TRANSFORMATIONS OF DUBINIDINE METHIODIDE AND RELATED COMPOUNDS IN AN ALKALINE MEDIUM AND ON PYROLYSIS

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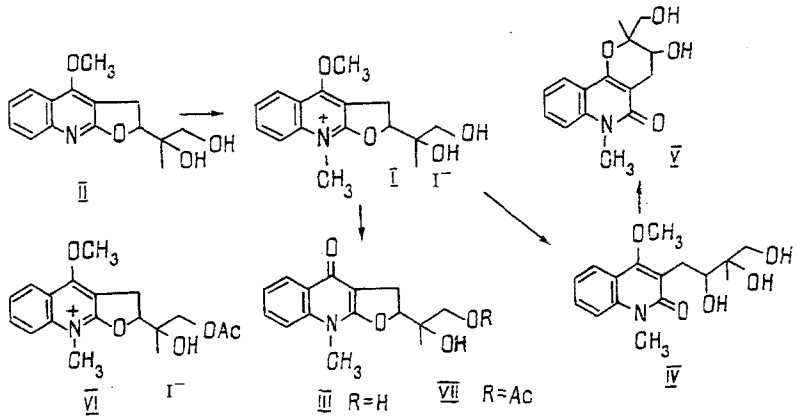
The interaction of dubinidine methiodide with dilute aqueous ammonia solution and with pyridine at room temperature has been studied. In the first case the dihydrofuran ring opens, and in the second case dequaternization takes place. The dynamics of the latter process have been investigated with the aid of PMR spectroscopy. the pyrolytic transformation of dubinidine and dubinine methiodides has been studied by electron-impact mass spectrometry.

A characteristic feature of the quaternary 4-methoxydihydrofuroquinoline alkaloids is their sensitivity to bases. Under the action of nucleophilic reagents the dihydrofuran ring is split, which leads to 3-substituted 4-methoxy-N-methylquinolin-2-one derivatives [1-3]. The formation of quinolin-2-ones is also characteristic for 2-alkoxyquinolinium salts [4]. The splitting out of the 2-alkoxy groups in the latter and the opening of the dihydrofuran ring in the quaternary dihydrofuroquinoline bases is due to an increase in the positive charge on the C-2 carbon atom.

When weak bases, such as pyridine, are used, no opening of the dihydrofuran ring takes place. Thus, when the methiodide (I) obtained from dubinidine (II) is heated with anhydrous pyridine an α-substituted N-methyldihydrofuroquinolin-4-one — folisine (III) — is formed. On the other hand, when (I) is treated with a methanolic solution of alkali not only the opening of the dihydrofuran ring with the formation of (IV) but also its subsequent cyclization to the angular N-methyldihydrofuroquinolin-2-one derivative isodubinidine (V) take place [6]. With the aim of obtaining the intermediate product of this reaction, we treated (I) with dilute aqueous ammonia solution at room temperature. We then obtained a substance with mp 130-131°C, composition $C_{16}H_{21}NO_5$, which, according to its PMR and mass spectra had the structure (IV). Heating (IV) in a methanolic solution of alkali gave isodubinidine. Thus, the mechanism of the formation of isodubinidine (V) suggested previously [6] has been confirmed experimentally.



The compound types (I)-(IV) shown in the scheme occur in plants of the Rutaceae family [7] and are biogenetically linked with one another. Such a parallelism between biosynthetic and chemical transformations induced us to study in more detail the qualitative and quantitative aspects of certain reactions and, in particular, the action of pyridine on dubinidine

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TABLE 1

Compound	Time after dissolution, days	Relative intensities of the signals of the C−CH_3 groups, mole-%		
		I(1.57 ppm)	III(1.38 ppm)	II (1.48 ppm)
Dubinidine methiodide (I)	0	90	10	0
	1	58	40	2
	3	40	55	5
	7	16	76	8
	9	12	80	8
	45	0	92	8
		D_3-I (1.57 ppm)	D_3-III (1.38 ppm)	
D_3-Dubinidine methiodide D_3-(I)	0	96	4	
	1	79	21	
	2	66	34	
	3	58	42	
	6	41	59	
	7	37	63	
	8	31	69	
		VI (1.50 ppm.)	VII (1.25 ppm.)	
Dubinine methiodide (VI)	0	99	1	
	4	25	75	
	8	10	90	
		D_3-VI (1.51 ppm)	D_3-VII (1.27 ppm)	
D_3-Dubinine methiodide (D_3-(VI)	0	97	3	
	1	71	29	
	2	51	49	
	3	39	61	
	6	23	77	
	7	15	85	
	8	15	85	

TABLE 2. Mass Numbers and Relative Intensities (%) of the Main Fragments in the Mass Spectra of (II), (III), and (V)

II	275(M^+, 33), 244(20), 226(13), 202(27), 201(47), 200(100), 186(20), 185(23), 173(17), 172(20), 158(15), 156(10)
III	275(M^+, 37), 257(6), 244(20), 241(12), 226(52), 214(35), 202(57), 200(100), 189(37), 188(41), 176(23), 175(16), 172(11), 146(10), 144(11), 134(26)
V	275(M^+, 35), 258(6), 256(4), 244(12), 226(100), 216(12), 214(16), 212(11), 200(16), 189(41), 188(50), 176(15), 160(12), 146(12), 134(21)

methiodide and a number of related compounds. It was also necessary to make a careful check of information on the pyrolytic transformations of (I).

It was found that in pyridine the transformation (I) → (III) takes place almost completely at room temperature. Eight days after the dissolution of (I) in pyridine, crystals of folisine (III) deposited, and a very small amount of dubinidine (II) was isolated from the mother liquor. It was therefore convenient to study the dynamics of these transformations with the aid of PMR spectra of a solution of (I) in D_5-pyridine, using the difference in the chemical shifts of the signals of the protons of the CH_3 groups of the side-chains of the alkaloids. For comparison we investigated dubinine methiodide (VI) and the N-CD_3 analogues of dubinidine methiodide, [D_3-(I)], and of dubinine methiodide, [D_3-(VI)], by the same method.

The integral intensities of the signals shown, expressed as percentages of the sum of the intensities of these starting compounds and the products of their transformation in deuterated pyridine solution are given in Table 1. It can be seen from this table that the transformation of the methiodides (I), [D_3-(I)], (VI), and [D_3-(VI)] into the N-methyldihydrofuroquinolin-4-ones (III), [D_3-(III)], (VII), and [D_3-(VII)] is the main process and, indeed, in all cases except (I) the only one. Passage to the initial tertiary base (II) was observed only in the case of (I), but the contribution of this process was very small. The PMR spectrum of the solution showed the complete disappearance of the signal of the protons of the methyl group of dubinidine methiodide — i.e., its complete conversion into folisine (92%) and dubinidine (8%).

Thus, the partial transformation of (I) into the initial tertiary base (II) is an individual property of dubinidine methiodide that disappears even on the replacement of N—CH_3 by N—CD_3, which is obviously due to an increase in the energy of cleavage of the N—CD_3 bond in comparison with N—CH_3. So far as concerns the rates of transformation of the methiodides [D_3-(I)] and [D_3-(VI)] into the N-methyldihydrofuroquinolin-4-one compounds [D_3-(III)] and [D_3-(VII)], they are lower than the analogous transformations of the nondeuterated methiodides (I) and (VI).

TABLE 3. Relative Intensities of the Metastable Peaks in the *B/E/const.* Spectra of the M^+ ions of (II), (III), and (V), and the $[M - CH_3(CD_3)I]^+$ ions of, (I), [D_3-(I)], and [D_3-(VI)]

Compound	t° of the bulb	t° of the ioniz. chamber	Parent ion	Daughter ions
(II)	130	80	275	244(49), 243(37), 226(12), 214(6), 201(16), 200(100), 199(28)
(III)	130	80	275	258(10), 257(17), 244(37), 243(27), 232(28), 226(30), 214(27), 200(47), 199(100), 198(15), 188(73), 176(63), 175(25)
(V)	130	80	275	258(7), 257(7), 244(8), 227(23), 226(100) 214(3), 201(1), 200(3), 188(10), 176(5)
(I)	120	100	275	244(40), 232(20), 226(50), 214(30), 200(60), 199(100), 188(60), 175(50)
	150	130	275	258(16), 257(15), 244(22), 243(28), 232(25), 226(38), 214(31), 200(53), 199(100), 188(53), 175(50), 174(19)
	170	150	275	258(20), 257(18), 244(20), 243(35), 232(30), 226(40), 214(35), 201(20), 200(50), 199(100), 188(95), 175(75), 174(30)
(D_{3-I})	150	100	275	235(4), 232(5), 229(4), 217(15), 203(8), 202(32), 200(15), 191(75), 179(100), 178(46)
	150	100	278	261(20), 260(21), 247(19), 246(20), 235(38), 232(18), 229(20), 217(35), 202(60), 192(15), 191(100), 179(75), 178(37)
(D_3-VI)	140	130	320	303(3), 302(3), 278(4), 262(4), 261(7), 247(12), 230(8), 229(44), 217(4), 203(26), 202(100), 201(8), 191(2), 190(2)
	170	150	320	303(2), 302(2), 278(4), 262(4), 261(7), 247(10), 230(7), 229(38), 217(4), 203(27), 202(100), 201(8), 191(2), 190(2)
	180	180	320	303(2), 302(1), 278(4), 262(4), 261(6), 247(13), 230(8), 229(48), 217(4), 203(31) 202(100), 201(9), 191(2), 190(2)

During the performance of the experiments we repeatedly convinced ourselves that the quantitative aspect of the transition (I) → (II) in pyridine needed checking by an independent method because it was difficult to monitor by chromatography the completeness of the formation of the methiodides from dubinidine and dubinine. For this purpose we recorded the PMR spectra of (I) in neutral solvents — D_2O and CD_3OD — immediately after dissolution and after 8 days. In all cases, only the singlets of the protons of the methyl group of dubinidine methiodide (I) appeared, at 1.12 ppm (D_2O) and at 1.24 ppm (CD_3OD). The individuality of the methiodides (I) and (VI), and [D_3-(I)] and [D_3-(VI)] was also checked by secondary-ion mass spectrometry, which provides the possibility of separating the quaternary cations of the methiodides (*m/z* 290, 332, and 293, 335) from the protonated molecular ions of the corresponding tertiary bases with *m/z* 276 and 318.

The pyrolytic transformations of dubinidine methiodide were investigated by the EI mass-spectrometric method. It had been established previously on the basis of a comparison of the spectra of (I) obtained in the interval of temperature of the inlet system of 150-220°C with the spectra of (II), (III), and (V) recorded under similar conditions that at the lowest temperature (I) was converted predominantly into dubinidine (II) + CH_3I; at 190°C indications of the presence of folisine (III) appeared; and at 220°C, in addition to this, an increased intensity was observed of the *m/z* 226 ions that are characteristic of the spectrum of isodubinidine (V) or the products of its thermal decomposition.

At the present time we have repeated the experiment with the temperature dependence of the EI spectra of dubinidine methiodide (I). Considering together with its synoptic spectra the spectrum of the N—CD_3 analogue [D_3-(I)] and the spectra of the model isomers (II), (III), and (IV), and, in addition to this, we have used *B/E/const.* linked-scanning of the ions with *m/z* 275 (I-III and V) or 278 [D_3-(I)]. The *B/E* spectra permit the presence of the molecular ions with *m/z* 275 of compounds (II), (III), and (V) in a mixture to be determined. Here, in contrast to the synoptic spectra, the contribution made by possible products of more far-reaching pyrolytic decomposition of the methiodide (I) with molecular masses <275 a.m.u. is excluded. Nevertheless, no appreciable temperature dependence was detected in the spectra of (II), (III), and (V), which excluded the formation of pyrolysis products with smaller molecular masses.

Let us recall the most characteristic processes in the fragmentation of the isomers (the relative intensities of the main peaks are given in Table 2): alternative methods of eliminating the α-substituent from the dihydrofuran ring with the predominant formation of ions having *m/z* 200 and 201 [dubinidine (II)]; together with the 100% peak of the ion with *m/z* 200 there is an increase in the contribution of the *m/z* 202 ion, and *m/z* 188, 189 ions of medium intensity arise [folisine (III)]; and aromatization or retrodiene decomposition of the dihydrofuran ring [isodubinidine (V)]. In spite of the appreciable difference between these spectra, the determination of qualitative composition of a mixture of isomers in the pyrolysis of (I) under conditions in which the main product is folisine [5], is extremely difficult, since contamination with dubinidine and isodubinidine can be detected mainly from the peaks of ions with *m/z* 202 (II) and 226 (V), which also occur in the spectrum of folisine (III).

The *B/E* spectra of the M^+ ions of the three isomers have few lines and possess clearly distinguishable individual features (Table 3). In accordance with this, in the *B/E* spectra of the *m/z* 275 ion from the methiodide (I) obtained at different temperatures the predominant formation of folisine (III) is easy to detect.

At the same time, the gradual increase in the ratio between the heights of the peaks of transitions to the ions with *m/z* 199 and 200 and a simultaneous decrease in the peaks of transitions to the ions with *m/z* 244, 243 show the presence of a small amount of dubinidine (II) at a low temperature. Contamination with a small amount of the iso compound (V) is indicated by an increase in the intensity at the peak of transition to the *m/z* 226 ion in one of the spectra (Table 3).

To check the presence of dubinidine as one of the products of the pyrolytic decomposition of (I), we considered the EI spectra of its N—CD_3 analogue [D_3-(I)]. We first obtained the secondary-ion spectrum of this compound, which, together with the peak of the $(M - I)^+$ ion, *m/z* 293, contained the peak of an ion with *m/z* 296 (height ratio 15:1). The synoptic EI spectra of [D_3-(I)] were recorded at various temperatures of the inlet system. In both cases the peaks of ions the mass numbers of which were shifted by +3 m.u. in relation to the spectrum of substance (I) (*m/z* 278, 247, 229, 217, 205, 203, 192, 191, 179, 178) were more intense. In addition to this, the peaks of the nondeuterated bases were observed in the spectrum, their relative heights decreasing with a rise in the temperature. In order to elucidate the origin of the components of the mixture, we obtained the *B/E* spectra of the *m/z* 278 and 275 ions at various temperatures (Table 3). The *B/E* spectrum of the *m/z* 278 ion coincided almost completely with the *B/E* spectrum of the M^+ ion of folisine; however, the peaks of all the metastable ions were shifted by +3 m.u., in agreement with the presence of the CD_3 group.

The spectra of the *m/z* 275 ion unexpectedly revealed peaks of transitions to ions with shifted mass numbers — *m/z* 217, 202, 191, 179. This means that the bulk of the *m/z* 275 ions corresponds to $(M - 3H)^+$ ions of N—CD_3-folisine formed by the loss of hydrogen atoms from the side chain of the dihydrofuran ring. In the low-temperature spectrum of the *m/z* 275 ion, likewise, a transition to a *m/z* 200 ion is observed, which indicates the presence of a small amount of dubinidine. If this impurity is of pyrolytic origin, on its formation the [D_3-(I)] molecule loses CD_3I. On analyzing the region of the spectrum where the ions of methyl iodide appear, we were unable to detect the peaks of CD_3I^+ ions with *m/z* 145, but only the peaks of ions with *m/z* 142 (CH_3I^+). This is unambiguous evidence in favor of an incompleteness of the (II) → [D_3-(I)] (I) transition when the latter is obtained in a reaction with CD_3I (CH_3I). However, no contaminating initial compound is recorded in an analysis of PMR spectra.

In addition to this, we performed an experiment on the pyrolytic decomposition of dubinine D_3-methiodide [D_3-(VI)] in the regime of an EI source. With a rise in the temperature we recorded no appreciable differences whatever either in the synoptic spectra or in the *B/E* spectra of the *m/z* 320 ion (Table 3). These facts indicate a 100% formation of (VII). There were no indications of the presence of contamination with dubinine (transition to a daughter ion with *m/z* 200).

Thus, the dequaternization of the methiodides of dubinidine and related bases in pyridine solution and on pyrolysis takes place predominantly through the splitting out of CH_3 from the methoxy group and only to a slight extent from the methylimide group. Dequaternization through the elimination of a methyl group from the nitrogen atom has been observed in the polymethylenequinazolone series [8].

EXPERIMENTAL

MKh-1310 mass spectrometer. IÉ 24 ion source, SVP5 direct introduction of the specimen, temperature of the ionization chamber 80-180°C, temperature of the evaporator bulb 120-220°C, ionizing voltage 70 V, collector current 60 μA. For the conditions of obtaining the *B/E* = const. spectra, see [9]. IAP RAN [Institute of Agrochemistry and Soil Science of the Russian Academy of Sciences] secondary-ion source, energy of the accelerated Cs^+ ions 7 keV, glycerol matrix.

PMR spectra were obtained on a BS-567 A 100 MHz instrument with the participation of M. G. Levkovich (δ scale, 0 — HMDS).

Chromatographic monitoring was performed by TLC (LSL 5/40 alumina, neutral, and Silufol) in the solvent systems ethyl acetate—methanol (3:1 and 2:1).

Dubinidine Methiodide (I). A mixture of dubinidine and methyl iodide (2 ml) in methanol (15 ml) was heated in the water bath for 10 h. On cooling, the solution deposited crystals which were crystallized three times from methanol. mp 155-156°C.

The formation of (III) from (I) by heating in anhydrous pyridine and by pyrolysis has been described in [5], and that of (V) by boiling (I) in a methanolic solution of alkali in [6].

Compound (IV) was obtained by treating (I) (0.3 g) with 7% aqueous ammonia solution at room temperature. After a day, the solution was acidified and was extracted with chloroform. Distillation of the chloroform yielded a semicrystalline mass from which the crystals (0.1 g) were separated by treatment with acetone. mp 131-132°C (from acetone). Soluble in chloroform, sparingly soluble in methanol and acetone, insoluble in ether.

EI mass spectrum (*m/z*, %): 289 [$(M - H_2O)^+$, 2], 276 (5), 271 (4), 258 (5), 232 (100), 216 (10), 203 (30), 202 (25), 188 (28), 172 (10).

Secondary-ion mass spectrum (*m/z*): 615 $(2M + H)^+$, 308 $(M + H)^+$, 232, 216, 202, 188, 172.

PMR spectrum ($CDCl_3$): 1.16 (3H, s, C—CH_3), 2.63-4.00 (unresolved multiplets), Ar—CH_2, CH—OH, CH_2OH), 3.69, 3.94 (s, 3H each, N—CH_3, OCH_3), 5.04 (s, 1H, OH), 7.17-7.62 (3H, m, 3H—Ar), 7.89 (1H, dd, J = 3.9 Hz, H-5).

Production of Isodubinidine (V) from (IV). A mixture of 0.05 g of substance (IV), 0.5 g of caustic potash, and 3 ml of methanol was heated in the water bath for 2 h. Then the solvent was evaporated off to dryness, and the residue was treated with 3 ml of water and was extracted with ether. The concentrated ethereal solution deposited crystals with mp 215°C (from methanol) which were shown to be identical with a specimen of isodubinidine (V) (TLC, mixed melting point, IR spectra).

Conversion of (I) into Folisine (III) and Dubinidine (I). A mixture of 0.1 g of dubinidine methiodide and 1 ml of pyridine was left to stand at room temperature. After 8 days, crystals (0.06 g) of (II) had deposited, with mp 233-234°C (from methanol), and these were shown to be identical with a specimen of folisine (TLC, mixed melting point, IR spectra). By chromatography on alumina, the mother liquor yielded dubinidine, mp 126-127°C (from chloroform eluates) and folisine (from chloroform—methanol eluates).

Preparation of Dubinine Methiodide (VI). A mixture of 0.1 g of dubinine and 2 ml of methanol was boiled with 1 ml of methyl iodide for 6 h. The dubinine methiodide that precipitated on the cooling of the solution was crystallized from a mixture of ethyl acetate and methanol, mp 165-166°C.

The deuterated methiodides of dubinidine [D_3-(I)] and of dubinine [D_3-(VI)] were obtained similarly from dubinidine and dubinine by the corresponding reactions with deuterated methyl iodide in deuteromethanol.

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