Experimental Antiulcer Drugs. 3. Some Unusual Transformations of the Cyclopenta[*c*]pyrroles

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The cyclopenta[*c*]pyrrole-4-carbonitrile (**3**) is transformed by hydroxylamine in hot alcohol to 4,5,6,6a-tetrahydro-1-imino-3,5,5,6a-tetramethyl-4-cyclopenta[*c*]pyrrole methyl ketone oxime (**5**) in contrast to the cyclopentapyrrole **10** which afforded 1,2-diacetyl-3,3,5,5-tetramethylcyclopentene dioxime (**11**). The cyclopenta[*c*]pyrrole-4-carboxamide **1** (R = C_6H_5) yielded the isomeric 2a,3,4,4a,5,6,6a,6b-octahydro-2a,4,4,6a-tetramethyl-5-(phenylimino)pentaleno[1,6-*bc*]-pyrrol-2-(1*H*)one (**12**) in hot dilute hydrochloric acid or hot 99% phosphoric acid. The amide **1** (R = C_6H_5) was transformed in the solid state by oxygen over a period of several months to a mixture of the isomeric anils, **13** and **14** of 1,7-diacetyl-7-hydroxy-4,6,6-trimethyl-2-azabicyclo-[2.2.1.]heptan-3-one (**16**).

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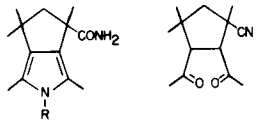
Cyclopenta[*c*]pyrrole-4-carboxamides **1** display gastric antisecretory activity in the rat and the dog. During the course of our investigation of the chemistry of this class of compounds, we encountered several unusual transformations, a common feature of which was the opening of the pyrrole ring with participation of the functional group at C-4.

An intermediate of obvious utility for synthesis of a variety of 2-substituted cyclopenta[*c*]pyrrole-4-carboxamides is the diketone **2**. A logical precursor to **2** appeared

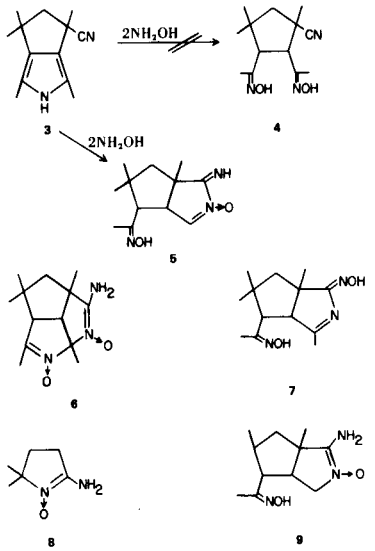


1 2

to be the readily available cyclopenta[*c*]pyrrole-4-carbonitrile (**3**) (1) since it is known that pyrroles may undergo ring opening with hydroxylamine to the corresponding diketoximes (2). Exposure of **3** to hydroxylamine in hot alcohol yielded, in a slow but efficient transformation, a crystalline product whose analytical figures and parent ion in the mass spectrum corresponded to the desired dioxime **4**. In the infrared spectrum, however, the compound lacked an absorption band in the nitrile region. Furthermore, it exhibited an ultraviolet absorption maximum at 233 mμ (ε 10,200); compound **4** would be expected to display only end absorption. We believe the product is a new cyclopenta[*c*]pyrrole which possesses structure **5**. The presence of the nitrone group would account for the ultraviolet spectrum since nitrones characteristically absorb in the 230 mμ region (3).

The nmr spectrum is compatible in every respect with structure **5** but this information alone did not allow us to rule out the two alternative structures **6** and **7**. Compound **6** contains two isolated nitrone chromophores but one of

Scheme 1

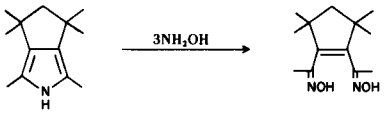


them is an aminonitrone. We were unable to find a report of the ultraviolet spectrum of an aminonitrone although there are many examples of this type of structure in the literature. We prepared an example, **8**, according to the literature procedure (4) and found, interestingly, that the presence of the amino group does not affect the ultraviolet spectral characteristics of the nitrone group. Compound **8** exhibited an ultraviolet maximum at 232 mμ (ε, 8,700). With this information available, structure **6** may be ruled out since with two independent nitrone chromophores an extinction coefficient of about twice that observed would be expected.

Although it would not be expected that a compound of of structure **7** would have formed in preference to **5**, none of the data on hand seemed sufficient to dismiss this possibility independently. The structure of the compound which formed upon potassium borohydride reduction of

the unknown did provide a basis for deciding between **5** and **7**. The reduction product displayed an ultraviolet maximum at 232 mμ (ε, 9,200). It must, therefore, be the aminonitrone **9** which could only have been derived from **5**. Compound **7** would have yielded an ultraviolet-transparent amidoxime. Compound **5** is an iminonitrone and may be the first example reported in a non-aromatic system. An iminonitrone has been proposed as an intermediate in the potassium ferricyanide oxidation of an aminonitrone (5).

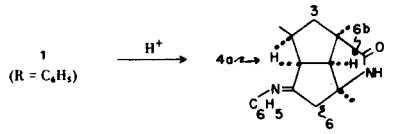
Hydroxaminolysis of the cyclopentapyrrole **10** (1), which differs from **3** only in the absence of a functional group at C-4, yielded the unsaturated diketoxime **11**. This unexpected product is formally the result of a Semmler-



10 11

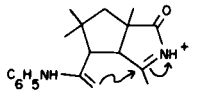
Wolf type fragmentation (6) of the expected saturated diketoxime followed by reaction with a third mole of hydroxylamine.

In an effort to hydrolyze **1** (R = C_6H_5) to the corresponding carboxylic acid, it was boiled with dilute hydrochloric acid. A basic, crystalline product was isolated from the reaction mixture which is isomeric with the starting amide. Structure **12** appears to uniquely satisfy the observed spectral properties: (1) infrared absorption peaks



12

at 1690 cm^{-1} and 1632 cm^{-1} due to the presence of the lactam and Schiff base (2) ultraviolet absorption maxima at 233 mμ (ε, 8,180) and 283.5 mμ (ε, 2,150) ascribed to the anil chromophore (3) four unsplit methyl resonances and the non-equivalent hydrogens at C-3 in the nmr spectrum (4) deuterium oxide exchange: prior to exchange the hydrogens at C-6 and C-4a are clearly visible in the nmr spectrum, the latter coupled to the hydrogen at C-6b. Exchange with deuterium oxide resulted in loss of the C-4a and C-6 signal and collapse of the C-6b signal to a singlet. The *cis* stereochemistry of the perhydropentalene ring system is required by the presence of the lactam bridge. Finally, the failure of the Schiff base to hydrolyze in aqueous mineral acid is probably the result of the steric interactions with the lactam and the *gem* dimethyl group which would be encountered in the tetrahedral hydrolysis



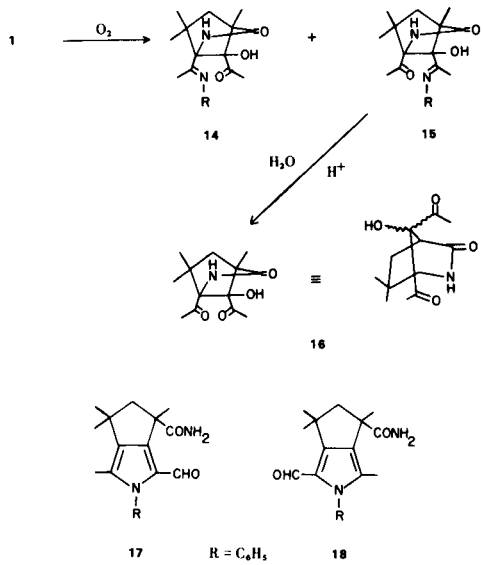
13

intermediate. Compound **12** may be regarded as the product of simultaneous formation of the pyrrolidone ring and opening of the pyrrole ring of **1** (R = C_6H_5) with the formation of **13** or its equivalent followed by ring closure as indicated by the arrows in formula **13**. The overall results is, in effect, an exchange of positions of the carbon atom at C-1 and the pyrrole ring nitrogen atom.

The last transformation to be described is the oxidation of **1** (R = C_6H_5) in the solid state by atmospheric oxygen. Large supplies of the compound had been prepared for advanced pharmacological studies and kept for periods of time ranging from several months up to 2 years. During this period the stability of the compound was monitored. It was soon discovered that if atmospheric oxygen and water were not excluded extensive decomposition occurred.

By direct crystallization an approximately 1:1 mixture of isomeric oxidation products could be obtained from aged samples of **1** (R = C_6H_5). The isomers were separated by thick layer chromatography and the mixture was hydrolyzed in good yield by dilute hydrochloric acid at room temperature to a third product. The initial mixture of oxidation products appeared to consist of the isomeric anils **14** and **15**, which upon hydrolysis yielded the common parent 1,4-diketone **16**. The compounds **14** and **15**

Scheme 2



are the products of the action of a mole of oxygen and water on **1**. All three compounds could be detected by tlc and glc of extensively transformed samples of **1** along with small amounts of the isomeric aldehydes **17** and **18** (7). The two aldehydes were not isolated but were identified by comparison of their retention times with those of authentic samples.

The evidence for the structure of the anils is based on

the fact that they have the same parent ion in the mass spectra, essentially the same ultraviolet spectra, and completely compatible nmr spectra. The latter consisted of five unsplit methyl signals, the resonances due to the nonequivalent hydrogen atoms of the methylene group, and signals which indicated the presence of the phenyl ring, hydroxyl, and NH group. Hydrolysis to **18** resulted in loss of the phenyl ring signals. Some exploratory experiments were carried out which had been designed to reproduce the oxidation process in solution. They were uniformly unsuccessful in that only products of the oxidation at the C-1 and C-3 methyl groups were isolated.

EXPERIMENTAL

Nmr spectra were determined with a Varian Model A-60 nmr spectrometer. TMS was used as the internal standard. Uv spectra were measured using a Carey model 15 spectrometer. Ir spectra were measured with a Perkin Elmer model 21 spectrometer. Mass spectra determinations were carried out using a Jeolco JMS OISC model instrument. The high pressure liquid chromatograph consisted of a Waters C 903 pumping system, a chromatronix LC-9MA-29 glass column equipped with a model 164 A 11 off-column system injector, a Laboratory Data Control UV monitor (model 1285) and a Beckman model DBG recorder. A glass column packed with Corasil II (Waters Associates) was used at a pressure of about 50 p.s.i. The chloroform flow rate was 1.9 ml./minute. Melting points are uncorrected.

4,5,6,6a-Tetrahydro-1-imino-3,5,5,6a-tetramethyl-4-cyclopenta[*c*]-pyrrole Methyl Ketone Oxime 2-Oxide (**5**).

The nitrile **3** (50 g., 0.25 mole), hydroxylamine hydrochloride (70 g., 1 mole), sodium methoxide (54 g., 1 mole) in 750 ml. of absolute alcohol was stirred at reflux under nitrogen for two days. The hot reaction mixture was filtered and the residue washed with chloroform. The combined filtrates were evaporated to dryness under vacuum and the residue treated with 200 ml. of chloroform. The suspension was filtered and the filtrate concentrated to dryness under reduced pressure. The residual gum was crystallized from acetonitrile to afford 56 g. (90%) of **5**, m.p. 215-217°. Recrystallization from acetonitrile furnished a sample, m.p. 218-220°; uv max (95% ethanol): 233 mμ (ε, 10,200); ir (potassium bromide): 3195, 1689, 1669, 1595, 837 cm^{-1}; nmr (deuterium oxide): δ 1.40 (3H, s), 1.72 (3H, s), 1.87 (3H, s), 2.12 (3H, s), 2.40 (2H, d, J = 2.5 Hz), 2.55 (3H, d, J = 1 Hz), 3.55 (1H, d, J = 10 Hz), 3.74 (1H, d, J = 10 Hz), 5.08 (2H, s); mass spectrum: m/e 251 (M^+).

Anal. Calcd. for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.34; H, 8.63; N, 16.83 (all three found values are corrected for the presence of 1.97% water as determined by the Karl Fischer method).

1-Amino-3,3a,4,5,6,6a-hexahydro-3,5,5,6a-tetramethyl-4-cyclopenta[*c*]pyrrole Methyl Ketone Oxime 2-Oxide (**9**).

A solution of 3.5 g. (13.9 mmoles) of **5** and 1.0 g. (18.5 mmoles) of potassium borohydride in 10 ml. of water was stirred overnight at ambient temperature. The precipitate was filtered off, washed with water and dried, 2.2 g. (65%), m.p. 230° dec. The analytical sample was prepared by recrystallization from methanol-acetonitrile, m.p. 230-233° dec.; uv max (95% ethanol): 232 mμ (ε, 9,200); ir (potassium bromide): 3356, 1669, 882 cm^{-1}; nmr (deuterium oxide, deuteriotrifluoroacetic acid): δ 1.52 (3H, s), 1.55 (3H, s), 180 (3H, d, J = 7.5 Hz), 1.87 (3H, s), 2.08 (3H, s), 2.2 (1H, d, J = 13 Hz), 2.51 (1H, d, J = 13 Hz), 2.73-3.13 (1H, m), 3.82-4.13 (1H, m), 5.88 (3H, s); mass spectrum: m/e 253 (M^+).

Anal. Calcd. for $C_{13}H_{23}N_3O_2$: C, 61.63; H, 9.15; N, 16.59. Found: C, 61.54; H, 8.97; N, 16.44.

2-Amino-5,5-dimethylpyrroline 1-Oxide (**8**) (4).

This compound was prepared following the published procedure, m.p. 247-248° (sealed evacuated capillary) (lit. m.p. 238°); uv max (95% ethanol): 232 mμ (ε, 8,707); ir (potassium bromide): 3135, 1678, 881 cm^{-1}; nmr (deuterium oxide): δ 1.80 (6H, s), 2.3-2.75 (2H, A_2B_2), 3.05-3.4 (2H, A_2B_2), 5.25 (2H, s).

1,2-Diacetyl-3,3,5,5-tetramethylcyclopentene Dioxime (**11**).

A solution of 2.5 g. (13 mmoles) of the pyrrole **10** (1), 3.65 g. (52 mmoles) of hydroxylamine hydrochloride, and 2.82 g. (52 mmoles) of sodium methoxide in 30 ml. of absolute ethanol was refluxed for about 90 hours. The hot suspension was filtered, concentrated to dryness, and the residue triturated with chloroform in which the product is insoluble. After washing with water and drying, the product weighed 0.40 g., m.p. 192.5-194° raised to 194-195° by recrystallization from aqueous alcohol; nmr (DMSO-d_6): δ 1.14 (12H, s), 1.70 (2H, s), 1.80 (6H, s), 10.7 (2H, broad); uv max (95% ethanol): 230 mμ (ε, 7,320); mass spectrum: m/e 238 (M^+).

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.55; H, 9.42; N, 11.86.

2a,3,4,4a,5,6,6a,6b-Octahydro-2a,4,4,6a-tetramethyl-5-(phenylimino)pentaleno[1,6-*bc*]pyrrol-2-(1*H*)one (**12**).

The amide **1** (R = C_6H_5) (50 g., 0.17 mole), 6*N* hydrochloric acid (500 ml.), and benzene (500 ml.) were refluxed for 18 hours. The benzene was separated, and the aqueous phase extracted with chloroform. The aqueous phase was made basic by addition of 35% sodium hydroxide and the solid precipitate (17.1 g.) collected and washed with water. Recrystallization from ethanol-water yielded 15.0 g. (30%), m.p. 174-177°; nmr (20% deuteriochloroform): δ 1.12 (3H, s), 1.18 (3H, s), 1.35 (3H, s), 1.40 (3H, s), 1.66 (1H, d, J = 13 Hz), 2.33 (1H, d, J = 13 Hz), 2.83 (1H, d, J = 11 Hz), 3.16 (1H, d, J = 11 Hz), 3.4 (2H, s, broad), 7.0-7.8 (6H, m); mass spectrum: m/e 296; ir (potassium bromide): 3405, 1690, 1632 cm^{-1}; uv max (95% ethanol): 233 (ε, 8,180), 283.5 (ε, 2,150). The yield of crude product was 60% when the reaction was carried out in 99% phosphoric acid at 160° for 4 hours.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.80; H, 8.30; N, 9.53.

1,7-Diacetyl-7-hydroxy-4,6,6-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (**16**) and the Mono Anils **14** and **15**.

A 5-month old sample (200 g.) of the amide **1** (R = C_6H_5), which had been kept in a brown bottle with no special precautions to exclude the atmosphere, was added to 500 ml. of ether. The material dissolved and a white crystalline product separated, 12.9 g., m.p. 148-153°. After treatment with hot ether, it melted at 151-153° and was shown by glc and nmr analysis to be a 1:1 mixture of **14** and **15**.

Anal. Calcd. for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.63; H, 7.67; N, 8.57.

Compounds **14** and **15** were separated by high pressure liquid chromatography and arbitrarily designated isomer A and isomer B. Both isomers had M^+ = 328 in the mass spectrum and each had essentially the same uv spectrum; uv max (95% ethanol): isomer A, 218 mμ (ε, 13,100), 281 (1,500), 292 (1,550). The ir and nmr spectra were significantly different: ir (potassium bromide): isomer A, 3455, 3300, 1715, 1690, 1660 cm^{-1}; isomer B, 3450, 3340,

3220, 1705, 1675 (sh), 1660, 1620 cm^{-1}; nmr (deuteriochloroform): isomer A, δ 1.21 (3H, s), 1.51 (3H, s), 1.55 (3H, s), 1.95 (3H, s), 2.22 (3H, s), 1.5-2.1 (2H, not clearly discernible), 5.92 (1H, broad), 6.85 (1H, broad), 6.5-7.5 (5H, m); isomer B, δ 1.32 (3H, s), 1.38 (3H, s), 1.76 (3H, s), 2.00 (3H, s), 2.22 (3H, s), 1.55 (1H, d, J = 13 Hz), 2.02 (1H, d, J = 13 Hz), 6.02 (2H, broad), 6.5-7.5 (5H, m).

The filtrate from the mixture of isomers which had been crystallized directly from aged **1** (R = C_6H_5) was shown by tlc to consist of **1**, **14**, and **15**. It was extracted several times with 0.5*N* hydrochloric acid. From the ether phase could be isolated directly 48 g. of **16**, m.p. 183-185°, raised to 185-186° by recrystallization from chloroform-ethyl acetate; nmr (deuteriochloroform): δ 1.20 (3H, s), 1.34 (3H, s), 1.62 (3H, s), 2.23 (3H, s), 2.30 (3H, s), 1.30 (1H, d, J = 13 Hz), 1.95 (1H, d, J = 13 Hz), 6.08 (2H, broad); ir (potassium bromide): 3420, 3180, 1714, 1683, 1630 cm^{-1}.

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.69; H, 7.52; N, 5.44.

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