analyzed by paper chromatography in various solvent systems. The following were identified: cannogenol (aglycon), D-glucose, erycordinobiose, cellobiose, and, presumably, a trisaccharide.

SUMMARY

A new cardiac glycoside has been isolated from the seeds of plains erysimum Cheiranthus allioni Hort., (Erysimum asperum), and has been called glucoerycordin. Glucoerycordin is 3β-[O-β-D-glycopyranosyl-(1 → 4)-O-β-glucopyranosyl-(1 → 4)-β-D-gulomethylopyranosyloxy]-14,19,dihydroxy-5β,14β-card-20(22)-enolide.

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2-BENZOPYRYLIUM SALTS.

XXXV.* SYNTHESIS OF THE NATURAL ALKALOID DEHYDRONORCORALDINE AND OTHER SUBSTITUTED DIBENZO[a,g]QUINOLIZINIUM SALTS

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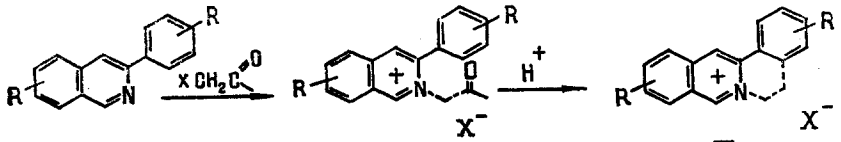
The interaction of 6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-2-benzopyrylium perchlorate with α-aminocarbonyl compounds forms N-α-aminocarbonyl-substituted isoquinolinium compounds which on treatment with acids are converted into dibenzo[a,g]quinolizinium compounds, one of which is the natural alkaloid dehydronorcoraldine. The products were characterized by the results of elementary analysis and IR, PMR, and UV spectroscopy.

One of the most convenient synthetic approaches to alkaloids of the berberine and protoberberine classes is based on the use of 3-arylisoquinolines (I) as the initial structural units. Their alkylation with α-halogenocarbonyl compounds leads to the isoquinolinium salts (II) which readily cyclize in the presence of acids into dibenzo[a,g]quinolizinium structures of type (III) [2].



I II III

However, the multistage synthesis of the initial 3-arylisoquinolines that are used [2-4] and the difficulty of their alkylation [2], due, apparently, to the steric influence to the aryl substituent in position 3 are fundamental limitations of this method which do not allow its preparative use in the chemistry of natural alkaloids.

*For Communication XXXIV, see [1].

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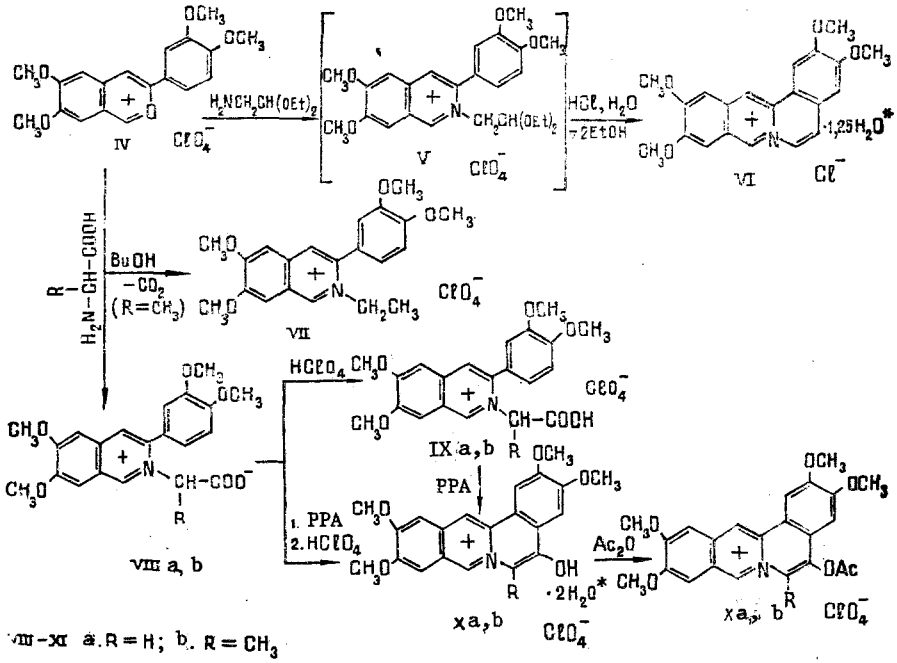
Thus, the main route in the practical solution of this problem is leading to the search for convenient methods for synthesizing N-carbonylmethyl-substituted 3-arylisoquinolinium salts (II) – blocks ready for the formation of the tetracyclic compounds (III).

Suitable compounds for the direct approach to the required structures are 3-aryl-2-benzopyrylium salts of (IV), which readily replace the oxygen heteroatom by nitrogen both on interaction with ammonia, with the formation of isoquinolines [5, 6], and in reactions with primary amines, leading with good yields to N-alkylisoquinolinium salts [7]. We assumed that the use of α-aminocarbonyl compounds in the latter reaction, without changing its preparative suitability, would lead to the desired compound of type (II).

In actual fact, when the perchlorate (IV) interacted with aminoacetaldehyde acetal in ethanol, the isoquinolinium salt (V) was formed, and when this was treated with hydrochloric acid it cyclized in situ to the dibenzo[a,g]quinolizinium chloride (VI) – the natural alkaloid dehydronorcoraldine. The overall yield of the salt (VI) in this case was an order of magnitude greater than that based on the best of the known methods [2], and this with a decrease in the number of stages of synthesis [8].



The interaction of perchlorate (IV) with amino acids took place ambiguously. Thus, when it was heated for an hour with an excess of glycine in ethanol, the expected recyclization product was formed with a yield of 85% and it was ascribed the structure of the betaine (VIIIa) on the basis of the results of spectroscopy and elementary analysis. The use of alanine under these conditions led to the formation solely of the product of the opening of salt (IV) containing no amino acid fragments, which indicates the absence of a heterorecyclization stage. The use of a higher-boiling alcohol – butanol – permitted heterocyclization to be achieved but caused the decarboxylation of the desired product (VIIIb) with the formation of the N-ethylisoquinolinium salt (VII) with a yield of 60%.

It is known that the process of recyclizing monocyclic pyrylium salts into pyridinium salts is facilitated by acid catalysis [11]. On the other hand, an acid medium should prevent the decarboxylation of the salt (IXb) formed as the result of the heterorecyclization, which takes place on basic catalysis. In actual fact, the use of acetic acid as solvent in the interaction of salt (IV) with an excess of alanine for 30 min followed by treatment of the reaction product with ammonia enabled the betaine (VIIIb) to be obtained with a yield of 70%.

*The formation of solvates is extremely characteristic for the dibenzo(a,g)quinolizinium salts [9].

TABLE 1. Some Characteristics of the Compounds Synthesized

Compound	Yield, %	mp, °C	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)
VI	70	232—234 (decomp.)[2]	3400, 1605, 1560, 1515, 1500, 1285	277 (4,68), 315 (4,72), 415 (4,01) (ethanol)
VII	50	209*(decomp.)	1633, 1620, 1605, 1590, 1100	
VIII a	85	208	1620 (s), 1600 (w), 1430, 1365, 1215	
VIII b	70	184**	1620 (s), 1605 (w), 1420, 1260	
IX a	98	234*	3580 (br), 1775 (w), 1735, 1630, 1610, 1100	255 (4,92)
IX b	98	178(decomp.)	3480 (br), 1747, 1627, 1607, 1094	
X a	65	>230*** (decomp.)	3500, 1650, 1610, 1500, 1250, 1100	315 (4,58), 405 (4,04)
X b	60	>230*** (decomp.)	3540, 1634, 1607, 1487, 1087	
XI a	70	>300***	1775, 1600, 1478, 1090	315 (4,81), 420 (4,20)
XI b	70	>300***	1770, 1600, 1480, 1085	

*From acetic acid.
**From propanol.
***From formic acid.

The IR spectra of compounds (VIIIa and VIIIb) contained strong bands of the stretching vibrations of a carboxylate anion at 1620 and 1420-1430 cm^{-1} (Table 1), which were replaced by the band of a carboxy group at ~1740 cm^{-1} in the salts (IXa and IXb) obtained when the betaines (VIIIa and b) were treated with perchloric acid. The PMR spectra of betaines (VIIIa and b), taken only in trifluoroacetic acid because of their poor solubility, coincided completely with the spectra of the corresponding perchlorates (IXa, b).

In contrast to the isoquinolinium salt (V), the cyclization both of the betaines (VIIIa, b) and of the perchlorates (IXa, b) took place only in polyphosphoric acid at 140°C. The 5-hydroxydibenzo[a,g]quinolizinium salts (Xa, b) produced in this process exist as hydroxy forms, as was shown by the absence of carbonyl absorption in their IR spectra and the presence of the vibrations of OH groups in the 3500 cm^{-1} region. It must be mentioned that close structural analogs of the salts (Xa, b) – substituted 6-oxodibenzo[a,g]quinolizinium perchlorates – exist both in the keto and in the enol forms [12].

Heating the perchlorates (Xa, b) in acetic anhydride, led, as in the case of their 6-oxo analogs [12, 13], to the ready formation of the acetates (XIa, b).

A comparison of the electronic spectra of 5-hydroxy- (Xa), 5-acetoxy- (XIa), and 6-hydroxy- and 6-acetoxydibenzo[a,g]quinolizinium salts [12] showed the complete identity of their extensive π-systems.

The treatment of the salts (Xa, b) or their acetates (XIa, b) with various bases led to deeply colored compounds soluble in water but insoluble in organic solvents and apparently consisting of double salts [sic] analogous to the betaines described in [12], which was impossible to obtain in a form convenient for identification. Similar difficulties exist in the isolation of the betaines obtained from β-hydroxyquinolinium salts [14], of which the 5-hydroxydibenzo[a,g]quinolinizium salts (Xa, b) are structural analogs.

It is known that β-hydroxy-substituted nitrogen heterocycles [15] possess bioantioxidant activity and are promising for the treatment of cancerous tumors, which is due to their ready capacity for forming radicals. A tendency to undergo one-electron reduction in the case of the compound under investigation played an adverse role in an attempt to obtain the PMR spectra both of the salts (Xa, b) and of the presumed betaines – their solutions proved to be paramagnetic.

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-487 instrument with a working frequency of 60 MHz at 20°C in CF_3COOH solutions with HMDS as internal standard. IR spectra were obtained

on a Specord 75-IR instrument in paraffin oil. UV spectra were taken on a Specord UV-VIS instrument in ethanol and acetonitrile solutions. The characteristics of the compounds synthesized are given in Table 1. In all cases the results of elementary analysis corresponded to the calculated figures.

2,3,10,11-Tetramethoxydibenzo[a,g]quinolinizium Chloride (VI). A mixture of 0.43 g (0.001 mole) of 3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium perchlorate (IV) [5] and 0.2 g (0.0015 mole) of aminoacetaldehyde acetal in 5 ml of ethanol was boiled for 9 h. The mixture was filtered hot, the filtrate was evaporated in vacuum to one third, and the residue was cooled and treated with 5 ml of concentrated hydrochloric acid. After a day, the yellow precipitate that had deposited was filtered off and dried. This gave 0.27 g of the salt (VI) (see Table 1).

N-Ethyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinolinium Perchlorate (VII). A mixture of 0.42 g (0.001 mole) of the salt (IV) and 0.45 g (0.005 mole) of alanine in 5 ml of n-butanol was heated for 4.5 h, and then 3 ml of n-butanol was added and it was cooled. The colorless crystals that deposited were filtered off and were washed with cold propanol and with ether. This gave 0.25 g of the salt (VII) (see Table 1). PMR spectrum, ppm: 1.10 (t, $CH_2\underline{CH_3}$), 3.52 (s, OCH_3), 3.58 (s, OCH_3), 3.70 (s, $2OCH_3$), 4.15 (q, $\underline{CH_2}CH_3$), 6.75 (s, 3H), 7.05 (s, 1H), 7.25 (s, 1H), 7.60 (s, 1H), 8.85 (s, 1H).

3-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisoquinolioacetate (VIIIa). A mixture of 4.26 g (0.01 mole) of the salt (IV) and 3.75 g (0.05 mole) of glycine in 30 ml of ethanol was heated for 1 h. After the suspension formed on boiling had cooled, the precipitate was separated off and was treated with 100 ml of 25% aqueous ammonia solution, and it was filtered off and was carefully washed with hot ether to eliminate unchanged glycine. After the precipitate had been dried, 3.35 g of the colorless betaine (VIIIa) was obtained, and this was purified by crystallization from acetic acid–water (1:2).

α-[3-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisoquinolinio]propionate (VIIIb). A mixture of 4.26 g (0.01 mole) of the salt (IV) and 1.8 g (0.02 mole) of alanine in 30 ml of glacial acetic acid was boiled for 30 min. The solution was cooled and was diluted with 200 ml of cold water. After 2 h, the precipitate that had deposited was separated off and was treated with 100 ml of 25% aqueous ammonia solution. After a day, the colorless product was filtered off and was carefully washed with cold water and dried. This gave 2.68 g of the colorless betaine (VIIIb) (see Table 1).

2-Carboxymethyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinolinium Perchlorate (IXa). Five drops of 70% $HClO_4$ were added to a boiling suspension of 0.38 g (0.001 mole) of the betaine (VIIIa) in 3 ml of ethanol, water, or glacial acetic acid. The foreign matter dissolved and the colorless perchlorate immediately precipitated, and, after cooling, it was separated off and dried. This gave 0.47 g of the salt (IXa). PMR spectrum, ppm: 3.45 (s, OCH_3), 3.52 (s, OCH_3), 3.70 (s, $2OCH_3$), 4.85 (br. s, CH_2), 6.65 (m, 3H), 6.95 (s, 2H), 7.60 (s, 1H), 8.75 (br. s, 1H).

2-(α-Carboxyethyl)-3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinolinium perchlorate (IXb) was obtained similarly from the betaine (VIIIb) (see Table 1).

5-Hydroxy-2,3,10,11-tetramethoxydibenzo-[a,g]quinolinizium Perchlorate (Xa). A mixture of 0.38 g (0.001 mole) of the betaine (VIIIa) or 0.48 g (0.001 mole) of the perchlorate (IXa) and 2 g of polyphosphoric acid was heated at 140°C with vigorous stirring for 1.5 h. After cooling, the solution was treated with 30 ml of cooled water, and 3 ml of 57% $HClO_4$ was added. After 2 h, the precipitate that had deposited was filtered off, washed with cold water, and dried. This gave 0.26 g of the salt (Xa).

5-Hydroxy-2,3,10,11-tetramethoxy-6-methyldibenzo[a,g]quinolizinium perchlorate (Xb) was obtained similarly from the betaine (VIIIb) or the perchlorate (IXb) (see Table 1).

5-Acetoxy-2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium Perchlorate (XIa). Three drops of 70% $HClO_4$ were carefully added to a suspension of 0.5 g (0.001 mole) of the salt (Xa) in 15 ml of acetic anhydride. The mixture was kept at 50°C for 5 min and was cooled, and after 1 h it was diluted with ether until the deposition of a precipitate ceased. This gave 0.35 g of the salt (XIa).

5-Acetoxy-2,3,10,11-tetramethoxy-6-methyldibenzo[a,g]quinolizinium perchlorate (XIb) was obtained similarly from the salt (Xb) (see Table 1).

SUMMARY

1. It has been shown that the interaction of 3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-benzopyrylium perchlorate with α-aminocarbonyl compounds forms N-α-carbonyl-substituted isoquinolinium salts in preparative yield.

2. The acid-catalyzed cyclization of the isoquinolinium compounds synthesized has given dibenzo[*a*,g]quinolizinium salts, including the natural alkaloid dehydronorcoraldine, and some of their properties have been studied.

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