Pyrrolo[1,4]benzodiazepines. III. Synthesis of 5,11-Dioxo-1,10,11,11a-tetrahydro-2-vinyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine

S. Massa*, G. De Martino (1) and F. Corelli

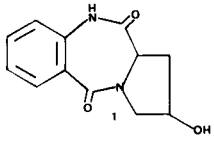
Istituto di Chimica Farmaceutica e Tossicologica, 2ª Cattedra, Università di Roma, 00100 Roma, Italy

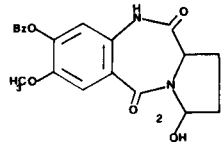
Received April 12, 1982

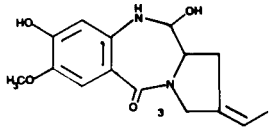
Some pyrrolo[2,1-*c*][1,4]benzodiazepines having a chain of two carbon atoms, as it is found in antibiotic tomaymycin, were prepared. The first reaction was the *C*-acetylation of 1-(2-nitrobenzoyl)-Δ^4-pyrroline-2,2-dicarboxylic acid diethyl ester; successive transformations of the acetyl group and cyclization gave the proposed structures.

J. Heterocyclic Chem., **19**, 1497 (1982).

In our previous papers (2-4) concerning the preparation of some pyrrolo[2,1-*c*][1,4]benzodiazepines starting from the reaction between 2-nitrobenzoylaminomalonates and acrolein, our attention was focused on the pyrroline double bond formed in a step of the reaction sequence. Thus we were able to obtain hydroxy derivatives **1** and **2** substituted in the 2 and 3 positions of the tricyclic ring system. These types of derivatives were selected as the key intermediates to obtain the complete structure of the antitumor antibiotics anthramycin and neotramycin. Thus following this approach, this paper reports the development of a *C*-acetylation reaction on the pyrroline double bond, which should be useful in the total synthesis of tomaymycin (**3**), another pyrrolobenzodiazepine antibiotic.







Treatment of 1-(2-nitrobenzoyl)-Δ^4-pyrroline-2,2-dicarboxylic acid diethyl ester (5) with glacial acetic acid and polyphosphoric acid, afforded the 2-acetyl derivative **4**. Reduction of the ketone with sodium borohydride gave the corresponding secondary alcohol **5**.

The diene system of **6** was obtained by dehydration of **5** with phosphorus pentoxide.

Cyclization of **6** to 5,11-dioxo-11a-ethoxycarbonyl-1,2,10,11-tetrahydro-2-vinyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**7**) was carried out in one step using iron(II) sulphate in ammonia solution as the reducing agent. Alkaline hydrolysis of **7** and subsequent decarboxylation gave compound **8** in good yield. Catalytic hydrogenation of **7** readily furnished the saturated derivative **9**, which was then hydrolyzed and decarboxylated to give **10**.

With the objective of obtaining a structure more similar to tomaymycin, **5** was directly cyclized to **11**, as described for **7**, and the double bond of **11** was then saturated by catalytic hydrogenation to give **12**. Dehydration of this compound should have afforded **13** containing the double bond in the side chain.

The use of phosphorus pentoxide under various experimental conditions (boiling benzene, pyridine, *etc.*) was not successful because unchanged **12** was always recovered. Similarly no positive results were obtained by using other dehydrating agents (see Scheme). Lastly, alkaline hydrolysis of **12** was attempted before dehydration. The desired product was not isolated.

Table I

Analytical Data of Compounds **4-9**

Compound No.	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
4	$C_{19}H_{20}N_2O_6$	56.43	4.99	6.93	56.25	4.93	6.87
5	$C_{19}H_{22}N_2O_6$	56.15	5.46	6.89	56.12	5.14	6.90
7	$C_{17}H_{16}N_2O_4$	65.37	5.16	8.97	65.12	5.22	8.83
8	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66	70.05	4.98	11.38
9	$C_{17}H_{20}N_2O_4$	64.54	6.37	8.86	64.27	6.42	8.93
10	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	69.11	6.48	11.33
11	$C_{17}H_{18}N_2O_5$	61.81	5.49	8.48	62.01	5.51	8.29
12	$C_{17}H_{20}N_2O_5$	61.43	6.07	8.43	61.54	5.97	8.39

SCHEME

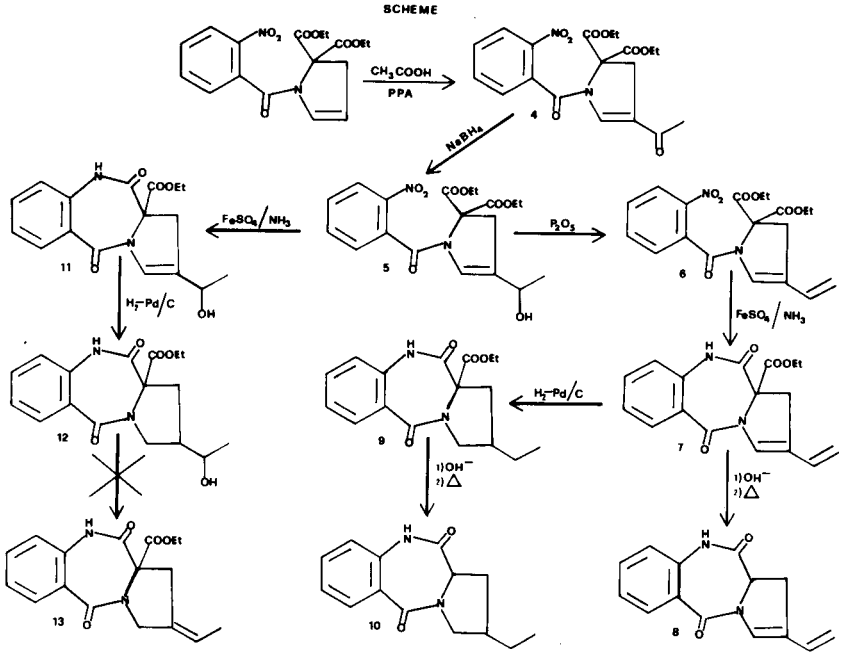


Table II

Spectral Data of Compounds **4-9**

Compound No.	IR (cm^{-1})	NMR (δ ppm)	MS (m/e)
4	1740, 1650, 1620	1.38 (t, 6H), 2.13 (s, 3H), 3.5 (s, 2H), 4.38 (q, 4H), 6.82 (s, 1H), 7.3-8.4 (m, 4H) (deuteriochloroform)	404 (M^+), 150 (100%)
5	3400, 1740, 1625	1.27 (m, 9H), 2.19 (broad, 1H), 3.29 (near s, 2H), 4.36 (m, 5H), 5.92 (near s, 1H), 7.3-8.4 (m, 4H) (deuteriochloroform)	406 (M^+), 150 (100%)
6	1750, 1670, 1640	—	—
7	3240, 1750, 1700, 1610	0.75 (t, 3H), 3.02 and 4.15 (dd, 2H), 3.83 (q, 2H), 5.11 (s, 1H), 5.27 (d, 1H), 6.68 (dd, 1H), 7.1-7.9 (m, 5H), 19.93 (broad, 1H) (DMSO-d_6)	312 (M^+), 146 (100%)
8	3230, 1690, 1620	—	240 (M^+), 120 (45.3%), 28 (100%)
9	3230, 1740, 1700, 1610	0.83 (t, 3H), 0.97 (t, 3H), 1.2-4.4 (un, 9H), 6.9-7.6 (m, 3H), 7.97 (d, 1H), 9.0 (broad, 1H) (deuteriochloroform)	316 (M^+), 243 (100%)
10	3220, 1690, 1620	—	244 (M^+), 146 (27.5%), 28 (100%)
11	3480, 3220, 1750, 1680, 1610	0.83 (t, 3H), 1.33 (d, 3H), 2.90 and 4.17 (dd, 2H), 3.30 (m, 1H), 3.83 (q, 2H), 7.0-8.0 (m, 5H) (perdeuteriomethanol)	330 (M^+), 146 (100%)
12	3400, 3200, 1740, 1680, 1620	0.70 (t, 3H), 1.10 (d, 3H), 1.3-4.3 (un, 8H), 4.77 (d, 1H), 7.1-7.9 (m, 4H), 10.67 (broad 1H) (DMSO-d_6)	332 (M^+), 259 (100%)

EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (nujol mulls) were run on a Perkin-Elmer Model 279 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-390 instrument (TMS as the internal standard). Mass spectra were recorded on a Hewlett-Packard 5980 A instrument. Merck alumina (activity according to Brockmann) was used for chromatographic purifications. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

Analytical and spectral data are summarized in Tables I-II.

4-Acetyl-1-(2-nitrobenzoyl)-Δ^4-pyrroline-2,2-dicarboxylic Acid Diethyl Ester (**4**).

To a mixture of polyphosphoric acid (181 g) and acetic acid (60 ml) vigorously stirred at 90° 1-(2-nitrobenzoyl)-Δ^4-pyrroline-2,2-dicarboxylic acid diethyl ester (**5**) (18.1 g) was added in small portions. The mixture was heated with stirring for one hour. After cooling, crushed ice (800 g) was poured into the reaction flask and the yellow precipitate was extracted with chloroform (3 × 150 ml). The organic layers were washed

first with 5% aqueous sodium hydroxide, then with saturated aqueous sodium chloride and dried over anhydrous sodium sulphate. After evaporation of the solvent, the solid residue was treated with ether and filtered. Pure **4** (11.8 g) was obtained after crystallization from benzene as light needles, mp 172-173°.

4-(1-Hydroxyethyl)-1-(2-nitrobenzoyl)-Δ^4-pyrroline-2,2-dicarboxylic Acid Diethyl Ester (**5**).

To a solution of **4** (9.4 g) in tetrahydrofuran (300 ml) containing water (5 ml), solid sodium borohydride was added in small portions and the mixture was stirred at room temperature two hours. Water (100 ml) was then poured into the reaction mixture and the organic solvent removed by distillation. The aqueous suspension was extracted with ethyl acetate (2 × 100 ml) and the organic layers were washed with water and dried over anhydrous sodium sulphate. After evaporation of the solvent the residue was triturated with ether and filtered to give **5**, yield 6.0 g, mp 128-129° after crystallization from benzene.

5,11-Dioxo-11a-ethoxycarbonyl-1,10-11,11a-tetrahydro-2-vinyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**7**).

A solution of **5** (6.0 g) in anhydrous benzene (200 ml) was heated two hours under reflux in the presence of phosphorus pentoxide (2.0 g). After cooling, the benzene solution was decanted, washed with aqueous sodium hydrogen carbonate, dried and evaporated. The crude oily residue was purified by just passing through an alumina column eluting with benzene-chloroform (1:1). The eluates gave the intermediate **6** (3.9 g).

A solution of **6** (3.9 g) in ethanol (100 ml) was blended with a solution of iron(II) sulphate (23 g) in water (100 ml); 32% ammonia (5 ml) was added and the mixture was stirred and refluxed three hours. During this time period 32% ammonia (35 ml) was added dropwise. The warm mixture was filtered and the ethanol was removed by distillation. The suspension was extracted with ethyl acetate (3 × 50 ml) and the organic layers were washed with water, dried and evaporated. The residue gave pure **7** after crystallization from ethanol, yield 1.4 g, mp 270° dec.

5,11-Dioxo-1,10,11-11a-tetrahydro-2-vinyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**8**).

The ester **7** (1.5 g) was added to 5% aqueous potassium hydroxide (15 ml) and the suspension was heated two hours under reflux. The cloudy solution obtained was filtered through activated charcoal, cooled and acidified with concentrated hydrochloric acid. The solid precipitate was collected, dried and then heated thirty minutes at 140° under reduced pressure to give **8**, yield 0.5 g, mp >280° after crystallization from ethanol-DMF.

5,11-Dioxo-11a-ethoxycarbonyl-2-ethyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**9**).

A solution of **7** (1.6 g) in ethanol (80 ml) was hydrogenated in a Parr apparatus at 40 psi in the presence of 10% palladium on charcoal as the catalyst. After filtration and evaporation of the solvent the residue was crystallized from benzene to give pure **9**, yield 1.2 g, mp 185-186°.

5,11-Dioxo-2-ethyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine (**10**).

Hydrolysis of **9** (0.9 g) in alkaline medium and successive decarboxylation, using the same experimental conditions as for **8**, gave **10** which was crystallized from ethanol, yield 0.5 g, mp >280°.

5,11-Dioxo-11a-ethoxycarbonyl-2-(1-hydroxyethyl)-1,10,11,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**11**).

A solution of **5** (8.1 g) in ethanol (150 ml) was treated with iron(II) sulphate and ammonia to give **11**, as already described for the preparation of **7**, yield 3.9 g, mp 173-174° after crystallization from benzene-chloroform.

5,11-Dioxo-11a-ethoxycarbonyl-1,2,3,10,11,11a-hexahydro-2-(1-hydroxyethyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**12**).

A solution of **11** (1.1 g) in ethanol (50 ml) was hydrogenated in a Parr apparatus at 40 psi using 10% palladium on charcoal as the catalyst. Compound **12** was obtained as a light solid, yield 0.7 g, mp 188-189° after crystallization from ethanol.

Acknowledgement.

We thank the Italian National Council of Research for financial aid.

REFERENCES AND NOTES

(1) Present address: Istituto di Chimica farmaceutica e tossicologica, Via L. Rodinò 22, Napoli, Italy.

(2) S. Massa and G. De Martino, *Farmaco, Ed. Sci.*, **34**, 666 (1979).

(3) G. De Martino, S. Massa and S. Selleri, *Eur. J. Med. Chem. Chim. Ther.*, **12**, 572 (1977).

(4) G. De Martino, S. Massa and F. Corelli, *Farmaco, Ed. Sci.*, **33**, 604 (1978).

(5) G. De Martino, S. Massa and R. Giuliano, *ibid.*, **31**, 785 (1976).