Kinetic Measurements. A. The kinetics of the transformation of CNF-3 were determined on ethanolic solutions. The solutions were filled into glass tubes and placed in a boiling solvent — methylene chloride, bp 40°C, or acetone, bp 56.2°C. After predetermined intervals of time, the tubes were extracted successively and each was rapidly cooled to −(7-10)°C. The quantitative analysis of the samples was carried out by the use of paper chromatography by a known method [3, 4].

B. The acetylation of the conformers was performed with acetic anhydride in pyridine at 20°C. The quantitative analysis was similar to that described in [3, 5].

SUMMARY

A rare case of separable conformational isomers (conformers) has been found in the 5,10-diketo-19-nor-5,10-secocardenolide series. The method of separating the four conformers, their properties, the IR, mass, and PMR spectra, the kinetics of the acetylation reactions, and the kinetics of thermal transformations are described. Conformational structures as the most probable have been put forward on the basis of the experimental results obtained.

LITERATURE CITED

1. I. F. Makarevich and L. N. Dikan', Khim. Prir. Soedin., 71 (1985) [in this issue].
2. A. V. Wartburg, J. Binkert, E. Angliker, and J. Renz, US Patent No. 3,211,719; Helv. Chim. Acta, 45, 2122 (1962).
3. I. F. Makarevich, Khim. Prir. Soedin., 221 (1968).
4. I. F. Makarevich, Khim. Prir. Soedin., 260 (1969).
5. L. Fuchs, M. Wichtl, and H. Jachs, Archiv. d. Pharmazie, 291, 193 (1958).
6. I. V. Berezin and A. A. Klesov, A Practical Course of Chemical and Enzyme Kinetics [in Russian], Moscow (1976).

QUATERNARY 7-OXO-4,5,6,6a-TETRAHYDROHOMOPROAPORPHINE ALKALOIDS OF *Cochicum kesselringii*

A. M. Usmanov, B. Chommadov, and M. K. Yusupov

UDC 547.994.6

On the basis of additional information obtained by PMR and mass-spectral methods and chemical transformations, the structures of regelinone and isoregelinone, isolated from *Cochicum kesselringii* Rgl., have been established as quarternary 7-oxotetradehydrohomoproaporphine alkaloids.

We have previously [1, 2] reported on the isolation from *Colchicum kesselringii* Rgl. of regelinone (I) and isoregelinone (II), for which probable structures were proposed as epimeric 7-oxohomoproaporphines. Additional information that we have now obtained has permitted their complete structures to be established.

In the PMR spectrum of regelinone (Fig. 1) the signals stand out of three aromatic protons (7.76 ppm, s; 8.47 and 8.36 ppm, dd, J = 6.8 Hz); of two methyl groups (3.85 and 4.80 ppm); and of a tertiary proton (4.34 ppm, s). In addition, in the PMR spectrum taken in trifluoroacetic acid a two-proton singlet appears at 2.90 ppm which is due to the protons of a methylene group located next to a carbonyl group (at C_8).

A signal at 7.76 ppm relates to the H_3 proton of the benzene ring A, and signals at 8.47 and 8.63 ppm forming an AB system correspond to the H_4 and H_5 protons. On the basis of the fact that in the spectrum of an isoquinoline the signal of the H_α proton with respect

V. I. Lenin Tashkent State University. M. I. Kalinin Turkmen Agricultural Institute.

Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 81-84, January-February, 1985. Original article submitted February 23, 1984.

0009-3130/85/2101-0076$09.50

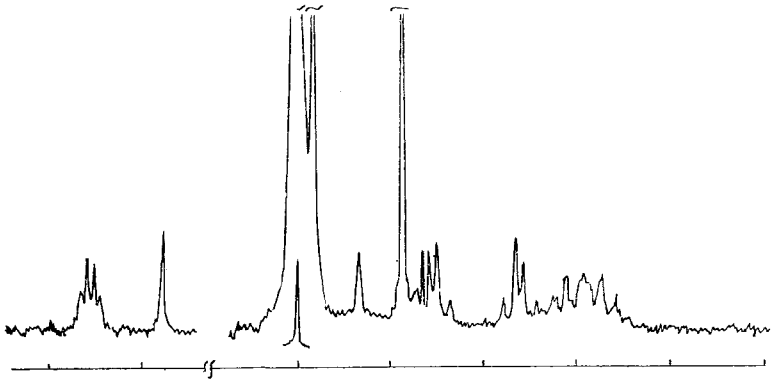


Fig. 1. PMR spectrum of regelinone.

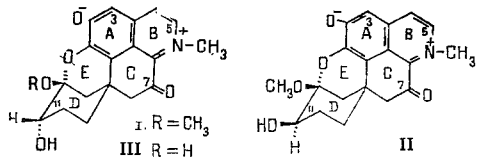
to the N-methyl group is located in a weaker field than that of a Hβ proton [3-5], the signal at 8.63 ppm was assigned to the H_5 proton and that at 8.47 ppm to the H_4.

In a study of the intranuclear Overhauser effect between the protons and the methyl groups in 12-demethylregelinone (III), it was found that the effect was positive (55%) in the case of the H_5 proton and the methyl group remaining after the acid hydrolysis of the base. From this it followed that in (I), as in the homoproaporphine alkaloids of the kesselringine group [6, 7], the ketal methoxy group was hydrolyzed, and the retained methyl group was located at the nitrogen atom, i.e., the base contained a N-methyl group in the place of the second O-methyl group that we suggested previously [1, 2].

The pronounced downfield shift of the signal of the protons of the N-methyl group in the PMR spectrum (4.80 ppm) in regelinone indicated the quaternary nature of the nitrogen atom [8-10].

In the mass spectra of (I) and (II), the strongest peak was that of the molecular ion (M^+ 341) and the peaks of the $(M - 15)^+$ and $(M - 43)^+$ ions were also strong. The $(M - 15)^+$ ion is apparently formed as the result of the ejection of the methyl of the N-methyl group, and the $(M - 43)^+$ ion by the splitting out of a CO fragment, as well, from ring C. Such fragmentation can be explained by the location of the N-methyl group in the isoquinoline nucleus. Consequently, with respect to the formation of the group of ions, compounds (I) and (II) differ substantially from the other homoproaporphine alkaloids with a spirocyclohexanol ring [11].

Their good solubility in water and the small degree of extraction by chloroform from solutions made alkaline with ammonia also showed that compounds (I) and (II) could be quaternary ammonium bases. The relationship of the empirical formula $C_{19}H_{19}O_5N$ to the number of rings and double bonds in (I) and (II) showed that there was not a hydroxy group but an oxygen atom forming an anion in the C_2 position. Consequently, regelinone and isoregelinone are compounds of the betaine type and have the following structures:



The absence of a hydroxy group at C_2, in contrast to the homoproaporphine bases kesselringine [6] and luteine [12], also explains the fact that under the action both of diazomethane and of dimethyl sulfate on (I) and (II) the initial compounds were isolated unchanged. It was impossible to methylate the bases in the C_2 positions under the action of methyl iodide in the presence of potassium carbonate, as well.

The acetylation of regelinone gave a monoacetyl derivative (IV) formed through the C_{11}-hydroxy group, which was confirmed by the appearance in its PMR spectrum of the signal of the protons of an acetoxy group at 2.00 ppm and by a downfield displacement of the signal of the tertiary proton geminal to the acetoxy group (5.18 ppm).

The presence of carbonyl groups in bases (I) and (II) was confirmed by the preparation of an oxime (V). The structures of rings C, D, and E in them were studied with the aid of the INDOR spectrum [2].

On exhaustive reduction with zinc dust in acetic acid, regelinone was converted into kesselringine (VI) and isoregelinone into luteine (VII), as was confirmed by a direct comparison of the products obtained with authentic samples.

The facts given above completely confirm the epimeric structures (I) and (II), respectively, for regelinone and isoregelinone.

Thus, regelinone and isoregelinone are the first representatives of the quaternary 7-oxo-4,5,6,6a-tetradehydrohomoaporphine alkaloids.

Only a few 7-oxotetradehydroaporphine alkaloids have been isolated from plants previously [4,5,8-10], and compounds with such a structure were unknown among the homopropaporphine and proaporphine bases.

We also confirmed structure (I) for regelinone by partial synthesis from kesselringine using periodate oxidation.

EXPERIMENTAL

The individuality of the compounds was studied by chromatography on Filtrak No. 2 paper in the solvents n-butanol—hydrochloric acid—water (50:7.5:13.5) (system 1) and n-butanol—12% aqueous ammonia (1:1) (system 2).

12-Demethylregelinone (III). A mixture of 0.1 g of (I) and 5 ml of 5% sulfuric acid was heated in the water bath for 2 h. Then the solution was evaporated and the residual substance was extracted with a mixture of chloroform and methanol and the solution was purified by passage through a layer of alumina. Compound (III) was isolated with R_f 0.24 and 0.34 (systems 1 and 2, respectively).

PMR spectrum (in D_2O + HCl): 4.76 (3 H, s, NCH_3); 7.63 (1 H, s, H_3); 8.41 and 8.59 (2 H, dd, H_4 and H_5).

O-Acetylregelinone (IV). A mixture of 0.2 g of (I) and 4 ml of acetic anhydride to which 0.7 g of freshly fused sodium acetate had been added was left at 40-50°C for 50 h. The excess of acetic anhydride was evaporated off, the residue was dissolved in water and the solution was acidified with hydrochloric acid to pH 1 and was extracted with chloroform. Then the acid solution was made alkaline with ammonia to pH 8 and the acetyl derivative was extracted with chloroform. Compound (IV) was isolated with R_f 0.68 and 0.57 (systems 1 and 2). IR spectrum: 1740 cm^{-1} ($OCOCH_3$).

PMR spectrum (in CF_3COOH): 1.90 (3 H, s, $OCOCH_3$); 3.25 (3 H, s, OCH_3); 4.20 (3 H, s, NCH_3); 5.08 (1 H, s, H_{11}); 7.25 (1 H, s, H_3); 7.84 (2 H, s, H_4 and H_5).

Mass spectrum (*m/z*): 383 (M^+), 368, 341, 340, 325, 324, 298, 294, 282, 242, 241, 228, 226, 149.

Regelinone Oxime (V). A mixture of 0.04 g of (I) and 4 ml of ethanol was treated with 0.1 g of hydroxylamine hydrochloride, 0.1 g of sodium acetate, and three drops of water and was heated for 3 h. After the solvent had been distilled off, the residual substance was extracted with a mixture of methanol and chloroform. Compound (V) was isolated, with mp 246-248°C (after charring); R_f 0.64 and 0.13 (systems 1 and 2).

IR spectrum: no absorption maximum at 1690 cm^{-1} (CO).

Mass spectrum (*m/z*): 356 (M^+), 340, 326, 314, 295, 281, 267, 256, 253, 241, 226, 209, 149.

Reduction of Regelinone to Kesselringine (VI). Regelinone (0.2 g) in 30% acetic acid solution was treated with 1 g of zinc dust and the mixture was heated on the water bath for 30 h. Then it was filtered, made alkaline, and extracted with chloroform. Kesselringine was isolated, with mp 196-198°C (from acetone); R_f 0.50 and 0.75 (systems 1 and 2).

Reduction of Isoregelinone to Luteine (VII). Compound (II) (0.1 g) was treated in the same way as regelinone. Luteine was isolated with mp 224-226°C (from acetone); R_f 0.39 and 0.32 (systems 1 and 2).

Partial Synthesis of Regelinone from Kesselringine (VI). The periodate oxidation of (VI) to regelinone was carried out by a known method [13]. A solution of 0.42 g of iodine

and 0.22 g of freshly fused sodium acetate was added dropwise with heating on the water bath under reflux to a solution of 0.20 g of kesselringine in 30 ml of ethanol, and the mixture was evaporated completely. The residual substance was dissolved in water, and the solution was made alkaline with ammonia and was extracted with chloroform. Compound (I) was isolated with mp 314-315°C (from acetone), Rf 0.33 and 0.44 (systems 1 and 2).

SUMMARY

1. The structures of regelinone and isoregelinone have been established on the basis of the results of a study of PMR spectra and chemical transformations as the first representatives of quaternary 7-oxo-5,5,6,6a-tetradehydrohomoproaporphine bases.

2. The structures of regelinone and isoregelinone have been confirmed by interconversions with kesselringine and with luteine, respectively.

LITERATURE CITED

1. M. K. Yusupov, A. M. Usmanov, A. K. Kasimov, and Kh. Turdikulov, Khim. Prir. Soedin., 867 (1977).
2. A. M. Usmanov and M. K. Yusupov, Khim. Prir. Soedin., 195 (1981).
3. A. R. Katritzy, Physical Methods in the Chemistry of Heterocyclic Compounds, Academic Press, New York (1963).
4. L. Castedo, D. Dominguez, J. M. Saá, and R. Suau, Tetrahedron Lett., 4589 (1979).
5. H. Guinaudeau, M. Shamma, B. Tantisewie, and K. Pharadai, Chem. Commun., 1118 (1981).
6. M. K. Yusupov and A. S. Sadykov, Khim. Prir. Soedin., 350 (1976).
7. D. A. Abdullaeva, M. K. Yusupova, and Kh. A. Aslanov, Khim. Prir. Soedin., 783 (1976).
8. J. Ribas, J. Sueiras, and L. Castedo, Tetrahedron Lett., 3093 (1971).
9. J. Kunitomo, M. Ju'ichi, Y. Yoshikawa, and H. Chikamatsu, Experientia, 29, 518 (1973).
10. I. A. Israilov, S. U. Karimova, and M. S. Yusupov, Khim. Prir. Soedin., 415 (1979).
11. E. Kh. Timekov, A. K. Kasimov, D. A. Abdullaeva, M. K. Yusupov, and Kh. A. Aslanov, Khim. Prir. Soedin., 328 (1976).
12. N. L. Mukhamed'yarova, M. K. Yusupov, M. G. Levkovich, and Kh. A. Aslanov, Khim. Prir. Soedin., 801 (1976).
13. M. P. Cava, A. Venkateswarlu, and D. L. Edie, Tetrahedron, 28, 4299 (1972).