

PERACID OXIDATION OF 2,4-DIMETHYL-3-ETHYLPYRROLE (KRYPTOPYRROLE)

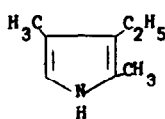
Josefina Awruch and Benjamin Frydman

Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires,

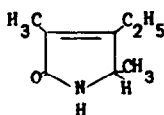
Junin 954, Buenos Aires, Argentina

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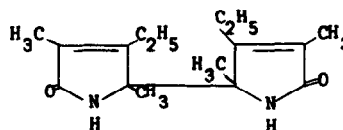
The autooxidation (1) and the photooxidation (2) of various alkylpyrroles afforded compounds of definite structures. Peracids although commonly used for the oxidation of the pyrrole ring of indoles (3), were never used as oxidizing agents of pyrroles, probably due to the recognized instability of the latter both to acids and oxygen. In this report we describe the first peracid oxidation of an alkylpyrrole. It was known that kryptopyrrole (2,4-dimethyl-3-ethylpyrrole) when oxidized with hydrogen peroxide in pyridine (4) afforded 3,5-dimethyl-4-ethyl-3-pyrrolin-2-one (kryptopyrrolone) (II), together with a second not identified oily product; while its autooxidation with oxygen afforded as the only product the dipyrrolone (III) (1).



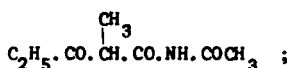
(I)



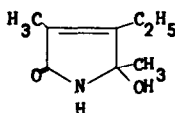
(II)



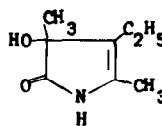
(III)



(IV)



(V)



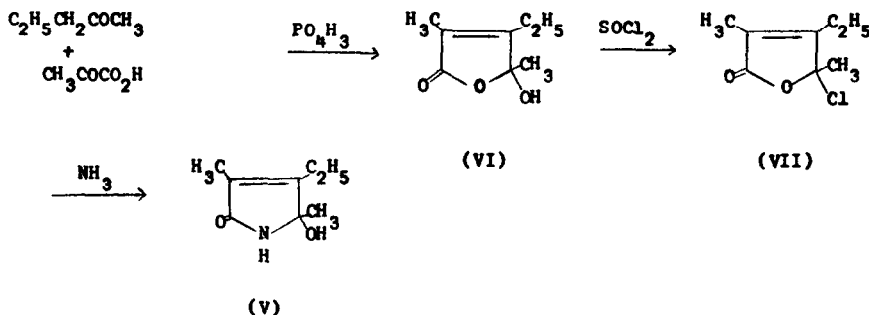
(VIII)

Kryptopyrrole (2 gr) dissolved in ethyl ether (100 ml) was oxidized with two equivalents of *m*-chloroperbenzoic acid (or *p*-nitroperbenzoic acid) at 10° during 45 minutes. The oxidation products were extracted with water, the aqueous solution was evaporated to dryness and the residue (2.19 gr) was chromatographed on a silica gel column (Fluka AG) prewashed with a 5% methanol in chloroform solution. The same solvent eluted four compounds which were located

by thin layer chromatography on silica gel using the above mentioned solvent as developer.

A product with Rf 0.55 (19% yield) was identified as 3-keto-2-methyl-valeroacetamide (IV). Structure (IV) was established on the basis of its nuclear magnetic resonance spectrum (nmr) (5): (CDCl_3) δ 1.1 (t, 3H, CH_3 , $J=8\text{Hz}$), 1.38 (d, 3H, CH_3 , $J=6\text{Hz}$), 2.3 (s, 3H, CH_3CO), 2.6 (q, 2H, CH_2 , $J=8\text{Hz}$), 4.05 (q, 1H, CH, $J=6\text{Hz}$), 9.4 (s, 1H, NH); its mass spectrum: (6) m/e (relative intensity) 171 [M^+] (8%), 115 [$\text{M}-\text{CH}_3\text{CHCO}$] (100%), 100 [$115-\text{CH}_3$] (20%); its infrared spectrum: (CHCl_3) 1700 cm^{-1} (CO); and its correct elemental analysis (7). Its alkaline hydrolysis afforded diethylketone, identified by glpc. A second oxidation product with Rf 0.18 (9.5% yield) proved to be 4-ethyl-3,5-dimethyl-5-hydroxy-3-pyrrolin-2-one (V), mp $130-131^\circ$. The structure was established from its nmr spectrum; nmr (CDCl_3) δ 1.18 (t, 3H, CH_3 , $J=8\text{Hz}$), 1.51 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.38 (q, 2H, CH_2 , $J=8\text{Hz}$), 4.3 (s, 1H, OH), 7.3 (s, 1H, NH); its mass spectrum m/e (relative intensity), 155 [M^+] (50%), 140 [$\text{M}-\text{CH}_3$] (80%), 138 [$\text{M}-\text{OH}$] (87%), 126 [$\text{M}-\text{C}_2\text{H}_5$] (90%), 122 [$140-\text{H}_2\text{O}$] (100%), 108 [$126-\text{H}_2\text{O}$] (20%); and its infrared spectrum: (CHCl_3) 3450 cm^{-1} (OH); 1690 (CO). The structure (V) was confirmed by synthesis using an approach modeled on the method of Scheffold and Dubs (8). Condensation of 2-pentanone with pyruvic acid by heating in phosphoric acid afforded the pseudoacid (VI) (Scheme I), bp $104^\circ-106^\circ/0.2\text{ mm}$; nmr (CDCl_3) δ 1.2 (t, 3H, CH_3 , $J=8\text{Hz}$), 1.8 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.35 (q, 2H, CH_2 , $J=8\text{Hz}$), 4.35 (b, 1H, OH); infrared spectrum (CDCl_3), 3450 cm^{-1} (OH). By treatment of the acid (VI) with thionyl chloride the corresponding pseudochloride (VII) was obtained (70% yield); bp $72-76^\circ/0.25\text{mm}$; nmr (CDCl_3) δ 1.2 (t, 3H, CH_3 , $J=8\text{Hz}$), 1.8 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 2.4 (q, 2H, CH_2 , $J=8\text{Hz}$). Treatment of the pseudochloride (VII) with liquid ammonia afforded the compound (V) in 70% yield. The synthetic product proved to be identical with the oxidation product when compared by tlc, nmr and ir.

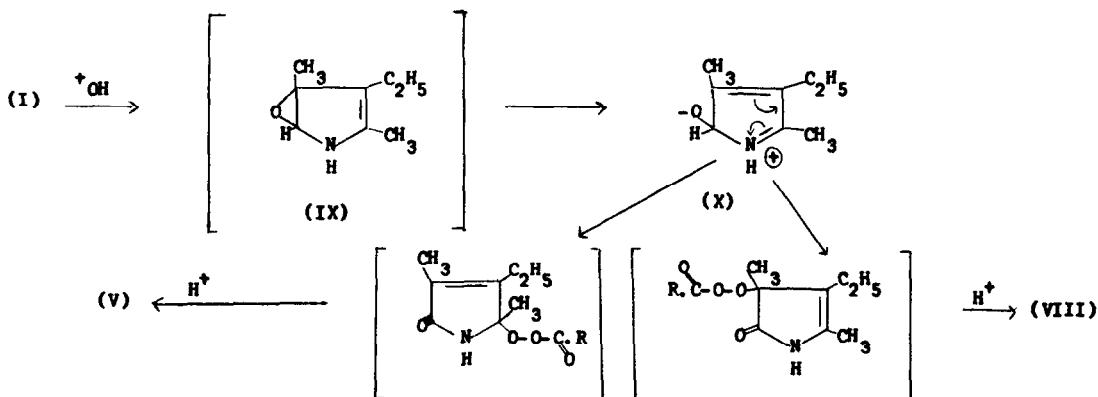
Scheme I



The major product, Rf 0.31 (37%) was isomeric with the pyrrolinone (V) described above and its spectroscopic properties secured for it the structure (VIII). It had mp 121-123° (crystallized from carbon tetrachloride); nmr spectrum (CDCl₃), δ 1.12 (t, 3H, CH₃, J=8Hz), 1.48 (s, 3H, CH₃), 1.72 (s, 3H, CH₃), 2.31 (q, 2H, CH₂, J=8Hz), 4.2 (s, 1H, OH), 9.6 (s, 1H, NH); mass spectrum m/e (relative intensities): 155 [M⁺] (30%), 138 [M-OH] (100%), 126 [M-C₂H₅] (60%), 122 [M-CH₃-H] (20%); infrared spectrum (CDCl₃) 3350 cm⁻¹ (broad, bridged OH), 1715 (CO). The substance with Rf 0.14 (0,05%) present in very small amounts was dipyrrolone (III); mass spectrum m/e, 276 [M⁺], identical in its properties (Rf, ir, nmr and mp) with the dipyrrolone (III) obtained during the autooxidation of kryptopyrrole (1).

The peracid oxidation of an alkylpyrrole is a fast reaction which proceeds in good overall yields. The amide (IV) was identical with the hitherto unknown compound formed in the hydrogen peroxide oxidation of kryptopyrrole (4) (see above). Hence, both hydrogen peroxide in pyridine and peracids oxidize the pyrrole ring (at least in part) in a similar way to that described for the peracid oxidation of the indole ring (3). The formation of the dipyrrolone (III) must originate in a dimerization of the hydroxylactam (V) (or its dehydrated derivative), very likely by the mechanism advanced by Plieninger (9). Its exclusive formation during the autooxidation of kryptopyrrole (1) should be ascribed to the very slow rate of the autooxidation process which allows for the dimerization to take place.

Peracid oxidations of alkylpyrroles presumably start with the formation of the unstable epoxide (IX) (Scheme II).



Epoxides across the 2,3-double bond have never been isolated in pyrrole or indole chemistry since they will open fast to give the hydroxy derivatives. The oxypyrrole derivative (X), will then undergo a second oxidation reaction either at the α -carbon (to give (V)), or at the β -carbon (to give (VIII)).

REFERENCES

1. E. Hoft, A.R. Katritzky and M.R. Nesbit, Tetrahedron Lett., 3041 (1967).
2. G.B. Quistad and D.A. Lightner, Tetrahedron Lett., 4417 (1971); *ibid.*, Angew. Chem. (Int. Ed) 11, 215 (1972).
3. B. Witkop and H. Fiedler, Liebig's Ann. Chem., 558, 91 (1947).
4. H. Fischer and H. Orth, Die Chemie des Pyrrols, Band I, Akademische Verlagsgesellschaft M.B.H., Leipzig (1934) p. 130.
5. All nuclear magnetic resonance spectra were run on a Perkin-Elmer R-12 instrument; infrared spectra were recorded on a Perkin-Elmer 21 instrument.
6. Mass spectra were determined by the Morgan and Schaffer Corp. (Montreal).
7. Elemental analysis were carried out by the Alfred Bernhart Mikroanalytisches Laboratorium (Elbach).
8. R. Scheffold and P. Dubs, Helv. Chim. Acta, 50, 798 (1967).
9. H. Plieninger, U. Lerch and A. Tapia, Liebig's Ann. Chem., 698, 191 (1966).

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