SOME PAPAVERINE DERIVATIVES

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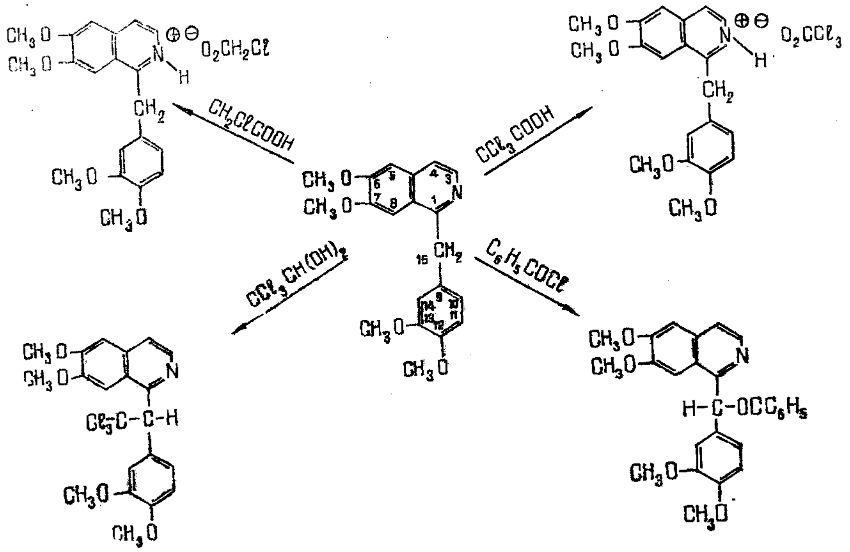
Heating papaverine with chloral hydrate and benzoyl chloride formed products of the replacement of the hydrogen at the 15-C atom of papaverine: 15-(β-trichloro-α-hydroxyethyl)papaverine and 15-benzoylpapaverine. In reactions with monochloro- and trichloroacetic acids under mild conditions in the cold, salts at the nitrogen atom were formed: the monochloroacetate and the trichloroacetate. The products were characterized by the results of TLC (type KSK silica gel fixed with gypsum), elementary analyses, and IR and PMR spectroscopy.

A series of compounds containing an isoquinoline nucleus is known which exhibits hypotensive and spasmolytic activity [1-5]. Such compounds include the alkaloid papaverine. In order to obtain new derivatives of papaverine (I) possibly possessing physiological activity, we have performed reactions of papaverine with monochloro- and trichloroacetic acids, with chloral hydrate, and with benzoyl chloride.



Analysis of the reaction products showed that, depending on the chlorine-containing agent, papaverine gives two different classes of compounds. In the reaction with the acids under mild conditions in the cold, salts are formed: papaverine monochloroacetate (II) and papaverine trichloroacetate (III).

Compounds (II) and (III) have the low chromatographic mobility that is characteristic for salts (Table 1). The PMR spectra of these compounds (Table 2) contain the signals of all the protons present in papaverine and the acid concerned, but the signals of the protons of the isoquinoline ring are shifted downfield in comparison with the initial papaverine because of the formation of a positive charge on the nitrogen atom. It was shown by special experiments that no breakdown of the monochloroacetate and trichloroacetate radicals took place during the reaction, since the salts formed did not give a positive reaction for the chloride ion with silver nitrate.

The reactions of papaverine with chloral hydrate and with benzoyl chloride took place under more severe conditions — on heating in chloroform. The reaction products had chromat-

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TABLE 1. Papaverine Derivatives

Compound	Yield %	Rf in system		mp, °C	Found, %			Empirical formula	Calculated, %		
		1	2		C	H	N		C	H	N
II. Papaverine monochloroacetate	75,6	0,71	0,53	125—128	60,78	4.94	3.85	$C_{22}H_{24}NO_6Cl$	60.80	5.33	3,21
III. Papaverine trichloroacetate	55,6	0,55	0.48	110—112	53,92	4,83	3,01	$C_{22}H_{22}NO_6Cl$	53,49	4,37	2,76
VI. 15-(β-Trichloro-α-hydroxyethyl)-papaverine	75,0	0,80	0,83	162—163	54,31	4,76	3,04	$C_{22}H_{22}NO_5Cl_3$	54,32	4,53	2,89
V. 15-Benzoylpapaverine	70,77	0,86	0,89	83( )	72,96	5,65	3,12	$C_{27}H_{25}NO_5$	73,13	5 64	3,16

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*Systems: 1) methyl acetate—ethanol (9:1). R_f for papaverine 0.68; 2) butan-1-ol—water—acetic acid (4:1:5); R_f for papaverine 0.46.

TABLE 2. Characteristics of the PMR Spectra of Papaverine and Its Derivatives

Compound	O-CH_3	$C_{15}H$	C_3H	C_4H	C_5H	C_8H	$C_{14}H$	$C_{11}H$	$C_{10}H$	Other protons*
I. Papaverine base	3,66 (3H) 3,71 (3H) 3,80 (3H) 3,88 (3H)	4,43 (2H)	7 68	7,62	7,35	7,1	6,70	6,58	6,77	
II. Papaverine monochloroacetate	3,70 (3H) 3,84 (3H) 3.90 (3H) 3,94 (3H)	4,60 (2H)	8,34	7,85	7,34	7,04	6,80	6.68	6,68	4,03 (2H)
III. Papaverine trichloroacetate	3,71 (3H) 3,73 (3H) 3,91 (3H) 4,00 (3H)	4,74 (2H)	8,44	7,79	7 47	7,14	6,95	6,69	6 75	
IV. 15-(β-Trichloro-α-hydroxyethyl)papaverine	3,72 (3H) 3,75 (3H) 3,89 (3H) 3,92 (3H)	5.69 (1H)	7,81	7,38	7,32	6,96	7,07	6,71	7,00	5,50 (1H)
V. 15-Benzoylpapaverine	3,45 (3H) 3,50 (3H) 3,76 (3H)	5,40 (1H)	7,90	7.60	7,35	7,10	6,90	6,65	6,62	7,20 (5H)

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*CH_2Cl in (II), $CH—CCl_3$ in (IV), C_6H_6 in (V).

ographic mobilities higher than those of the salts (II) and (III) (Table 1). The IR spectrum of 15-(β-trichloro-α-hydroxyethyl)papaverine (IV) contained the absorption bands of an OH group at 3440 cm^{-1}, of an OCH_3 group at 2838 cm^{-1}, of aromatic nuclei at 1620 and 1515 cm^{-1}, and of C—Cl bonds at 797 cm^{-1}. The mass of the molecular ion found mass-spectrometrically, m/z 486 corresponds to the composition $C_{22}H_{22}NO_5Cl_3$.

The PMR spectrum of 15-(β-trichloro-α-hydroxyethyl)papaverine (IV) and of 15-benzoylpapaverine (V) (Table 2) differed appreciably from the spectra of (II) and (III). In the PMR spectra of (IV) and (V) the positions of the signals of the protons of the isoquinoline ring had not changed as compared with papaverine and, consequently, the reaction had not taken place at the nitrogen atom. At the same time, the intensities and chemical shifts of the signals of the protons of the $C_{(15)}H_2$ group had changed sharply. In place of a two-proton intensity the signal now corresponded to one proton and had shifted sharply downfield, and in 15-(β-trichloro-α-hydroxyethyl)papaverine (IV) the signal was split into a doublet with a constant $J = 11$ Hz. In the PMR spectrum of 15-(β-trichloro-α-hydroxyethyl)-papaverine (IV) taken in acetone, a broadened signal of a hydroxylic proton was observed. These facts showed that in the reaction of papaverine with chloral hydrate and with benzoyl chloride it was not quaternary ammonium salts that were formed but the products of the replacement of the hydrogen at the 15-C atom in papaverine.

EXPERIMENTAL

PMR spectra were taken on a Varian HA-100 instrument in $CDCl_3$ and a Varian HA-60 instrument in $CDCl_3$ and CDCO* with HMDS as internal standard, the chemical shifts being given in the δ scale. IR spectra were taken on a UR-10 instrument (in KBr tablets), and mass spectra on a MKh-1303 mass spectrometer. The purity of the products was checked by TLC (type KSK silica gel fixed with gypsum) using as the mobile phases ethyl acetate—ethanol (9:1) (system 1) and butan-1-ol—water—acetic acid (4:1:5) (system 2). The spots were revealed with the Dragendorff reagent.

15-(β-Trichloro-α-hydroxyethyl)papaverine (IV). With heating, solution of 20 g (0.21 mole) of chloral hydrate in 30 ml of anhydrous chloroform was added to a solution of 10 g (0.0295 mole) of papaverine base (I) in 50 ml of anhydrous chloroform. The reaction mixture became yellow. Heating was continued for 30 min, and the reaction mixture was treated with water to eliminate unchanged chloral hydrate and was then dried with Na_2SO_4. The chloroform was distilled off from the dried solution in a rotary evaporator. The oily product that appeared was dissolved in ethyl acetate and separated on a column containing type KSK silica gel. The reaction product was eluted with ethyl acetate, and the solvent was distilled off in the rotary evaporator. The purified product was recrystallized from diethyl ether and was dried in vacuum over $CaCl_2$. Compounds (II) and (III) were obtained similarly at room temperature in ethyl acetate. Compound (IV) was obtained by heating papaverine with benzoyl chloride at 70°C for 30 min. The products were isolated by the method described.

SUMMARY

1. The reaction of papaverine with chloral hydrate and with benzoyl chloride leads to products of the replacement of hydrogen at the 15-C atom of papaverine.

2. The reaction of papaverine with monochloroacetic and trichloroacetic acids forms not substitution products but salts at the nitrogen atom.

LITERATURE CITED

1. S. S. Liberman and L. N. Yakhontov, Zh. Vses. Khim. Ova. D. I. Mendeleeva, 6, 616 (1965).
2. A. K. Tokarev, Author's Abstract of Candidate's Dissertation, Donetsk (1971).
3. A. A. Mndzhayan, L. Sh. Pirdzhanov, and M. T. Bkhiyan, Arm. Khim. Zh., 24, No. 11, 995 (1971).
4. French Patent Application, cl. A 61 K 27/00 No. 2,197,685.
5. British Patent Application, cl. A. 61 K 27/00, No. 1,417,542.

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*As in Russian original — Publisher.