine, namely, 2-R-3-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-ones. Our interest in these compounds was both from the point of view of the production of compounds with ansiolitic properties and the study of potentially interesting tricyclic system related to anthamicin by structural isomerism with its parent nucleus.

In this paper we report the synthesis of the title compounds by means of the reaction fo 2-(*o*-aminophenyl)-3-R-5-methylpyrrole (IIIa,b) with bromoacetyl bromide, and of 3-(*o*-nitrophenacyl)-2,4-pentanedione (Ia) or ethyl *o*-nitrophenacylacetoacetate (Ib) with the appropriate α-aminoacids.

The original scheme utilized 3-(*o*-nitrophenacyl)-2,4-pentanedione (Ia) or ethyl *o*-nitrophenacylacetoacetate (Ib) (6) as the starting material. Treatment of these ketones with ammonium acetate in acetic acid produced the corresponding pyrroles IIa and IIb (6). Subsequently, the nitro group was reduced over 10% palladium on charcoal and the aminoderivatives IIIa and IIIb were allowed to react with bromoacetyl bromide in dichloromethane in presence of triethylamine. The latter reactions led predominantly to the formation of several by-products,

SCHEME



a R = $COCH_3$; b R = $COOC_2H_5$; c R = $COCH_3$, R' = H;
d R = $COCH_3$, R' CH_3; e R = $COOC_2H_5$, R' = H;

0022-152X/79/020209-03$02.25

giving also the desired pyrrolobenzodiazepines (Vc and Vd), in 3-5% yield.

In a second approach, the reaction with bromoacetyl bromide was carried out under several different experimental conditions and with different condensing agents. However, our attempts to obtain pyrrolobenzodiazepines in better yields failed. The experimental and the by-products identified in the course of these reactions will be described in the near future. The poor yields of the reactions with bromoacetyl bromide prompted us to seek an alternative synthetic route to prepare the title compounds.

Diketones Ia and Ib reacted in acetic acid with glycine or alanine to give the corresponding pyrroles IVc-e in 90-50% yields. Catalytic reduction of the latter compounds in ethanol, over 10% palladium on charcoal reduced the nitro group, and simultaneously afforded pyrrolo-benzodiazepines Vc-e in crystalline form and in high yield. This unusual cyclisation is receiving our attention.

Evidences for the assigned structures were analytical data, molecular weight determined by mass spectrometry, ir and nmr spectra as well as the fact that Vc and Vd were obtained by two different routes. The ir spectra showed a NH band at 3180-3200 cm^{-1} and a strong carbonyl band at 1670-1690 cm^{-1}. ^1H nmr spectra showed, besides a multiplet of four aromatic protons and a singlet of methylic protons, a singlet at 4.45-4.50 ppm for the CH_2 protons of IVc and IVe (a quartet at 5.19 ppm for 5-H of IVd), a singlet at 6.22-6.75 ppm (1-H) and a broad peak at 8.75-10.00 ppm, exchangeable with deuterium oxide (7-H).

Compounds Vc-e were tested as sedative, depressive and miorilassant agents, but no activity was shown.

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 Joel 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 measurement were performed at 20,000 resolving power and were carried out to an accuracy of ± 10 ppm of the theoretical values.

3(*o*-Nitrophenacyl)-2,4-pentandione (Ia).

To a mixture of 2.72 g. (40 mmoles) of sodium ethylate in absolute ethanol (40 ml.), 4 g. (40 mmoles) of 2,4-pentandione and 9.8 g. (40 mmoles) of *o*-nitrophenacylbromide in 60 ml. of absolute ether were added dropwise with stirring and cooling on an ice bath. After standing at room temperature overnight, the residue was filtered off, shaken with water and recrystallized from ethanol (yield 50%), m.p. 122°; ir: cm^{-1} 1735 and 1710 (CO), the nmr spectrum was in agreement with the two tautomeric structures: $-CH_2-(CO-CH_3)CH-COCH_3$ (A) ⇌ $-CH_2-(CO-CH_3)-C=C(OH)CH_3$ (B) in equilibrium in DMSO-d_6: δ 2.14 (3H, s, CO-CH_3 B), 2.28 (6H, s, 2 x CH_3 A) 3.36 (3H, s, C (OH) CH_3 B), 3.52 (2H, d, CH_2 A), 3.53 (2H, s, CH_2 B) 4.10 (1H, s, OH B), 4.45 (1H, t, CH, A), 7.55-8.30 (8H, m, C_6H_4 A + C_6H_4 B).

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32; Found: C, 59.50; H, 5.00; N, 5.30.

2-Methyl-3-acetyl-5(*o*-nitrophenyl)pyrrole (IIa).

A mixture of 2.63 g. (10 mmoles) of Ia, 10 g. (130 mmoles) of ammonium acetate and acetic acid (40 ml.) was refluxed for 3 hours. After cooling, the resultant solution was poured into crushed ice. The solid precipitate was filtered off, air dried and recrystallized from ethanol (yield 88%), m.p. 208°; ir: cm^{-1} 3150 (NH), 1640 (CO); nmr (DMSO-d_6): δ 2.25 (3H, s, CH_3), 2.42 (3H, s, CH_3), 6.50 (1H, d, CH, J = 1.5 Hz a singlet appeared upon exchange with deuterium oxide), 7.20-8.00 (4H, m, C_6H_4), 11.35 (1H, broad, NH); ms: m/e (relative intensities) 244 (100 M^+), 229 (40), 185 (13), 183 (30), 113 (15), 104 (20), 51 (14), 43 (40).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.83; H, 4.89; N, 11.50.

2-Methyl-3-acetyl-5-(*o*-aminophenyl)pyrrole (IIIa).

A mixture of 2 g. of IIa (8 mmoles), 50 ml. of ethanol and 0.2 g. of 10% palladium on charcoal was hydrogenated in a Parr apparatus at 45 p.s.i. for 12 hours at room temperature. Removal of the catalyst and evaporation of ethanol left a residue which was recrystallized from benzene (yield 85%), m.p. 132°; ir: cm^{-1} 3410, 3320, 3200 (NH_2 and NH), 1645 (CO); nmr (deuteriochloroform): δ 2.40 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.90 (2H, broad, NH_2), 6.56 (1H, d, CH J = 2.0 Hz, a singlet appeared upon exchange with deuterium oxide), 6.65-7.30 (4H, m, C_6H_4), 9.20 (1H, broad, NH); ms: m/e (relative intensities) 214 (100 M^+), 200 (11), 199 (68), 197 (4), 172 (25), 171 (35), 170 (9), 169 (11), 156 (8), 154 (10), 144 (13), 143 (7), 130 (13), 129 (6), 128 (5), 119 (7), 118 (5), 117 (5), 77 (8), 65 (7), 43 (10).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.90; H, 6.60; N, 13.00.

2-Methyl-3-R-5-(*o*-nitrophenyl)pyrrol-1-yl-R′-acetic Acids (IVc-e).

The preparation of substituted acetic acids (IVc-e) was carried out in acetic acid by condensation of equimolar amounts of 1,4-diketones Ia,b and appropriate α-aminoacids.

The mixture was refluxed for 3 hours, cooled, poured into crushed ice and aqueous sodium hydrate (20%) until alkaline *p*H was added. The residue was filtered off, the clear solution was acidified with 1*N* hydrochloric acid and the precipitate recrystallized.

Compound IVc.

This compound was recrystallized from benzene (yield 93%), m.p. 184°; ir: cm^{-1} 3070 (broad OH), 1740 (CO), 1620 (CO); nmr (deuteriochloroform): δ 2.30 (3H, s, CH_3), 2.46 (3H, s, CH_3), 4.49 (2H, s, CH_2), 6.30 (1H, s, CH), 7.10-8.00 (4H, m, C_6H_4), 9.20 (1H, broad, OH): ms: m/e (relative intensities) 302 (M^+ 100), 287 (33), 240 (21), 213 (15), 199 (20), 197 (17), 186 (18), 185 (14), 184 (15), 172 (15), 171 (13), 170 (20), 169 (13), 168 (24), 167 (19), 115 (21), 104 (18), 100 (27), 72 (30), 43 (85).

Anal. Calcd. for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.70; H, 4.70; N, 9.20.

Compound IVd.

This compound was recrystallized from benzene (yield 65%), m.p. 122°; ir: cm^{-1} 2550 (broad, OH), 1735 (CO), 1625 (CO); nmr (deuteriochloroform): δ 1.70 (3H, d, CH-*CH*$_3$), 2.35 (3H, s, CH_3), 2.55 (3H, s, CH_3), 4.67 (1H, q, *CH*, CH_3), 6.39 (1H, s, CH),

7.10-8.05 (4H, m, C_6H_4), 9.65 (1H, s, OH); ms: m/e (relative intensities) 316 (M^+ 78), 301 (14), 227 (14), 213 (16), 211 (21), 186 (35), 170 (26), 128 (20), 115 (26), 114 (27), 104 (25), 86 (16), 78 (88), 77 (35), 51 (30), 50 (20), 43 (100).

Anal. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.80; H, 5.05; N, 8.90.

Compound IVe.

An analytical sample of this compound was purified by chromatography on a column of silica gel with 15% water (100 g.), and petroleum ether (50-70°)-ethylacetate (1:1) as eluent, and recrystallized from benzene (yield 50%), m.p. 146°; ir: cm^{-1} 2680 (broad OH), 1720 and 1690 (CO); nmr (DMSO-d_6): δ 2.27 (3H, t, CH_2-CH_3), 2.40 (3H, s, CH_3), 4.17 (2H, q, CH_2-CH_3), 4.27 (2H, s, CH_2), 5.70 (1H, broad, OH), 6.22 (1H, s, CH), 7.30-8.10 (4H, m, C_6H_4); ms: m/e (relative intensities) 332 (M^+ 100), 287 (65), 240 (16), 225 (18), 215 (20), 212 (25), 199 (20), 198 (48), 197 (58), 172 (44), 171 (45), 168 (25), 167 (25), 146 (25), 127 (20), 115 (30), 104 (38), 100 (35), 77 (20), 72 (37), 51 (15), 28 (30).

Anal. Calcd. for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.70; H, 4.90; N, 8.50.

2-R-3-Methyl-5-R'-5,6-dihydro-7*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-6-ones (Vc-e).

Method A.

To a solution of 5 mmoles of IIIa,b, 11 mmoles of triethylamine in dichloromethane (20 ml.) were added dropwise, cooling (water bath) and stirring, 5 mmoles of bromoacetylbromide in dichloromethane (10 ml.). After standing 4 days with stirring, tlc showed a very complex mixture. The desired compounds were isolated by chromatography on a column (4 x 65 cm) of silica gel with 15% water (340 g.) and petroleum ether (50-70°)-ethylacetate (1:1) as eluent.

Method B.

Compounds IVC-e were reduced on 10% palladium on charcoal in ethanol in a Parr apparatus at 45 p.s.i. for 12 hours at room temperature. The catalyst was filtered and the solvent evaporated under reduced pressure. The crystalline solid obtained was recrystallized from appropriate solvent.

Compound Vc.

This compound was recrystallized from ethanol (yield 70%), m.p. 231°; ir: cm^{-1} 3180 (NH), 1680 and 1660 (CO); nmr (DMSO-d_6: δ 2.32 (3H, s, CH_3), 2.51 (3H, s, CH_3), 4.42 (2H, s, CH_2), 6.75 (1H, s, CH), 6.90-7.60 (4H, m, C_6H_4), 10.00 (1H, s, NH); ms: m/e (relative intensities) 254 (M^+ 70), 239 (100), 211 (13), 183 (10), 127 (10), 43 (10), M^+, 254.105 (± 0.003), for $C_{15}H_{14}N_2O_2$ required M^+ 254.105.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.91; H, 5.57; N, 11.12.

Compound Vd.

This compound was recrystallized from ethanol (yield 65%), m.p. 214°; ir: cm^{-1} 3070 (NH), 1680 and 1660 (CO); nmr (deuteriochloroform): δ 1.40 (3H, d, CH-CH_3), 2.43 (3H, s, CH_3), 2.68 (3H, s, CH_3), 5.19 (1H, q, CH-CH_3), 6.72 (1H, s, CH), 6.90-7.75 (4H, m, C_6H_4), 9.11 (1H, s, NH); ms: m/e (relative intensities): 268 (M^+ 100), 253 (93), 225 (26), 182 (17), 43 (15), M^+ 268.120 (± 0.003) for $C_{16}H_{16}N_2O_2$ required M^+ 268.121.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.54; H, 6.12; N, 10.51.

Compound Ve.

This compound was recrystallized from ethanol (yield 76%), m.p. 214°; ir: cm^{-1} 3180 (NH), 1710 and 1680 (CO); nmr (deuteriochloroform): δ 1.38 (3H, t, CH_2-CH_3), 2.65 (3H, s, CH_3), 4.30 (2H, q, CH_2-CH_3), 4.50 (2H, s, CH_2), 6.78 (1H, s, CH), 6.95-7.80 (4H, m, C_6H_4), 8.75 (1H, s, NH); ms: m/e (relative intensities) 284 (M^+ 95), 255 (100), 239 (24), 211 (12), 210 (11), 31 (12), M^+ 284.114 (± 0.003) for $C_{16}H_{16}N_2O_3$ required M^+ 284.116.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.67; H, 5.72; N, 9.91.

REFERENCES AND NOTES

(1a) See, for example, I. R. Ager, G. W. Danswan, D. R. Harrison, D. P. Kay, P. D. Kennewell and J. B. Taylor, *J. Med. chem.*, **20**, 1035 (1977);

(b) A. Walser and G. Zenchoff, *ibid.*, **20**, 1694 (1977);

(c) T. Hara, Y. Kayama, T. Mori, K. Itoh, H. Fujimori, T. Sunami, Y. Hashimoto, and S. Ishimoto, *ibid.*, **21**, 263 (1978);

(d) J. B. Hester, A. D. Rudzik and B. V. Kamdar, *ibid.*, 14, 1078 (1971);

(e) N. W. Gilman and R. Ian Fryer, *J. Heterocyclic Chem.*, 14, 1171 (1977);

(f) K. Meguro and Y. Kuwada, *Tetrahedron Letters*, 47, 4039 (1970).

(2) W. Leimgruber, V. Stefanovic, F. Schenker, A. Karr and J. Berger, *J. Am. Chem. Soc.*, 87, 5791 (1965).

(3) W. Leimgruber, A. D. Batcho and F. Schenker, *ibid.*, 87, 5793 (1965).

(4) M. Scalzo, M. Artico, R. Giuliano, F. Chimenti, S. Vomero, V. Nacci, *Il Farmaco, Ed. Sci.* **32**, 579 (1977).

(5) For references to previous notes: E. Aiello, G. Dattolo and S. Plescia, *J. Heterocyclic Chem.*, **13**, 615 and 645 (1976)

(6) E. Aiello, *Atti Accad. Sci. Arti Palermo*, **30**, 237 (1970).