

A New Synthesis of 5,6-Dihydro-7H-pyrazolo[1,5-d][1,4]benzodiazepin-6-ones

G. Dattolo, G. Cirrincione, A. M. Almerico, I. D'Asdia and E. Aiello*

II Cattedra di Chimica Farmaceutica e Tossicologica dell'Università di Palermo,
Via Archirafi 32, 90123 Palermo, Italy
Received February 1, 1982

A new synthesis of 2-methyl-9-R'-10-R-5,6-dihydro-7H-pyrazolo[1,5-d][1,4]benzodiazepin-6-ones (**4a-c**) is described. Reaction of ethyl hydrazinoacetate hydrochloride with 1,3-diketones **1a-c** gave both 3-methyl-5-(4-R'-5-R-2-nitrophenyl)pyrazol-1-yl-acetate acids (**2a-c**) and the corresponding ethyl esters **3a-c**. Reduction with the appropriate reducing agent of compounds **2a-c** and **3a-c** directly gave the title compounds. Compound **4a** showed insecticidal properties against the house fly.

J. Heterocyclic Chem., **19**, 1237 (1982).

The great importance of the benzodiazepine nucleus in pharmacological and medicinal research is generally acknowledged. It is also well known that annelated 1,4-benzodiazepines show higher activities than the compounds from which they are derived, when the condensed benzodiazepines have similar pharmacological profiles to the parent nucleus (2-6).

In continuing our studies on poly-condensed nitrogen heterocycles with potential biological activity and considering that pyrazolobenzodiazepines were prepared for use as anxiolytics, sedatives, muscle relaxants and anticonvulsants (3,7,8), we became interested in finding a new synthetic approach to the pyrazolo[1,5-d][1,4]benzodiazepine ring system (9).

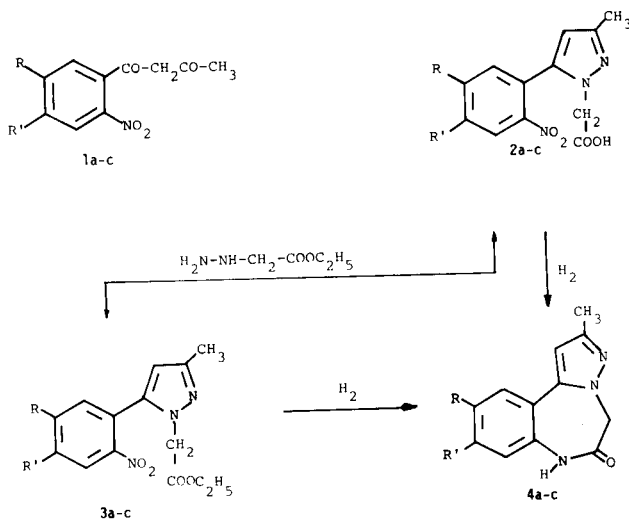
In this paper, we report a new series of reaction by which the title compounds can be obtained in high yields. For this purpose, 1,3-diketones **1a** (10), **b** (11) and **c**, were refluxed with ethyl hydrazinoacetate hydrochloride in acetic acid. Ethyl pyrazol-1-yl-acetates **3a-c** were obtained together with an equivalent amount of the corresponding pyrazol-1-yl-acetic acids **2a-c**.

The structure of acids **2a-c** was determined by analysis and ms as well as ir and nmr data. In fact the ir spectra showed a broad OH absorption at 2510-2480 cm^{-1} , while in the nmr spectra the presence of the OH group could be established by a decrease in the integral of the aromatic protons upon exchange with deuterium oxide.

The esters **3a-c** were obtained as uncrystallizable oils. Only in the case of compound **3b** was it possible for us to crystallize and identify this compound by analysis, ms, ir and nmr data.

Compounds **3a-c**, by hydrolysis, gave products that were found to be identical with the acid derivatives **2a-c** (mixed mp, ir).

The reduction of **2a-c** or **3a-c** was carried out by two different reducing agents depending on whether or not the compounds were halogenated. Compounds **2a** and **3a** ($R = R' = H$) were reduced catalytically over palladium on charcoal, while halogenated compounds **2b,c** and **3a,c** were reduced with iron-acetic acid at 70°. By both methods, the reduction of the nitro group and the simultaneous ring closure was achieved and pyrazolo[1,5-d][1,4]benzodiazepines **4a-c** were obtained in good yields (85-90%). The structures of compounds **4a-c** were supported by elemental analysis, exact mass measurements, ir and nmr spectral data. The ir spectra showed an NH band at 3200 cm^{-1} and carbonyl stretchings at 1695-1680 cm^{-1} . The nmr spectra, in addition to the signals due to the aromatic and substituent protons, exhibited one singlet for two protons attributable to CH_2 at δ 4.70-4.74 and one singlet for one proton at δ 10.46-10.55, exchangeable with deuterium oxide, due to the amide NH. Pyrazolobenzodiazepines **4a-c**, tested as anxiolytics, sedatives, muscle relaxants and anticonvulsants, did not demonstrate any significant activities. Nevertheless, the same compounds **4a-c** were tested as insecticides and herbicides and pyrazolo[1,5-d][1,4]benzodiazepine **4a** demonstrates interesting insecticidal activity against the house fly.



a $R = R' = H$; b $R = H$, $R' = Cl$; c $R = Cl$, $R' = H$.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. The ir spectra were determined (nujol mull) with a Perkin-Elmer 299 spectrophotometer. The nmr spectra were obtained with a Varian FT 80 spectrometer using TMS as the internal reference. Mass spectra were run on a JOEL 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 theoretical values.

1-(2-Nitro-4-R'-5-R-phenyl)-butane-1,3-dione (**1c**).

This compound was prepared according to the procedure described in the literature for **1b** (11). The compound was recrystallized from ethanol (yield 40%), mp 78°; ir: 2720 (broad OH) and 1620 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 2.16 (3H, s, CH_3), 3.97 (1H, s, exchangeable OH), 5.75 (1H, s, CH), 7.26-7.97 (3H, m, C_6H_3); ms: $M^+ = 241.035$, $\text{C}_{10}\text{H}_8\text{ClNO}_4$ requires: $M^+ = 241.014$.

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{ClNO}_4$: C, 49.70; H, 3.34; N, 5.80. Found: C, 50.09; H, 3.45; N, 6.00.

Reaction of Ethyl Hydrazinoacetate Hydrochloride on 1,3-diketones **1a-c**. (Compounds **2a-c** and compounds **3a-c**).

To 10 mmoles of **1a-c** in acetic acid (20 ml), a solution of ethyl hydrazinoacetate hydrochloride (10 mmoles) in water (5 ml) (previously neutralized with sodium bicarbonate) was added. The mixture was refluxed for 5 hours, then was poured onto crushed ice and extracted with ethyl acetate (3×100 ml). The organic layer was dried (sodium sulphate) and was evaporated under reduced pressure (steam bath). The residual oil was treated with cold benzene and the precipitate obtained was filtered and recrystallized giving the 3-methyl-5-(2-nitro-4-R'-5-R-phenyl)pyrazol-1-yl-acetic acids (**2a-c**).

Compound **2a**.

This compound was recrystallized from benzene (yield 40%), mp 245°; ir: 2500 (broad OH) and 1730 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.21 (3H, s, CH_3), 4.66 (2H, s, CH_2), 6.14 (1H, s, CH), 7.47-8.19 (5H, m, C_6H_4 and exchangeable OH); ms: $M^+ = 261.054$, $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_4$ requires $M^+ = 261.075$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.22; H, 4.18; N, 16.15.

Compound **2b**.

This compound was recrystallized from benzene (yield 41%), mp 256°; ir: 2480 (broad OH) and 1745 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.20 (3H, s, CH_3), 4.70 (2H, s, CH_2), 6.16 (1H, s, CH), 7.38-8.27 (4H, m, C_6H_3 and exchangeable OH); ms: $M^+ = 295.061$, $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}_4$ requires $M^+ = 295.036$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}_4$: C, 48.74; H, 3.41; N, 14.21. Found: C, 48.90; H, 3.35; N, 14.41.

Compound **2c**.

This compound was recrystallized from benzene (yield 45%), mp 230°; ir: 2510 (broad OH) and 1730 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.18 (3H, s, CH_3), 4.70 (2H, s, CH_2), 6.16 (1H, s, CH), 7.55-8.22 (4H, m, C_6H_3 and exchangeable OH); ms: $M^+ = 295.022$, $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}_4$ requires $M^+ = 295.036$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}_4$: C, 48.74; H, 3.41; N, 14.21. Found: C, 48.81; H, 3.37; N, 14.38.

The filtered benzene solution was evaporated and chromatographed on a dry column of silica gel deactivated with water (15%) and petroleum ether (bp 50-70°) ethyl acetate (4:1) as eluent. The combined fractions (25-40) (30 ml each) gave the ethyl 3-methyl-5-(2-nitro-4-R'-5-R-phenyl)pyrazol-1-yl-acetate (**3a-c**) as uncrystallizable oils except in the case of **3b** which was recrystallized from benzene (yield 30%); mp 79°; ir: 1740 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 1.15 (3H, t, CH_2CH_3), 2.20 (3H,

s, CH_3), 4.10 (2H, q, CH_2CH_3), 4.80 (2H, s, CH_2), 6.18 (1H, s, CH), 7.49-8.29 (3H, m, C_6H_3); ms: $M^+ = 323.062$, $\text{C}_{14}\text{H}_{14}\text{ClN}_3\text{O}_4$ requires $M^+ = 323.067$.

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{ClN}_3\text{O}_4$: C, 51.94; H, 4.36; N, 12.98. Found: C, 52.13; H, 4.30; N, 13.31.

The compounds **3a-c** were refluxed in ethanolic potassium hydroxide (5%) for one hour. The solvent was evaporated under reduced pressure and the residue was treated with 1N hydrochloric acid. The precipitate was filtered, air dried, recrystallized and identified as the corresponding acids **2a-c** (mixed mp and ir) (yield 90%).

2-Methyl-5,6-dihydro-7H-pyrazolo[1,5-d][1,4]benzodiazepin-6-one (**4a**).

Compound **2a** or **3a** was reduced on 10% Palladium on charcoal in ethanol in a Parr apparatus at 45 psi for 12 hours at room temperature. The catalyst was filtered and the concentrated solution was allowed to crystallize giving the desired product.

Compound **4a**.

This compound was recrystallized from ethanol (yield 85%); mp 281°; ir: 3200 (NH) and 1680 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.20 (3H, s, CH_3), 4.70 (2H, s, CH_2), 6.44 (1H, s, CH), 7.11-7.63 (4H, m, C_6H_4), 10.46 (1H, broad exchangeable NH); ms: $M^+ = 213.10$, $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$ requires 213.090.

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.82; H, 5.11; N, 19.88.

2-Methyl-9-R'-10-R-5,6-dihydro-7H-pyrazolo[1,5-d][1,4]benzodiazepin-6-ones (**4b,c**).

A solution of compounds **2b,c** or **3b,c** (5 mmoles) in acetic acid (50 ml) was heated at 70° while iron powder (1 g) was added over a period of one hour. After the addition was complete, the mixture was kept at 70° for 12 hours. It was then poured onto crushed ice and the precipitate was filtered and recrystallized.

Compound **4b**

This compound was recrystallized from ethanol (yield 90%); mp 286°; ir: 3200 (NH) and 1695 (CO) cm^{-1} ; nmr (DMSO- d_6): 2.19 (3H, s, CH_3), 4.74 (2H, s, CH_2), 6.46 (1H, s, CH), 7.26-7.68 (3H, m, C_6H_3), 10.55 (1H, Broad exchangeable NH); ms: $M^+ = 247.069$, $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}$ requires $M^+ = 247.051$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.33; H, 4.15; N, 17.05.

Compound **4c**.

This compound was recrystallized from ethanol (yield 90%); mp 277°; ir: 3200 (NH) and 1695 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.19 (3H, s, CH_3), 4.73 (2H, s, CH_2), 6.53 (1H, s, CH), 7.24-7.70 (3H, m, C_6H_3), 10.55 (1H, Broad exchangeable NH); ms: $M^+ = 247.048$, $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}$ requires $M^+ = 247.051$.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{ClN}_3\text{O}$: C, 58.19; H, 4.07; N, 16.97. Found: C, 58.35; H, 3.95; N, 16.80.

Acknowledgement.

A part of this work was supported by a grant from C.N.R. Rome.

REFERENCES AND NOTES

A preliminary account of this work was presented at XIV Congresso della Società Chimica Italiana, Catania, September, 1981.

(1) For the preceding paper in this series see: G. Dattolo, G. Cirrincione, A. M. Almerico, I. D'Asdia and E. Aiello, *Heterocycles*, **19**, 681 (1982).

(2) A. Nawojski, *Wiad Chem.*, **31**, 735 (1977); *Chem. Abstr.*, **89**, 24185c (1978).

(3) N. W. Gilman and R. I. Fryer, *J. Heterocyclic Chem.*, **14**, 1171 (1977) and references cited therein.

- (4) A. Walser and G. Zenchoff, *J. Med. Chem.*, **20**, 1694 (1977).
(5) T. Hara, Y. Kayama, H. Fujimori and T. Kadonami, Japan Kokai 78 73,600 (Cl.CO7D487/04) Jun 1978; *Chem. Abstr.*, **89**, 197615w (1978).
(6) T. Hara, Y. Kayama, T. Mori, K. Itoh, H. Fujimori, T. Sunami, Y. Hashimoto and S. Ishimoto, *J. Med. Chem.*, **21**, 263 (1978).
(7) N. W. Gilman, B. C. Holland and R. I. Fryer, *J. Heterocyclic Chem.*, **14**, 1163 (1977).
(8) N. W. Gilman and R. I. Fryer, U. S. Patent 4,130,716 (Cl. 548-369; CO7D487/04) Dec 1978, *Chem. Abstr.*, **90**, 137877u (1979).
(9) G. F. Field, W. J. Zally and L. H. Sternbach, *J. Org. Chem.*, **36**, 2968 (1971).
(10) W. O. Kermack and J. F. Smith, *J. Chem. Soc.*, 814 (1929).
(11) N. J. Leonard and S. N. Boyd, *J. Org. Chem.*, **11**, 405 (1946).