Intramolecular Cyclization of 4-Acetyl-2,2-diethoxycarbonyl-2,3-dihydro-1-(2-nitrobenzoyl)pyrrole by Catalytic Reduction

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Catalytic hydrogenation of 4-acetyl-2,2-diethoxycarbonyl-2,3-dihydro-1-(2-nitrobenzoyl)pyrrole **2** afforded 3-acetyl-1,1-diethoxycarbonyl-1,2,3,3a,4,9-hexahydro-9-oxopyrrolo[2,1-*b*]quinazoline **3** and the 4-hydroxy derivative **4**, together with two tetrahydro analogs **5** and **6** of **3**. Compounds **5** and **6** were also obtained by dehydration of **4**.

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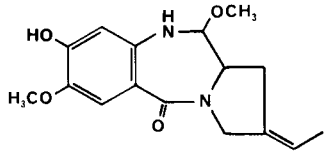
In the course of our research on pyrrolo[2,1-*c*][1,4]benzodiazepine derivatives aiming to insert the side chain characteristic of the antitumor antibiotic tomaymycin (**1**) [1], we used the title compound **2** [2] as starting material. The required tricyclic system was obtained when cyclization was accomplished after selective reduction of the acetyl group [2,3].



1 Tomaymycin

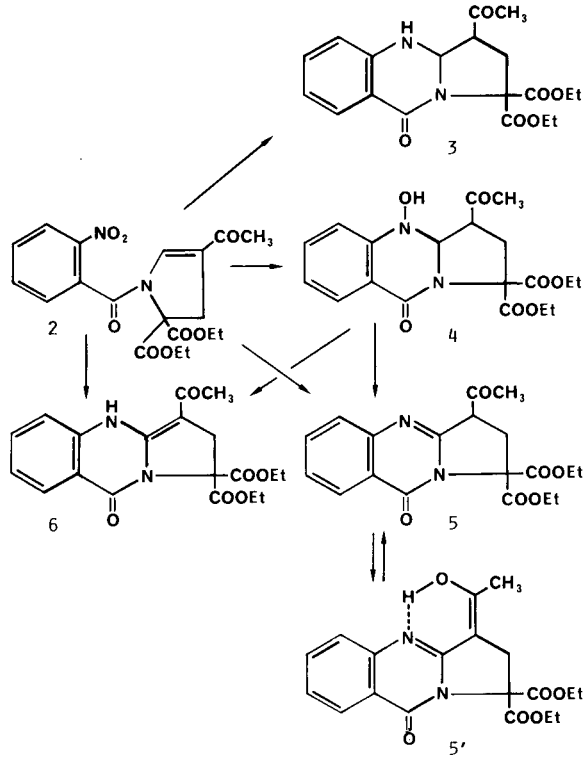
However, only pyrrolo[2,1-*b*]quinazoline derivatives were formed by direct catalytic hydrogenation of **2** (see Scheme 1) due to the speedy reduction of nitro group and the immediately subsequent cycloaddition on the unsaturated conjugated system C=C-C=O. When the starting compound was an analog of **2** bearing a not conjugated double bond, the reduction of NO_2 group afforded the corresponding pyrrolobenzodiazepine derivative by nucleophilic attack on the carbethoxyl group [4,5].

It is remarkable that compound **4**, coming from the partial reduction of nitro to hydroxylamino group, was obtained in all experiments together with the expected **3**, which in turn derives from the cyclization of the 2-aminobenzoyl intermediate. Compound **5** and its isomer **6**, which derived from **4** by elimination of water, were also formed during catalytic reduction of **2**. Moreover, we have obtained **5** and **6** in mixture by treatment of **4** with phosphorus pentoxide.

In conclusion, the catalytic hydrogenation of **2** afforded a mixture in which tlc experiments showed the presence of four different products and the absence of the starting compound **2**. By means of column chromatography we isolated products **3**, **4**, **5** and **6** in form of pure chemical species.

Compound **3** was 3-acetyl-1,1-diethoxycarbonyl-1,2,-3,3a,4,9-hexahydro-9-oxopyrrolo[2,1-*b*]quinazoline: such

SCHEME 1



structural assignment was based on analytical and spectral data, as detailed in the experimental part.

^1H and ^{13}C nmr spectra of compound **4** were similar to those of **3**, with some significant differences. The system of signals related to the four aliphatic protons in the 2, 3, 3a positions was better resolved; the presence of the hydroxyl group in position 4 was indicated by both the broad signal at δ 6.92 in the ^1H spectrum and the signal at δ 69.71 of 3a-CH in the ^{13}C spectrum: the latter signal was shifted downfield with respect to the corresponding signal of **3**, due to the presence of OH group on the adjacent nitrogen atom. Obviously, the broad signal at δ 4.85 in the ^1H nmr spectrum of **3** (4-NH) was lacking in the spectrum of **4**. Consequently, there is no doubt about the structure

of **4**, which is 3-acetyl-1,1-diethoxycarbonyl-1,2,3,3a,4,9-hexahydro-4-hydroxy-9-oxopyrrolo[2,1-*b*]quinazoline.

In the case of compound **5**, both ^1H and ^{13}C nmr spectra showed two different and clearly distinct series of signals which proved the existence in solution of a tautomeric mixture of the keto form **5** and the enol form **5'**, containing approximately 90% of the enol form. The predominance of the enol form is probably due to its stabilization by a hydrogen bond with the nitrogen atom in the 4 position.

The main features of the ^1H nmr spectrum of **5'**, namely 1,1-diethoxycarbonyl-3-(1-hydroxyethylidene)-9-oxo-1,2,3,-9-tetrahydropyrrolo[2,1-*b*]quinazoline, are the absence of both 3a-H and 3-H signals, the presence of a peak at δ 2.55 which exchanges very slowly with deuterium oxide (enol OH group) and the presence of a singlet at δ 3.45 due to the methylene in position 2. The corresponding features of ^{13}C nmr spectrum are the signals at δ 176.22 and δ 148.63 of the quaternary carbon atoms of the $>C=C-OH$ moiety and the signal at δ 93.41 of the quaternary carbon atom in the 3a position. The minor series of signals in both spectra were coherent with the structure of the keto from **5**, namely 3-acetyl-1,1-diethoxycarbonyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline.

The last product **6** was obtained in low yield: it is an isomer of **5**, with the double bond shifted between the carbon atoms in the 3 and 3a positions. The proposed structure, namely 3-acetyl-1,1-diethoxycarbonyl-9-oxo-1,2,4,9-tetrahydropyrrolo[2,1-*b*]quinazoline, is supported by ^1H and ^{13}C nmr spectral data, which show that the carbon atoms in the 3 and 3a positions are quaternary, whereas an hydrogen atom is linked to the nitrogen atom in position 4.

In conclusion, the experimental data provided conclusive evidences that the catalytic reduction of **2** afforded not only the cycloaddition products **3** and **4**, but also two other products **5** and **6** which clearly originated from the elimination of a water molecule from the 4-OH derivative **4**. In order to confirm this point of view, we have refluxed a benzenic solution of **4** in the presence of phosphorus pentoxide and we have then isolated from the reacted mixture two products, which were found identical to compounds **5** and **6**, respectively, obtained in the catalytic reduction of **2**.

EXPERIMENTAL

Precoated silica gel Whatman K6F plates were used for thin layer chromatography; detection of components was made by either uv light or treatment with iodine vapors. Chromatographic separations were performed on columns packed with silica gel 60 from Merck (70-230 mesh ASTM). Melting points were determined with a Kofler hot stage microscope and are uncorrected. Elemental analyses were performed on a Perkin-Elmer Elemental Analyzer Model 240. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform on a Bruker WM250 instrument [6].

Procedure for the Catalytic Hydrogenation of **2**.

A solution of **2** (3.4 g, 8.4 mmoles) in methanol (80 ml) was treated with hydrogen at atmospherical pressure and room temperature in the presence of 10% palladium on activated charcoal (1 g) until the absorption of hydrogen ceased. The mixture was filtered, the filtrate concentrated up to a small volume and then examined by tlc, eluting either with diethyl ether or with dichloromethane-methanol (95:5): such tlc experiments showed the presence of four products with different Rf, whereas the starting compound **2** was absent. The concentrated solution was chromatographed on a silica gel column, eluting with diethyl ether-*n*-hexane mixtures (initially 7:3 and then with decreasing percentages of *n*-hexane up to pure diethyl ether), to afford some groups of fractions, each containing a mixture of two components. Such binary mixtures were subjected to a second chromatographic separation on another silica gel column, eluting first with dichloromethane and then with dichloromethane-methanol (95:5), to give **3**, **4**, **5** and **6** in 30%, 38%, 24% and 3% yield, respectively.

3-Acetyl-1,1-diethoxycarbonyl-1,2,3,3a,4,9-hexahydro-9-oxopyrrolo[2,1-*b*]quinazoline (**3**).

This compound was obtained as colorless powder (*n*-hexane-benzene), mp 112-114°; ^1H nmr: δ 7.88 (d, 1H), 7.30 (t, 1H), 6.87 (t, 1H) and 6.72 (d, 1H) (aromatic protons), 5.29 (d, 1H, 3a-H, J = 8 Hz); 4.85 (broad, 1H, NH), 4.30 (two superimposed q, 4H, two ethyl CH_2), 3.27-3.05 (series of peaks, 2H, 3-H and one of geminal protons in position 2), 2.50 (dd, 1H, the other proton in position 2, J_{gem} = 14 Hz), 2.25 (s, 3H, acetyl CH_3), 1.30 (two superimposed t, 6H, two ethyl CH_3); ^{13}C nmr: δ 205.24 (acetyl CO), 167.99 (two carbethoxyl CO), 161.81 (9-CO), 147.57 (4a-C), 133.54, 128.75, 120.18, 115.43 (aromatic CH), 117.35 (8a-C), 71.50 (3a-CH), 70.39 (1-C), 62.52 (two ethyl CH_2), 56.09 (3-CH), 35.67 (2-CH_2), 28.84 (acetyl CH_3), 13.90 (two ethyl CH_3).

Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.81; H, 5.86; N, 7.50.

3-Acetyl-1,1-diethoxycarbonyl-1,2,3,3a,4,9-hexahydro-4-hydroxy-9-oxopyrrolo[2,1-*b*]quinazoline (**4**).

This compound was obtained as colorless crystals (*n*-hexane-benzene), mp 125-127°; ^1H nmr: δ 7.90 (d, 1H), 7.48 (t, 1H), 7.28 (t, 1H) and 7.13 (t, 1H) (aromatic protons), 6.92 (broad, 1H, N-OH; exchanges with deuterium oxide), 5.25 (d, 1H, 3a-H, J = 8 Hz), 4.30 (two superimposed q, 4H, two ethyl CH_2), 3.66 (m, 1H, 3-H), 2.95 (dd, 1H, J_{gem} = 14 Hz, $J_{2,3}$ = 6 Hz) and 2.65 (dd, 1H, J_{gem} = 14 Hz, $J_{2,3}$ = 10 Hz) (2-CH_2 geminal protons), 2.30 (s, 3H, acetyl CH_3), 1.30 (two superimposed t, 6H, two ethyl CH_3); ^{13}C nmr: δ 205.11 (acetyl CO), 167.87 and 167.60 (two carbethoxyl CO), 161.83 (9-CO), 147.61 (4a-C), 133.45, 128.57, 120.79 and 115.49 (aromatic CH), 117.37 (8a-C), 79.61 (3a-CH), 70.27 (1-C), 62.25 (two ethyl CH_2), 56.09 (3-CH), 35.71 (2-CH_2), 28.82 (acetyl CH_3), 13.80 (two ethyl CH_3).

Anal. Calcd. for $C_{19}H_{22}N_2O_7$: C, 58.45; H, 5.68; N, 7.18. Found: C, 58.19; H, 5.85; N, 6.94.

3-Acetyl-1,1-diethoxycarbonyl-9-oxo-1,2,3,9-tetrahydropyrrolo-[2,1-*b*]quinazoline (**5**).

This compound was obtained as pale yellow crystals (*n*-hexane), mp 116-118°; enol form **5'**; ^1H nmr: δ 8.15 (d, 1H), 7.62 (t, 1H) and 7.30 (m, 2H) (aromatic protons), 4.35 (q, 4H, two ethyl CH_2), 3.45 (s, 2H, 2-CH_2), 2.55 (s, 1H, OH, exchanges slowly with deuterium oxide), 2.04 (s, 3H, =C-CH_3), 1.33 (t, 6H, two ethyl CH_3); ^{13}C

nmr: δ 176.22 (=C-OH), 166.78 and 158.98 (two carbethoxy CO), 153.98 (9-CO), 148.63 (3-C), 144.22 (4a-C), 134.70, 127.80, 124.65 and 121.09 (aromatic CH), 118.91 (8a-C), 93.41 (3a-C), 71.56 (1-C), 62.83 (two ethyl CH_2), 35.51 (2-CH_2), 22.50 (ethylidene CH_3), 13.82 (two ethyl CH_3); keto form **5**; ^{1}H nmr: δ 8.30 (d), 7.75 (m) and 7.48 (t) (aromatic protons), 4.25 (dd, 3-H, J = 10 Hz, 6 Hz), 3.30 (dd, proton of 2-CH_2, J = 14 Hz, 6 Hz), 2.85 (dd, the other proton of 2-CH_2, J = 14 Hz, 10 Hz), 2.12 (s, acetyl CH_3), signals of ethyl protons are covered by the corresponding signals of **5'**; ^{13}C nmr: δ 200.61 (acetyl CO), 166.00 and 160.00 (two carbethoxyl CO), 155.00 (9-CO), 134.40, 127.63, 126.97 and 121.32 (aromatic CH), 84.00 (3a-C), 72.18 (1-C); 63.15 (two ethyl CH_2), 55.16 (3-CH), 32.83 (2-CH_2), 29.10 (acetyl CH_3), signals of 4a-C, 8a-C and two ethyl CH_3 are covered by the corresponding signals of **5'**.

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 60.99; H, 5.60; N, 7.48.

3-Acetyl-1,1-diethoxycarbonyl-9-oxo-1,2,4,9-tetrahydropyrrolo-[2,1-*b*]quinazoline (**6**).

This compound was obtained as yellowish powder (*n*-hexane), mp 89-91°; ^{1}H nmr: δ 8.34 (d, 1H), 7.75 (m, 2H) and 7.55 (t, 1H) (aromatic protons), 4.40 (m, 5H, two ethyl CH_2 and NH, after exchange with deuterium oxide this multiplet became a couple of superimposed quartets, which integrated for 4H), 3.29 (d, 1H) and 2.96 (d, 1H) (2-CH_2 geminal protons, J_{gem} = 14 Hz), 2.44 (s, 3H, acetyl CH_3), 1.30 (two superimposed t, 6H, two ethyl CH_3); ^{13}C nmr: δ 203.38 (acetyl CO), 166.41 and 166.28 (two carbethoxy CO), 159.48 (9-CO), 156.72 (3-C), 148.57 (4a-C), 134.60, 127.89, 127.59 and 127.19 (aromatic CH), 121.85 (8a-C), 83.99 (3a-C), 71.60 (1-C), 63.29 and 63.14 (two ethyl CH_2), 42.95 (2-CH_2), 24.47 (acetyl CH_3), 13.82 (two ethyl CH_3).

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 60.91; H, 5.53; N, 7.37.

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[6] Assignments of peaks of ^{1}H nmr spectra were confirmed by selective decoupling experiments, whereas in the case of ^{13}C nmr spectra the assignments were supported by DEPT sequence.