STUDY OF THE CLAISEN REARRANGEMENT OF BUCHARAINE AND ITS ACETONIDE DERIVATIVE

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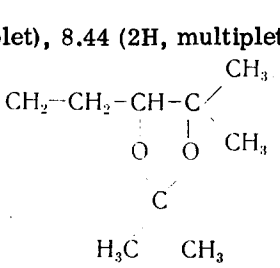
UDC 547.944/945

In a preceding communication [1], we described the isolation from H. bucharicum of the alkaloid bucharamine, for which the structure (VII) was proposed on the basis of spectroscopic characteristics and biogenetic considerations. In order to confirm this structure we decided to obtain bucharamine from bucharaine (I) by the Claisen rearrangement and to study the dependence of this reaction on the conditions.

It has been reported previously [2] that when (I) is heated in tetralin, an anamolous product of the Claisen rearrangement is formed – bucharidine (III). This transformation also takes place in the mass spectrometry of bucharaine [3]. We have performed the pyrolisis of bucharaine, but we isolated only bucharidine from the reaction product. The absence of appreciable amounts of other substances in the reaction mixture shows the preferred linkage of the tertiary hydroxy group with the allyl double bond with the formation of a six-membered ring.

In order to exclude the formation of bucharidine, we obtained bucharaine acetonide (II). The NMR spectrum of bucharaine was not studied because of its poor solubility in organic solvents and, therefore, we give the characteristics of the NMR spectrum of (II), which confirm the structure (I) proposed for bucharaine [2].

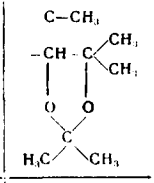
The spectrum of (II) has the signals of four adjacent aromatic protons of a benzene ring of the guinoline series at 2.18 ppm (1H, doublet, H_5) and 2.72 ppm (3H, multiplet, $H_{6,7,8}$) and a one-proteon singlet at 4.03 from H_3. The descreening of the H_5 proton relative to the center of the multiplet by 54 Hz agrees with the 4-alkoxyquinol-2-one structure (I) [4]. Other signals in the spectrum are found at 4.47 ppm (1H, broadened triplet, J = 6 Hz), 5.37 ppm (2H, doublet, J = 6 Hz), and 8.26 ppm (3H, broadened singlet), which are characteristic for compounds having the structural element Ar—O—CH_2—CH=C— [5]. The remaining protons appear at 6.35 ppm (1H, quadruplet), 7.82 (2H, triplet), 8.44 (2H, multiplet), and 8.65, 8.72, 8.79, and 8.94 ppm (4 singlets, 3H each) from the protons of the

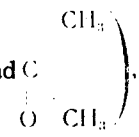
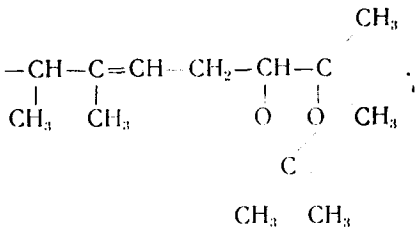


group. The signal from N–H appears at –2.72 ppm in the form of a broadened singlet which disappears on deuteration with CD_3OD. The Claisen rearrangement of (II) under the pyrolysis conditions gave a mixture of isomers with mol. wt. 371 (mass spectrometry) which was separated into acidic and neutral fractions. The acidic fraction (7%) yielded two substances, a spectroscopic study of which showed that one of them had the structure (IV). Thus, the IR spectrum in the 1660-1500 cm^{-1} region and the UV spectrum of (IV) are very similar to the corresponding spectra of 2,4-dihydroxyquinoline and bucharadine (III) [2]. The NMR spectrum of (IV) lacked the singlet from the proton at C_3, but signals are observed at 2.20 ppm (1H, doublet) and 2.70 ppm (3H, multi-

Order of the Red Banner of Labor Institute of the Chemistry of Plant Substances of the Academy of Sciences of the Uzbek SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 358-364, May-June, 1974. Original article submitted February 22, 1973.

TABLE 1. Chemical Shifts (δ scale)

Compound	H_5	$H_{6,7,8}$	NH	$CH-CH_3$	CH–O–	CH_2-CH_2	CH	CH_3	
(VI) with mp 236°C	2,35d	2,50–2,98	–2,5	6,60q	6,40	7,90–8,50	8,60 d		8,53 c 8,66 c; 8,75 c 8,84 c; 8,97 c
(VI) with mp 184°C	2,37d	2,50–2,98	–2,34	6,70q	6,34	7,90–8,50	8,62d		8,58 c 8,62 c; 8,70 c 8,76 c; 8,80 c
VIII	2,37	2,50–2,98		5,42q	6,44	7,90–8,50	8,47		8,47 c 8,71 c; 8,78 c 8,94 c; 9,11 c

plet) from the protons of the benzene ring, and at 4.23 (1H, triplet, =CH–) 5.80 (1H, quartet, J = 7.5 Hz, $C\underline{H}-CH_3$), 6.26 (1H, quadruplet –CH–O–), 7.30-8.10 (2H, broad multiplet, $-CH_2-$), 8.26 (3H, broadened singlet) 8.59 (9H doublet, $CH-CH_3$ and  , and 8.71 and 8.84 ppm (singlets, 3H) from the protons of of the side chain  . The signal from the NH group appears at –2.38 ppm.

The second substance from the acid fraction was isolated in very small amounts. Its IR and UV spectra show that it is a linear dihydrofuranoquinol-4-one [6]. The IR spectrum and the R_f value on TLC of this substance differ from those of bucharamine, and therefore structure (V) remains for it.

From the neutral fraction we obtained two products (93%) differing in their solubilities in acetone and petroleum ether. Their UV spectra have maxima at 282 and 292 nm, which are typical for quinol-2-ones and do not change on acidification. Their NMR spectra show signals at 6.60 and 6.70 ppm, respectively, in the form of one-proton quartets (Table 1), which are characteristic for the β protons of a dihydrofuran ring. The absence from the NMR spectra of the substances investigated of aromatic signals below 2.21 ppm and also the features of the IR and UV spectra show that they possess the angular structure (VI), from which it can be seen that the compound can exist in two racemic forms (VIa) and (VIb).

The mass spectra of these substances contain practically the same set of fragments, but their relative intensities differ.

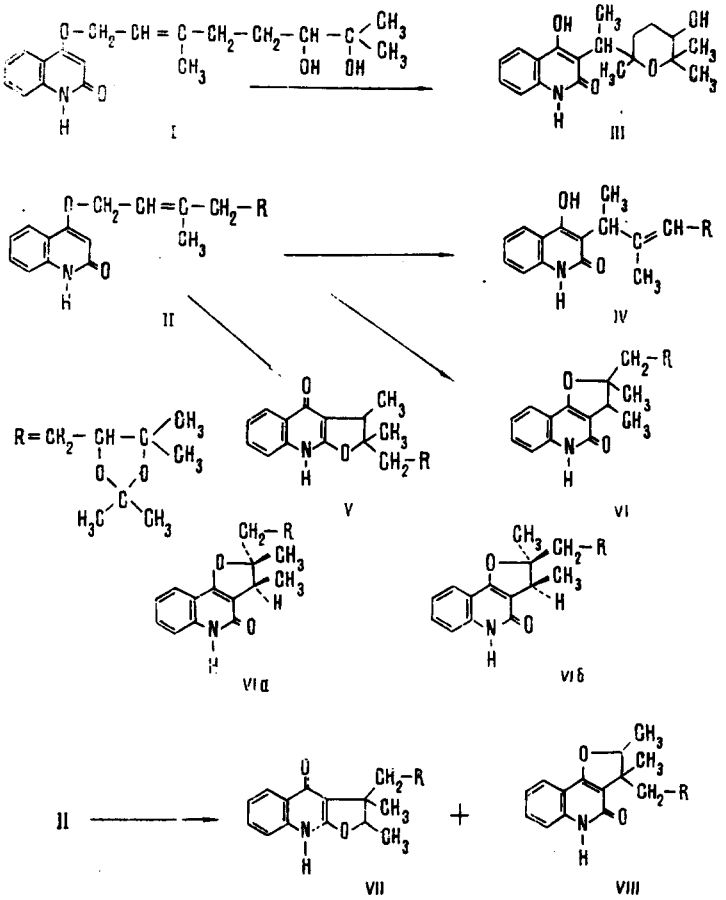
Substance, m/e	371	356	314	313	255	242	228	216	215
with mp 236°, I, %	80	100	85	30	44	69	30	28	16
with mp 184°, I, %	23	37	25	37	15	41	21	4	16
Substance, m/e	214	213	212	200	189	188	162	155	125
with mp 236°, I, %	96	22	26	18	50	57	41	41	56
with mp 184°, I, %	100	37	12	6	12	20	8	0	16

Such a redistribution of intensities can be explained by the assumption that these substances under consideration are diastereoisomers and have different arrangements of the substituents at the α-carbon atom of the dihydrofuran ring. It can be seen from the facts given that the splitting off of a CH_2R group from M^+, leading to the formation of an ion with m/e 214 in the compound with mp 184°C is a process far exceeding all other types of fragmentation. The molecular ion of the other substance is more stable, and the fragmentary ions are more uniformly distributed with respect to intensity. Fragments with m/e 189, 188, 162, and 125 arising after the opening of the dihydrofuran ring have the greatest intensity.

Thus, the Claisen rearrangement of bucharaine acetonide under thermal conditions takes place with the formation of the anomalous reaction products (IV), (V), and (VI) as in the case of a simpler compound – the 3,3-dimethylallyl ether of 4-hydroxy-1-methylquinol-2-one [7]. However, the rearrangment of bucharaine acetonide takes place rapidly with the almost quantitative formation of the products (VIa) and (VIb) – racemic diastereoisomers obtained by the cyclization of the 4-hydroxyquinol-2-one derivative (IV) [8].

According to the mechanism of the Claisen rearrangement, a normal product is first obtained as the result of a 3,3-sigmatropic shift, and this then rearranges into the anomalous product through a spirodienone [9], a base suppressing the formation of anomalous products. Heating (II) in dimethylformamide gives the angular dihydrofuranoquinoline derivative resulting from the normal Claisen rearrangement (VIII) (92%) and a substance of phenolic nature identical with (IV). The IR and UV spectra of (VIII) are typical for 4-alkoxyquinol-2-one bases [6]. The NMR spectrum of (VIII) (see Table 1) shows the same signals as (VI), but the value of the chemical shift of the quartet at 5.44 ppm (J = 6.5 Hz) is characteristic of the α proton of a dihydrofuran ring. Obviously, under these conditions a normal Claisen rearrangement takes place predominantly, but the product separates out exclusively in the cyclic form (VIII), similarly to what was shown by Chamberlain and Grundon [7]. The linear dihydrofuranoquinolin-4-one derivative (VII) (bucharamine) was not detected in the mixture even by chromatography.

When (II) was fused with alkali, a mixture of isomers was formed which was separated into acidic and neutral fractions. The neutral fraction yielded substance (VIII). Its diastereomer was not isolated in the individual form: the mother liquor deposited a mixture of crystals consisting, according to the NMR spectrum, of the two diastereomers.



The acid fraction yielded two substances differing in their solubilities in chloroform. Their IR- and UV-spectroscopic characteristics and also their solubilities in alkali showed that they have the linear dihydrofuranoquinolin-4-one structure [6]. The presence in the NMR spectra of a 1-proton quartet in the 5.10-5.60 region show that these substances are the products of the normal Claisen rearrangement with structure (VII).

The chloroform-soluble substance was identical with bucharamine (in melting point, mixed melting point, TLC, and IR, and UV spectra) [1]. The chloroform-insoluble compound is, according to its IR, UV,

and NMR spectra, a diastereomer of bucharamine. Its NMR spectrum, taken in CF_3COOH, shows the signals from four adjacent aromatic protons at 2.1 ppm (1H, doublet, H_5) and 2.52 ppm (3H, multiplet, $H_{6,7,8}$), the signal of the α proton of the dihydrofuran ring at 5.35 ppm (1H, quartet, J = 6.5 Hz) connected with a methyl group appearing in the form of a doublet at 8.74 ppm. The spectrum also contains signals at 6.65 (1H, multiplet, $\text{CH}-\text{O}-$), 8.35-8.9 (4H, multiplet, $-CH_2-CH_2$), 8.70, 9.03, and 9.10 (three singlets, 3H each, $C-CH_3$ and $-C(CH_3)(CH_3)-O-$) and a narrow six-proton singlet at 8.05 ppm from the protons of the acetonide group. The downfield shift of the latter may be caused by the influence of the CF_3COOH or by the saponification of the acetonide group by this acid to the diol and acetone. In order to investigate this question, we recorded the NMR spectrum of (VIII) in CF_3COOH, since we obtained the diol (IX) corresponding to the acetonide (VIII) by fusing bucharaine with alkali. The spectrum of (VIII) also showed a six-proton singlet at 8.05 ppm, but the substance isolated after the recording of the spectrum was identical with (IX) (VIII, $R=CH_2-CH_2-C(CH_3)(OH)-C(OH)(CH_3)-CH_3$) in melting point, mass spectrum, and TLC behavior. Thus, trifluoroacetic acid saponifies acetonides to the corresponding diols.

EXPERIMENTAL

For the conditions of recording the IR, UV, NMR, and mass spectra, see [11]. For TLC we used silica gel containing 5% of gypsum. The following solvent systems were used: 1) toluene–ethyl acetate – formic acid (5 : 4 : 1), and 2) ethyl acetate.

Claisen Rearrangement of Bucharaine. The base (0.02 g) was melted and kept at 160°C for 1 min. After cooling, the reaction mixture was treated with a 4% solution of caustic soda. The alkaline solution was washed with ether, saturated with ammonium chloride, and extracted with ether, and distillation of the extract yielded 0.14 g of (III) with mp 251°C (from ethanol). The substance gave no depression of the melting point with an authentic sample of bucharidine. The IR spectra and the R_f values on TLC were identical. For a description of the preparation of bucharame acetonide (II), see [10].

Claisen Rearrangement of Bucharaine Acetonide (II). A. Bucharaine acetonide (1.4 g) was heated 160-170°C for 1 min and, after cooling, the product was distributed between ether (a) and a 4% solution of caustic soda. The alkaline solution was saturated with ammonium chloride and extracted with ether. The ethereal extract was shaken with 10% sulfuric acid (b) and distilled. The residue consisted of substance (IV) with mp 221-222°C (from ethanol), $[\alpha]_D$ 0°, R_f 0.83 (system 1); 0.53 (system 2).

IR spectrum, cm^{-1}: 3390, 3290, 1645, 1620, 1578, 1508. UV spectrum, λ_{max}: 228, 264, 273, 283, 311 inflection, 318, 220, inflection (log ε 4.61, 3.66, 3.71, 3.72, 3.76, 3.83, 3.70). Mass spectrum: 371 (M^+, 18%); 313 (6%), 242 (100%), 214 (40%).

The acid solution (b) was made alkaline and extracted w th ether, and the extract was distilled. The residue consisted of substance (IV) with mp 221, 222°C (from ethanol), R_f 0.3 (system 1), 0.2 (system 2).

IR spectrum, cm^{-1}: 1640, 580, 1512 (bands of approximately equal intensity); UV spectrum, λ_{max}: 216, 233, 249 inflection, 297 inflection, 304, 316 nm (log ε 4.13; 4.15; 3.90; 3.64; 3.71; 3.62); in an acid medium the spectrum changes; mass spectrum: 371 (M^+ 45%), 313 (16%); 242 (86%), 214 (100%).

The ethereal extract (a) was washed with water, dried, and distilled. The residue consisted of 1.3 g of a crystalline substance (VI), which was treated with hot acetone. The acetone-insoluble part was repeatedly crystallized from mixtures of acetone and chloroform and of ethanol and chloroform; mp 236°C, R_f 0.75 (system 1), 0.35 (system 2).

IR spectrum, cm^{-1}: 1665, 1630, 1604, 1578, 1510. UV spectrum, λ_{max}: nm 217, 232, 282, 292, 318, 330 (log ε 4.62, 4.60; 3.87; 3.93; 3.90; 3.83). The spectrum did not change in an acid medium.

The mother liquors after the isolation of the substance with mp 236°C were boiled with petroleum ether. The fraction soluble in petroleum ether was chromatographed on alumina. Ethereal eluates yielded crystals with mp 184°C (from acetone), R_f 0.74 (system 1), 0.42 (system 2).

IR spectrum, cm^{-1}: 1660, 1630, 1605, 1580, 1517; UV spectrum, λ_{max}, nm: 218, 232, 283, 292, 318, 330 (log ε 4.50, 4.47, 3.68; 3.77, 3.73; 3.65). The spectrum did not change on acidification. The two substances were readily soluble in chloroform but did not dissolve in alkalis and mineral acids.

B. A mixture of 0.5 g of bucharaine acetonide and 5 ml of dimethylformamide was heated under reflux for 30 min. The dimethyl formamide was evaporated and the residue was distributed between ether and 4% caustic soda solution. Distillation of the ethereal solution yielded 0.46 g of (VIII) with mp 202°C (from acetone), R_f 0.79 (system 1), 0.56 (system 2).

IR spectrum, cm^{-1}: 1670, 1640, 1620, 1590, 1518, 1500; UV spectrum, λ_{max}, nm: 217, 232, 280, 292, 319, 329 (log ε 4.71; 4.69; 4.04; 4.14; 4.08; 3.99). The spectrum did not change in an acid medium. Mass spectrum: 371 (M^+ 1%); 356 (6%); 313 (30%), 242 (8%), 215 (45%), 214 (100%). From the alkaline solution a substance was obtained with mp 221-222°C (from ethanol) identical with (IV).

C. Compound (II) (1 g) was carefully triturated with 2 g of KOH, and then 0.5 ml of water was added and the mixture was fused at 200-220°C for 5 min. The mixture was cooled and distributed between ether and 4% caustic soda solution. The ether was distilled off, leaving 0.4 g of a crystalline substance, which was chromatographed on alumina. The first ethereal eluates yielded crystals with mp 200-201°C (from acetone) [identical with (VIII)]. The alkaline solution was saturated with ammonium chloride and extracted with ether, the distillation of which yielded 0.35 g of a substance which crystallized on the addition of ether. The crystals were separated off and treated with chloroform. The material soluble in chloroform gave crystals with mp 222-223°C (from acetone), R_f 0.42 (system 1), 0.42 (system 2). The substance gave no depression of the melting point with bucharamine [1]. Their IR and UV spectra and the spots on TLC were also identical.

The material insoluble in chloroform had mp 280°C (from acetone), R_f 0.42 (systems 1 and 2). IR spectra, cm^{-1}: 1630, 1580, 1518, 1504 (bands of approximately equal intensity): UV spectrum, λ_{max}, nm: 216, 233, 250 inflection, 298 inflection, 305, 317 (log ε 4.43, 4.46, 4.21, 3.91, 3.99, and 3.92). The spectrum changed in an acid medium. Mass spectrum: 371 (M^+ 2%), 356 (10%), 313 (36%), 215 (96%), 214 (100%), 200 (24%).

Fusion of Bucharaine with Alkali. A mixture of 1 g of bucharaine, 2 g of KOH, and 0.5 g of water was heated at 180°C for 5 min, and after cooling, was treated with water and ether. The ethereal solution was separated off, washed with water, and distilled. The residue consisted of a crystalline substance (IX) (0.6 g) with mp 236°C (from acetone and methanol); R_f 0.42 (system 1), 0.47 (system 2). UV spectrum: λ_{max}, nm: 217, 233, 283, 293, 319, 331 (log ε 4.55, 4.52, 3.80, 3.85, 3.85, 3.78). The spectrum did not change on acidification. IR spectrum, cm^{-1}: 3600-3300 (broad band), 1660, 1630, 1610, 1580, 1510. Mass spectrum: 331 (M^+, 6%), 316 (11%), 313 (32%), 272 (95%), 215 (32%), 214 (100%), 200 (12%). The acetonide obtained from (IX) in the usual way [10] was identical with (VIII).

CONCLUSIONS

The pyrolisis of bucharaine and its acetonide derivative (II) forms the products of an anomalous, and their fusion with alkali, the products of the normal, Claisen rearrangement. Product (VII) is identical with bucharamine.

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