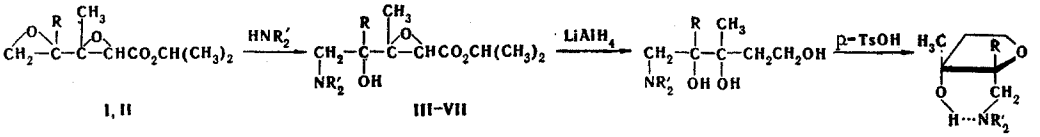
SYNTHESIS OF 2-DIALKYLAMINOMETHYLTETRAHYDROFURAN-3-OLS

L. S. Stanishevskii, I. G. Tishchenko,
V. I. Tyvorskii, L. A. Khil'manovich,
A. S. Zakharevskii, and A. V. Miklevich

UDC 547.723'722.6.07:542.942.4

The reaction of esters of 4-R-3-methyl-2,3,4,5-diepoxyvaleric acids with secondary amines leads to the formation of esters of 4-R-5-dialkylamino-4-hydroxy-3-methyl-2,3-epoxyvaleric acids. The reduction of the latter with lithium tetrahydroaluminate and the cyclization of the reduction products in the presence of p-toluenesulfonic acid has given 2-dialkylaminoethyltetrahydrofuran-3-ols, the methiodides of which possess ganglion-blocking activity.

We have previously obtained a number of esters of methyl-substituted 2,3,4,5-diepoxycarboxylic acids [1]. In order to study their reactivity and also to synthesize compounds of the 2-aminoethyltetrahydrofuran series, which possess valuable pharmacological properties [2], we have performed the conversion of the isopropyl esters of 4-R-3-methyl-2,3,4,5-diepoxyvaleric acids (I, II) into 2-dialkylaminoethyltetrahydrofuran-3-ols (XIII-XVII) by the following route:



R=H or CH_3; NR'_2=$N(CH_3)_2$, $N(C_2H_5)_2$, NC_5H_{10} or NC_4H_8O

The reaction of isopropyl 3,4-dimethyl-2,3,4,5-diepoxyvalerate and 3-methyl-2,3,4,5-diepoxyvalerate (I and II, respectively) with secondary amines takes place with the opening of the 4,5-epoxide ring and the formation of isopropyl 4-R-5-dialkylamino-4-hydroxy-3-methyl-2,3-epoxyvalerates (III-VII), as was confirmed by the results of a determination of active hydrogen and by IR and PMR spectra. In the IR spectra of (III-VII) the band of hydroxy absorption is found in the 3410-3430 cm^{-1} region; it does not change its position when the solution is diluted to a concentration of 10^{-3} M, and it characterizes the presence of an intramolecular hydrogen bond with the nitrogen atom [3]. There is also an absorption band at 850-860 cm^{-1} relating to the α-oxide ring, and a doublet of absorption bands of an ester carbonyl at 1735-1740 and 1755-1760 cm^{-1}, which is characteristic for esters of glycidic acids [4, 5]. The absence of the weak absorption band of a methylene group of an α-oxide ring which appears in the IR spectra of the initial diepoxides (I, II) in the 3045 cm^{-1} definitely shows the opening of the 4,5-epoxide ring. The PMR spectrum of (III, R = CH_3) shows the singlets of the protons of the 3- and 4-CH_3 groups at 1.14 and 1.26 ppm (on the δ scale) and of the dimethylamino grouping at 2.36 ppm, two doublets with centers at 1.26 and 1.29 ppm, and a quintet with its maximum at 5.02 ppm and a spin–spin coupling constant of 7 Hz, which corresponds to the protons of the methyl and methine groups of an isopropyl radical, a quadruplet of the protons of a methylene group with its center at 2.44 ppm and a spin–spin coupling constant of 14 Hz, and the singlets of the 2-H and hydroxyl protons at 3.46 and 3.60 ppm, respectively. The assignment of the signals of the latter two protons was made on the basis of a comparison of the PMR spectra of (III) and its acetate.

The reduction of compounds (III-VII) with lithium tetrahydroaluminate led to the formation of the 4-R-5-dialkylamino-3-methylpentane-1,3,4-triols (VIII-XII), which, according to the results of oxidation with

V. I. Lenin Belorussian State University, Minsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1443-1446, November, 1973. Original article submitted December 29, 1972.

TABLE 1. Characteristics of the Compounds Obtained

Compound	R	NR′₂	mp, bp (pressure, mm), °C	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Empirical formula	Found, % N	Found, % OH	Calc., % N	Calc., % OH	Yield, %	Hydrochlorides and methiodides: mp, °C	empirical formula	halogen, % found	halogen, % calc.
III	CH_3	$N(CH_3)_2$	129 (1)	1,0205	1,4480	64,45	64,88	$C_{12}H_{23}NO_4$	5,72	6,46	5,44	6,94	43	149	$C_{12}H_{24}NO_4Cl$	12,89	12,61
IV	CH_3	$N(C_2H_5)_2$	119 (1,5)	0,9918	1,4497	73,75	74,12	$C_{16}H_{27}NO_4$	5,27	6,13	5,12	6,22	38	102	$C_{16}H_{28}NO_4Cl$	11,72	11,48
V	CH_3	NC_5H_{10}	26—27					$C_{15}H_{27}NO_4$	4,98	5,87	4,92	5,96	67	156	$C_{15}H_{28}NO_4Cl$	11,12	11,03
VI	CH_3	NC_4H_8O	153 (1,5)	1,0955	1,4695	72,90	73,57	$C_{14}H_{25}NO_5$	4,60	6,28	4,87	5,92	78	165	$C_{14}H_{26}NO_5Cl$	11,20	10,98
VII	H	NC_5H_{10}	45					$C_{14}H_{25}NO_4$	5,02	6,46	5,17	6,27	62	141	$C_{14}H_{26}NO_4Cl$	11,35	11,61
VIII	CH_3	$N(CH_3)_2$	114—116 (1,5)	1,0549	1,4755	52,05	52,28	$C_9H_{21}NO_3$	7,24	26,68	7,33	26,73	89	105	$C_9H_{22}NO_3Cl$	15,31	15,60
IX	CH_3	$N(C_2H_5)_2$	131—132 (1,5)	1,0135	1,4752	60,85	61,51	$C_{11}H_{25}NO_3$	6,86	24,31	6,69	23,30	91	oil	$C_{11}H_{26}NO_3Cl$	14,42	14,46
X	CH_3	NC_5H_{10}	147—148 (1)	1,0690	1,4947	62,80	63,39	$C_{12}H_{25}NO_3$	6,13	22,79	6,07	22,10	75	135	$C_{12}H_{26}NO_3Cl$	13,38	13,29
XI	CH_3	NC_4H_8O	68					$C_{11}H_{23}NO_4$	6,14	20,87	6,01	21,95	92	122	$C_{11}H_{24}NO_4Cl$	13,51	13,17
XII	H	NC_5H_{10}	162 (2)	1,0693	1,4955	59,63	59,31	$C_{11}H_{23}NO_3$	6,50	23,26	6,44	23,48	77	141	$C_{11}H_{24}NO_3Cl$	14,56	14,40
XIII	CH_3	$N(CH_3)_2$	95 (17)	0,9640	1,4514	48,15	48,67	$C_9H_{19}NO_2$	8,28	9,51	8,08	9,81	61	169	$C_{10}H_{22}NO_2I$	40,61	40,27
XIV	CH_3	$N(C_2H_5)_2$	69 (2)	0,9429	1,4539	57,52	57,91	$C_{11}H_{23}NO_2$	7,12	8,49	6,96	8,54	58	78	$C_{12}H_{26}NO_2I$	37,25	37,03
XV	CH_3	NC_5H_{10}	89 (2)	1,0006	1,4766	60,50	60,32	$C_{12}H_{23}NO_2$	6,26	7,13	6,57	7,97	78	122	$C_{13}H_{26}NO_2I$	35,63	35,80
XVI	CH_3	NC_4H_8O	98 (2)	1,0760	1,4783	56,68	57,23	$C_{11}H_{21}NO_3$	6,40	7,30	6,51	7,90	50	144	$C_{12}H_{24}NO_3I$	35,98	35,53
XVII	H	NC_5H_{10}	92 (2)	1,0130	1,4812	55,80	55,71	$C_{11}H_{21}NO_2$	6,95	8,15	7,03	8,55	61	115	$C_{12}H_{24}NO_2I$	37,88	37,24

periodic acid, contain a vicinal glycol grouping and do not form formaldehyde on oxidation. The absence of formaldehyde from the products of periodic acid oxidation shows the opening of the 2,3-epoxide ring in (III-VII) from the side of the α-carbon atom, as is the case for β,β-disubstituted glycidic esters [6].

When compounds (VIII-XII) were heated with p-toluenesulfonic acid, the 2-dialkylaminomethyltetrahydrofuran-3-ols (XIII-XVII) were obtained; their IR spectra are characterized by strong absorption bands due to the antisymmetrical stretching vibrations of the C–O–C group (1030-1080 cm^{-1}) and the symmetrical (870-950 cm^{-1}) and antisymmetrical (1145-1210 cm^{-1}) vibrations of a ring, which, as has been established [7], are extremely characteristic for tetrahydrofurans, and by the band of hydroxyl absorption at 3150-3430 cm^{-1}. When the IR spectra of (XIII-XVII) were taken in a liquid film, the band of the hydroxyl absorption had two maxima, at 3390-3430 and 3150-3180 cm^{-1}. For 0.1 M solutions of (XIII-XVII) in CCl_4 there is no high-frequency maximum corresponding to the formation of an intermolecular hydrogen band [3], but the absorption band of a free hydroxy group does not appear. The low-frequency maximum does not change its position when the solution is diluted to a concentration of 10^{-3} M and characterizes the existence of an intramolecular hydrogen bond with the nitrogen atom [3] because of the cis arrangement of the hydroxy and dialkylaminomethyl groups. These facts show that in this case the formation of the ring is a stereospecific reaction. In the PMR spectrum of (XIII) there are singlets of the protons of the 2-CH_3, 3-CH_3, and dimethylamino groupings at 0.87, 1.15, and 2.33 ppm, respectively, a quadruplet of the protons of a methylene group with its center at 2.50 ppm and a spin–spin coupling constant of 14 Hz, multiplets with maxima at 1.87 and 3.81 ppm and widths of 22 and 40 Hz corresponding to the protons of the 4- and 5-CH_2 groups of the tetrahydrofuran ring, and the broadened singlet of the proton of the hydroxy group at 7.23 ppm. The characteristics of compounds (III-XVII) are given in Table 1.

We have obtained the methiodides of the 2-dialkylaminomethyltetrahydrofuran-3-ols (XIII-XVII) and have studied their toxicity and their influence on the cardiovascular system. An investigation of acute toxicity on white mice with intraperitoneal administration showed that the methiodides of 2-dimethylaminomethyl-2,3-dimethyl-, 2,3-dimethyl-2-piperidinomethyl-, and 2-diethylaminomethyl-2,3-dimethyltetrahydrofuran-3-ols (XIII-XV) differ appreciably in their toxicity indices: their LD_{50} values vary between 230 and 720 mg/kg. In experiments on cats, it was established that the above-mentioned methiodides, on intravenous administration in doses corresponding to 5 and 10% of the LD_{50} doses for white mice, exhibit a ganglion-blocking action. The duration of the disturbance of conductivity in the parasympathetic ganglions amounted to from 20 to 70 minutes, and in the sympathetic ganglions from 7 to 12 minutes. The capacity for blocking the parasympathetic ganglions was well-defined for the methiodide of (XIV), while with respect to the depressing action on the sympathetic ganglions the compounds investigated differed only slightly from one another. The results of a study of the physiological activity of all the amino alcohols synthesized (III-XVII) will be given in a separate communication.

EXPERIMENTAL

The IR spectra (in a film or in solution in CCl_4) were measured on a UR-20 infrared spectrophotometer in the 400-3700 cm^{-1} region. The PMR spectra of 10% solutions in CCl_4 were obtained on a Varian HA-100D-15 spectrometer with TMS as internal standard.

Isopropyl 3,4-dimethyl-2,3,4,5-diepoxyvalerate (I) and 3-methyl-2,3,4,5-diepoxyvalerate (II) were obtained as described previously [1] and had the following physicochemical constants: (I) bp 85-86°C (2 mm); d_4^{20} 1.0596; n_D^{20} 1.4403; (II) bp 95-97°C (3 mm); d_4^{20} 1.0863; n_D^{20} 1.4430.

Isopropyl 4-R-5-Dialkylamino-4-hydroxy-3-methyl-2,3-epoxyvalerates (III-VII). A solution of 0.15 mole of (I) or (II) and 0.15 mole of a secondary amine in 100 ml of isopropanol was kept at 18-20°C for 4-6 days. Then the solvent was distilled off, the residue was dissolved in 400 ml of absolute ether, and the solution was treated with a current of dry hydrogen chloride until a weakly acid reaction had been obtained. The precipitate of hydrochloride was separated off and crystallized from a mixture of acetone and isopropanol. Compounds (III-VII) were isolated by treating aqueous solutions of their hydrochlorides with a small excess of caustic potash and extracting with ether. The ethereal extracts were dried with anhydrous magnesium sulfate and, after the elimination of the ether, the residues were fractionated under reduced pressure. Compounds (V) and (VII) were crystallized from pentane.

4-R-5-Dialkylamino-3-methylpentane-1,3,4-triols (VIII-XII). With stirring, a solution of 0.1 mole of a compound (III-VII) in 100 ml of absolute tetrahydrofuran was added by drops to a suspension of 0.3 mole of lithium tetrahydroaluminate in 700 ml of absolute tetrahydrofuran. The reaction mixture was boiled for 1 h and was stirred at 18-20°C for 3 h, and the excess of lithium tetrahydroaluminate was decomposed as

described by the Fiesers [8]. The precipitate of hydroxides was separated off, the tetrahydrofuran was distilled off, the residue was dissolved in 200 ml of absolute ether, and a current of dry hydrogen chloride was passed into the solution until it had acquired a feebly acid reaction. The hydrochloride was separated off and recrystallized from a mixture of methyl ethyl ketone and isopropanol. Compounds (VIII-XII) were isolated by treating methanolic solutions of their hydrochlorides with methanolic solutions of equivalent amounts of caustic potash, separating off the precipitate of KCl, evaporating off the methanol, and distilling the residues under reduced pressure. Compound (XI) was crystallized from ether.

2-R-2-Dialkylaminomethyl-3-methyltetrahydrofuran-3-ols (XIII-XVII). A mixture of 0.10 mole of a compound (VII-XII) and 0.11 mole of p-toluenesulfonic acid was heated in the boiling-water bath for 1 h and was then treated with a solution of 0.12 mole of caustic potash in 50 ml of water. The reaction product was extracted with ether, and the combined ethereal extracts were dried with anhydrous magnesium sulfate, the ether was evaporated off, and the residue was distilled under reduced pressure. The methiodides of (XIII-XVII) were obtained by keeping a solution of 0.010 mole of a compound (XIII-XVII) and 0.015 mole of methyl iodide in 2 ml of isopropanol for 5-7 days. After the elimination of the ethanol, the residue was crystallized from a mixture of acetone and isopropanol.

LITERATURE CITED

1. L. S. Stanishevskii, I. G. Tishchenko, and V. I. Tyvorskii, Vestn. Belorusskogo Un-ta, Ser. II, No. 2, 70 (1971).
2. P. G. Waser, Pharmacol. Rev., 13, 465 (1961).
3. V. P. Gaidaenko, N. M. Ginzburg, and D. V. Ioffe, Optika i Spektroskopiya, 27, 620 (1969).
4. H. H. Morris and R. H. Young, J. Amer. Chem. Soc., 79, 3408 (1957).
5. H. O. House and J. W. Blaker, J. Amer. Chem. Soc., 80, 6389 (1958).
6. H. M. Walborsky and C. Colombini, J. Org. Chem., 27, 2387 (1962).
7. A. P. Kilimov, M. A. Svechnikova, V. I. Shevchenko, V. V. Smirnov, F. V. Kvasnyuk-Mudryi, and S. B. Zotov, Khim. Geterotskikl. Soedin., 579 (1967).
8. L. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. II, Wiley (1969).