5. V. V. Nalimov and N. A. Chernova, Statistical Methods of Planning Extremal Experiments [in Russian], Moscow (1965).

PRODUCTION OF A PYRIDINE DERIVATIVE OF GROSSHEMIN

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Information has appeared in recent years on new sesquiterpene lactones isolated from plants. The poor solubility of the susquiterpene lactones in water complicates their biological testing and, consequently, their practical use. In view of this, attempts have been made to convert the sesquiterpene lactones into soluble compounds. Thus, for example, for some compounds containing an α-methylene-γ-lactone ring derivatives with primary and secondary amines have been obtained which, in their turn, give water-soluble salts [1, 2]. The reaction of sesquiterpene lactones with tertiary amines has not been established.

We report the preparation of a pyridine derivative of grosshemin, which is formed by the reaction of pyridine and hydrochloric acid with grosshemin (I) in the presence of acetic anhydride.

The pyridine derivative of grosshemin (II), $C_{20}H_{24}O_4NCl \cdot H_2O$, mp 160-165°C, $[\alpha]_D^{20}+71.23°$ (c 1.33; water) is readily soluble in water, soluble in ethanol, and sparingly soluble in other organic solvents.

The pryridine derivative is formed only in the presence of acetic anhydride, which is a catalyst in this reaction. Grosshemin acetate (III) does not form a pyridine derivative, and the pyridine derivative of grosshemin is acetylated only under more severe conditions.

The IR spectrum of (II) has absorption bands at (cm^{-1}) 3450 (OH) and 3300 (H_2O), 1770 (γ-lactone), 1745 (cyclopentanone), and 1640 and 1620 (double bonds in conjugation).

The NMR spectrum of (II) (Fig. 1) has the following signals (ppm): doublet at 1.11-3 H_{15}; triplet at 3.96-H_4; multiplet at 4.28-H_6; two singlets at 4.54 and 4.85-2 H_{14}; quartet at 5.64 ($J_{13-13'}$ = 13.8 Hz; $J_{11,13}$ = 9.0 Hz)-H_{13}; quartet at 5.89 ($J_{13,13'}$ = 13.8 Hz; $J_{11,13'}$ = 5.0 Hz)-$H_{13'}$; two triplets at 8.02 (2 H) and 8.40 (1 H); and a doublet at 9.90 (2 H)-pyridine protons.

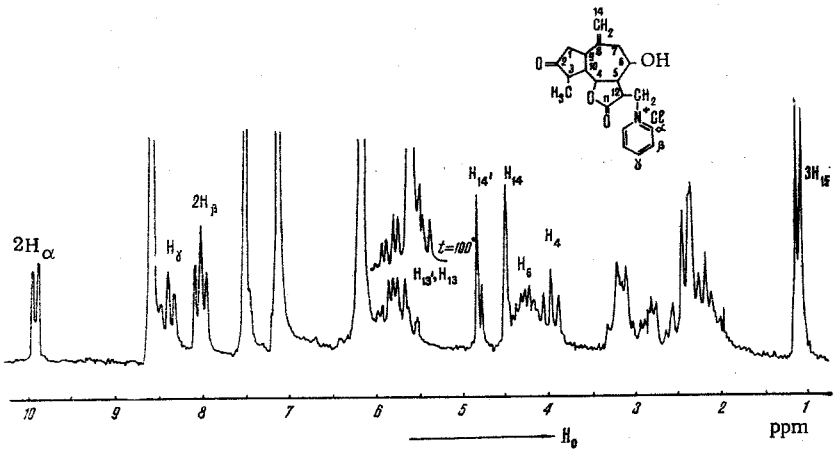

Fig. 1. NMR spectrum of the pyridine derivative of grosshemin in d-pyridine.

All-Union Scientific-Research Institute of Medicinal Plants, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 306-309, May-June, 1976. Original article submitted July 29, 1975.

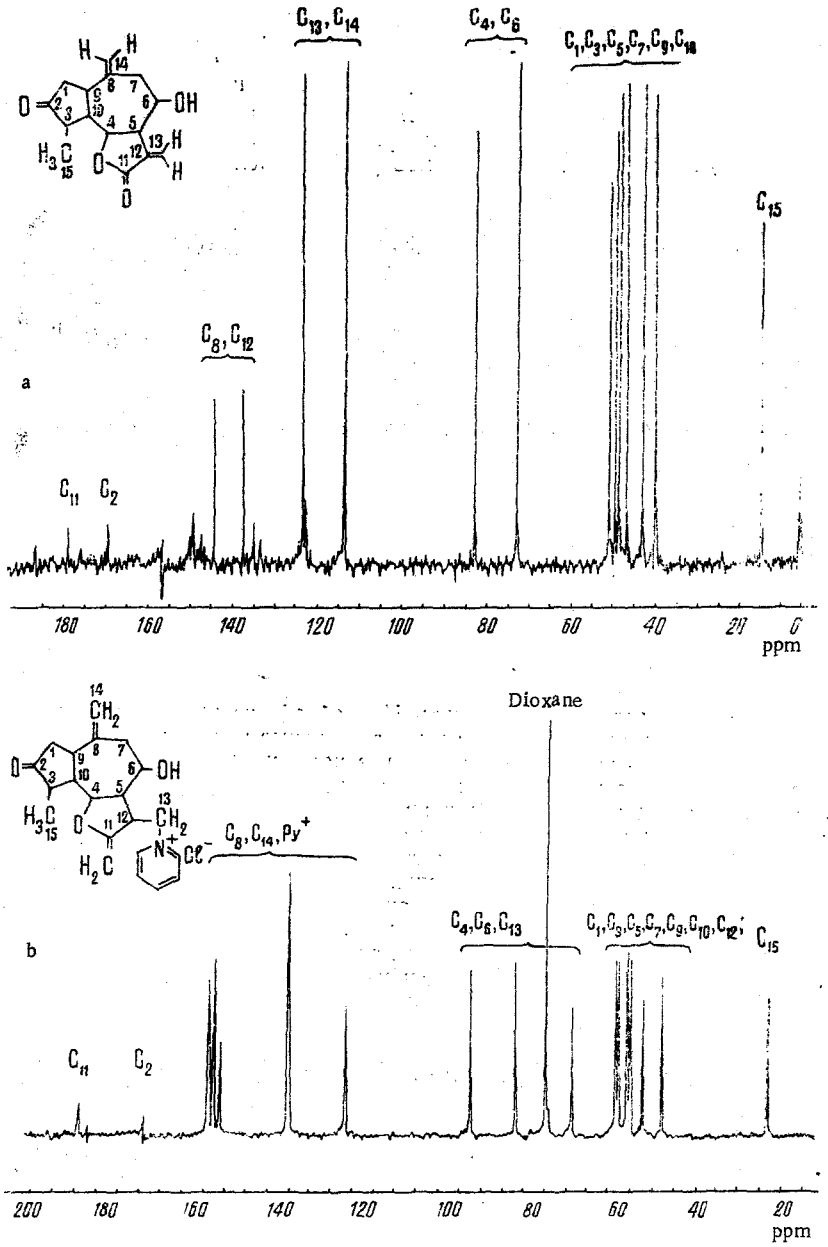

Fig. 2. ^{13}C NMR spectra: a) grosshemin in DMSO-d_6; b) pyridine derivative of grosshemin in dioxane.

Figure 2 shows the ^{13}C NMR spectra of (I) and (II), from which it follows that the molecule of the latter has five carbon atoms more than that of (I), i.e., the addition of pyridine has taken place. On treatment with alkali followed by acidification, (II) decomposes into the initial compounds.

It follows from the facts given that the substance obtained is the chloride of a quaternary ammonium base. The formation of such a compound is theoretically possible: On the one hand, the tendency of pyridine to give salts of quaternary ammonium bases is known and, on the other hand, the ease of opening of the exocyclic methylene group in conjugation with the carbonyl of the lactone ring to form condensation products (the Michael reaction) has been fairly well described in the literature. The Michael reaction is a reversible process. Some sesquiterpene lactones form Michael adducts even on chromatography; for example, in the chromatography of pulchellin on alumina and its elution with methanol, addition of the latter takes place [3-5].

EXPERIMENTAL

Preparation of the Pyridine Derivative (II). A mixture of 4 g of (I), 15 ml of acetic anhydride, and 30 ml of pyridine was kept at room temperature for 48 h and was then diluted with 1 ml of distilled water. The microcrystalline precipitate of (III) that deposited was filtered off and was washed with water (3 × 10 ml). This gave 0.9 g of (III). The filtrate was washed with chloroform (6 × 10 ml) for the final elimination of (III) and was then acidified with hydrochloric acid to pH 1-2 and left in an evaporating dish under a hood. After the complete elimination of water, heavy white crystals were obtained which were filtered off with the aid of a vacuum, washed on the filter with ethanol (2 × 15 ml) and dried over calcium chloride for three days. This gave 3 g of colorless prisms with mp 155-164°C.

Thin-layer chromatography in the acetone–ethanol (8 : 2) system gave one spot with R_f 0.3 (grosshemin has R_f 0.8 in this system); it was revealed with a 0.5% solution of $KMnO_4$ in 0.5% H_2SO_4.

For further purification, compound (II) was chromatographed on silica gel, eluted with acetone–ethanol (8 : 2), recrystallized from the same mixture, and dried over P_2O_5 under vacuum without heating for 24 h: mp 160-165°C, $[\alpha]_D^{20}$ +71.23 (c 1.33; water); $C_{20}H_{24}O_4NCl \cdot H_2O$.

On long standing, the mother liquors gave an additional 1 g of (II).

Decomposition of (II). To a solution of 0.2 g of (II) in 2 ml of water were added 4 ml of a 20% solution of NaOH. A strong odor of pyridine appeared. After the reaction mixture had been acidified with a 20% solution of HCl, crystals of grosshemin deposited which were identified by their mp (200-202°C) and their IR and NMR spectra.

SUMMARY

The reaction of pyridine and hydrochloric acid with grosshemin in the presence of acetic anhydride forms a substance with the composition $C_{20}H_{24}O_4NCl \cdot H_2O$, mp 160-165°C, $[\alpha]_D^{20}$ +71.23 (c 1.33; water), for which structure (II) is proposed.

LITERATURE CITED

1. S. V. Hiromath, G. H. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, Ind. J. Chem., 6, No. 6, 339 (1973).
2. L. Drajanowska-Noninska, P. Todorowa-Avramowa, E. Najdenowa, and L. Lobutowa, Pharmazie, No. 8 543 (1973).
3. E. D. Bergman, D. Ginsburg, and R. Pappo, Organic Reactions, 10, 179 (1959).
4. W. Herz, K. Veda, and S. Inayama, Tetrahedron, 19, No. 3, 483 (1963).
5. S. C. Srivastava, S. K. Paknikar, and S. C. Bhattacharyya, Ind. J. Chem., 8, No. 2, 201 (1970).