SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF 4-(γ-AMINO-β-HYDROXYPROPYL) ETHERS OF THE TETRAHYDROPYRAN AND TETRAHYDROTHIOPYRAN SERIES

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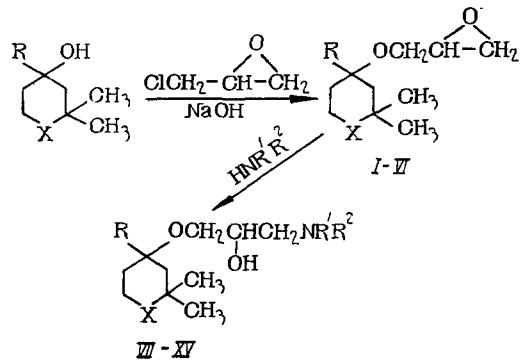
A large number of γ-amino-β-hydroxypropyl ethers of various structure which exert a β-adrenolytic action are known in the literature [1-3]. In the present work we have synthesized analogs of these aminohydroxy ethers which contain oxygen or sulfur in a six-membered ring, and have studied their β-adrenolytic properties.

The 2,2-dimethyl-4-alkyl(or aryl)-4-(β,γ-epoxypropyl) ethers of tetrahydropyranol and tetrahydrothiopyranol were prepared by the reaction of 2,2-dimethyl-4-alkyl(or aryl)-4-tetrahydropyranols or their sulfur-containing analogs with epichlorohydrin in an aqueous caustic alkali solution. These compounds form 2,2-dimethyl-4-alkyl(or aryl)-4-(γ-amino-β-hydroxypropyl) ethers of tetrahydropyranols or tetrahydrothiopyranols on reaction with secondary or primary amines, in accorance with the scheme:



I: R = H, X = O; II: R = C_2H_5, X = O; III: R = CH_2=CHC≡C, X = O; IV: R = C_6H_5, X = O; V: R = o-CH_3—C_6H_4, X = O; VI: R = H, X = S; VII: R = H, R^1 = H, R^2 = iso-C_3H_7, X = O; VIII: R = C_2H_5, X = O, R^1 = H, R^2 = iso-C_3H_7; IX: R = CH_2=CHC≡C, X = O, R^1 = H, R^2 = iso-C_3H_7; X: R = C_6H_5, X = O, R^1 = R^2 = C_2H_5; XI: R = C_6H_5, X = O, R^1 and R^2 = morpholyl; XII: R = C_6H_5, X = O, R^1 = H, R^2 = cyclohexyl; XIII: R = C_6H_5, X = O, R^1 and R^2 = pentamethylene XIV: R = o-CH_3—C_6H_4, X = O, R^1 = H, R^2 = iso-C_3H_7; XV: R = H, X = S, R^1 = H, R^2 = iso-C_3H_7.

The individuality of the aminoalcohols synthesized, VII-XV, was checked with the aid of thin-layer chromatography (TLC), which was performed on an unbonded layer of aluminum oxide of grade II activity, in the system ethyl acetate—acetone (2:7). Development was with iodine vapor. The structures of both the intermediate (I-V) and the final (VII-XV) products was confirmed by elemental analyses and IR spectroscopy. In the IR spectrum of the aminoalcohols (VII-XV) characteristic absorption bands were detected for the ether group (1050 cm^{-1}), the hydroxyl group (3400 cm^{-1}), and a C—O vibration (1100 cm^{-1}) which is inherent in secondary alcohols.

EXPERIMENTAL

Pharmacological

The β-adrenoblocking and hypotensive action of the preparations was studied in experi-

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ments on Nembutal-narcotized (50 mg/kg) rats by the procedure previously described [4].

The effect of the preparations on the β_1 adrenoreceptors of the heart and the β_2 adrenoreceptors of the blood vessels was judged from their blocking effect on the positive chronotropic and depressor effect of isadrin (0.5 μg/kg). The preparations tested were administered intravenously in a dose of 5 mg/kg (in this dose the well-known β_1 adrenoblockers propranolol and pronethalol manifested a definite β-adrenoblocking action under similar experimental conditions).

Experiments showed that the tetrahydropyran derivatives do not exert a marked effect on the frequency of the heartrate or arterial pressure in rats, nor on the positive chronotropic and depressor effects of isadrin. In distinction from them, the 2,2-dimethyl-4-(γ-isopropylamino-β-hydroxypropyl) ether of tetrahydrothiopyranol (XV) displays considerable β-adrenoblocking activity. In its strength of blocking action on the β adrenoreceptors of the heart and blood vessels, this preparation does not differ greatly from practolol (Tables 1 and 2), but is inferior to propranolol, especially in ability to eliminate the depressor effect of isadrin. Although this preparation, like propanolol, causes considerable reduction in arterial pressure, this action is accompanied by a speed-up in heart rate, which indicates the inadvisability of further detailed investigation of preparation XV as a promising β-adrenoblocking substance. It is interesting that the analog of preparation XV which contains oxygen in the heterocyclic system instead of sulfur (preparation VII) is devoid of β-adrenoblocking properties. Therefore it may be assumed that searches for β adrenoblockers should advisably the continued among the tetrahydrothiopyran derivatives.

Chemical

The compounds 2,2-dimethyl-4-ethyl-4-tetrahydropyranol [5], 2,2-dimethyl-4-vinylethynyl-4-tetrahydropyranol, 2,2-dimethyl-4-phenyl-4-tetrahydropyranol [6], and 2,2-dimethyl-4-tetrahydropyranone were synthesized by well-known methods.

2,2-Dimethyl-4-tetrahydropyranol. A mixture of 56.32 g (0.44 mole) of 2,2-dimethyl-4-tetrahydropyranone and 150 ml of methanol was cooled to 0°C; then, over a 1-h period, 8.4 g (0.22 mole) of sodium borohydride was added in portions, not allowing the temperature to rise. Water (150 ml) was added with stirring, plus a few drops of a concentrated sodium hydroxide solution, and the mixture was boiled for 2 h. The mixture was acidified with concentrated sulfuric acid, and the methanol was removed at reduced pressure. The residue was neutralized with a 40% sodium hydroxide solution to a weakly alkaline reaction, it was extracted with ether, and the extract was dried with magnesium sulfate. There was obtained 36.31 g (63.5%) of 2,2-dimethyl-4-tetrahydropyranol, bp 94-98°C (11 mm), n_D^{20} 1.4570, d_4^{20} 0.9812. MR_D 36.13; calculated, 35.49. Found, %: C 65.10; H 10.80. $C_7H_{14}O_2$. Calculated, %: C 64.58; H 10.84.

2,2-Dimethyl-4-tetrahydrothiopyranol was prepared by the method described above in 46.4% yield; bp 92-93°C (5 mm), n_D^{20} 1.4770, d_4^{20} 0.9976. MR_D 41.85; calculated, 41.85. Found, %: C 58.03; H 10.48; S 21.10. $C_7H_{14}O_2$. Calculated, %: C 57.56; H 9.65; S 21.93.

2,2-Dimethyl-4-o-tolyl-4-tetrahydropyranol. A Grignard reagent was prepared from 21.4 g (0.88 mole) of metallic magnesium and 150.5 g (0.88 mole) of o-bromotoluene in 100 ml of absolute ether. To this, with cooling in ice water, was added 56.39 g (0.44 mole) of 2,2-dimethyl-4-tetrahydropyranone. Further treatment was carried out in accordance with the prescription. There was obtained 44.5 g (46%) of 2,2-dimethyl-4-o-tolyl-4-tetrahydropyranol, bp 142-145°C (2 mm), n_D^{20} 1.5350, d_4^{20} 1.0557. MR_D 64.78; calculated, 64.22. Found, %: C 76.66; H 9.80. $C_{14}H_{20}O_2$. Calculated, %: C 76.32; H 9.15.

Reaction of 4-Tetrahydropyranols with Epichlorohydrin. To a mixture of 0.38 mole of the appropriate 4-tetrahydropyranol or its sulfur-containing analogs and 0.48 mole of sodium hydroxide in 220 ml of water was added 0.38 mole of epichlorohydrin, dropwise, thereupon the temperature of the mixture was maintained at a level of 20-22°C. The mixture was stirred for 20 h at 20°C. The product was extracted with ether, and the extract was dried with magnesium sulfate. The yields and constants of the epoxides obtained, I-VI, are given in Table 3.

Reaction of Epoxides I-VI with Amines. A mixture of 0.1 mole of the epoxide and the appropriate amine was boiled for 5-8 h.. After cooling, the mixture was acidified with hydrochloric acid and the neutral products were extracted with ether. The ether solution of amine salts was neutralized with potassium carbonate. The oily layer formed was extracted

TABLE 1. Action of Preparations on Frequency of Heart Rate and on Positive Chronotropic Effect of Isadrin in Narcotized Rats

Preparation	Number of animals	Frequency of heartbeats, number per min				Positive chronotropic effect of isadrin, % of control		
		control	time after administration of preparation, min					
			2	20	60	2	20	60
VII	3	445	464	464	469	72 (54÷90)	100,3 (31,5÷169,1)	73,7 (—0,2÷147,6)
VIII	3	454	468	415	429	98 (29,6÷166,4)	115,3 (36,5÷194,1)	136,8 (63,8÷209,8)
IX	3	454	479	461	470	138,3 (—44,4÷32,1)	142,2 (—37,5÷321,9)	120,2 (36,4÷204)
XIV	3	405	409	415	420	84,3 (69,3÷99,3)	114,1 (82,8÷145,4)	118,6 (67,6÷169,6)
XV	7	433	457	486	488	20 (—2÷42)	34 (—0,4÷68,4)	45,3 (0,3÷90,3)
X	3	410	398	379	403	84,5 (55,4÷113,8)	115,9 (45,5÷186,3)	121,9 (80,9÷162,9)
XIII	3	446	464	464	462	80 (9,5÷150,5)	104 (87,2÷120,8)	116,2 (42,5÷189,9)
XI	6	448	448	441	449	83,8 (49,9÷117,7)	81,5 (50,9÷112,1)	86,7 (38,4÷135)
XII	3	421	440	415	410	89,2 (43,7÷134,7)	117,6 (101,3÷133,9)	127,8 (49,4÷206,2)
Propranol	13	418	296	303	304	1,5 (1,3÷1,7)	46,1 (33,9÷58,3)	56,2 (41,3÷71,1)
Practolol	15	438	386	386	392	12 (8,2÷15,7)	63,9 (56,3÷71,5)	73,2 (59,3÷87,1)

Note. Here and in Table 2, limits of variation are indicated in parentheses.

TABLE 2. Action of Preparations on Arterial Pressure and on Depressor Effect of Isadrin in Narcotized Rats

Preparation	Number of animals	Arterial pressure, mm Hg				Depressor effect of isadrin, % of control		
		control	time after administration of preparation, min					
			2	20	60	2	20	60
VII	3	93	101	78	81	116 (97,3÷134,7)	86,8 (68,1÷105,5)	96,4 (49,4÷143,4)
VIII	3	101	103	77	68	117 (64,4÷169,4)	77,6 (15,3÷139,9)	70,7 (13,1÷128,3)
IX	3	93	75	78	80	78,1 (52,3÷103,9)	87,8 (62÷113,6)	85 (50,6÷119,4)
XIV	3	90	88	83	85	73,3 (14,3÷132,3)	64,8 (—5,2÷134,8)	78 (—11÷167)
XV	7	98	77	63	62	45 (21÷69)	40 (11,5÷68,5)	40 (10,7÷69,3)
X	3	90	90	76	95	111,2 (87,4÷135)	104,1 (80,1÷128,1)	97,1 (67,1÷127,1)
XIII	3	80	78	77	69	87,2 (46,8÷127,6)	78,7 (39,2÷118,2)	67,5 (—29÷164)
XI	6	100	100	78	68	104,5 (55,5÷153,5)	85 (48,8÷121,2)	80,3 (39,7÷120,9)
XII	3	94	94	92	88	97,3 (85,7÷108,9)	87,6 (69,5÷105,7)	103,2 (60,2÷146,2)
Propranolol	13	95	62	72	81	—7,2 (—5÷—9,4)	—12,2 (—10,5÷—13,9)	—10,8 (—8,4÷—13,2)
Practolol	15	95	84	82	82	58,6 (52,4÷64,8)	66,1 (57,2÷75)	70,6 (61,4÷79,8)

TABLE 3. 4-(β,γ-Epoxypropyl) Ethers of the Tetrahydropyran and Tetrahydrothiopyran Series

Compound	Yield, %	Bp, °C (pressure in mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	Found, % C	Found, % H	Empirical formula	Calc. % C	Calc. % H
I	32,6	125—30 (5)	1,0779	1,4760	48,74	48,91	63,56	9,80	$C_{10}H_{18}O_3$	64,48	9,74
II	31,9	109—11 (7)	1,0111	1,4690	59,03	58,15	67,82	10,66	$C_{12}H_{22}O_3$	67,25	10,25
III*	21,9	115—20 (3)	—	—	—	—	70,85	7,95	$C_{14}H_{20}O_3$	71,15	8,53
IV	46,9	105—10 (3)	1,1512	1,5530	72,91	72,02	73,46	8,50	$C_{16}H_{22}O_3$	73,25	8,45
V	37,6	132—4 (4)	1,1407	1,5400	76,04	77,63	73,03	9,05	$C_{17}H_{24}O_3$	73,88	8,75
VI*	18,5	79—81 (3)	1,0628	1,4860	54,38	54,17	60,26	8,07	$C_{10}H_{18}O_2$	59,36	8,96

*MP, 82-81°C.
†Found, %: S, 15.90. Calc., %: S, 15.84

TABLE 4. 4-(γ-Amino-β-hydroxypropyl) Ethers of the Tetrahydropyran and Tetrahydrothiopyran Series

Compound	Yield, %	Bp, °C (pressure in mm)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Found, % C	Found, % H	Found, % N	Empirical formula	Calc. % C	Calc. % H	Calc. % N	R_f	Mp of oxalate, °C
II	21,3	118—21 (5)	1,4680	1,0113	66,90	66,31	63,78	10,93	5,76	$C_{13}H_{27}NO_3$	63,64	11,09	5,71	0,67	237
III	39,2	78—80 (3)	1,4770	0,9672	77,01	77,68	65,73	11,23	5,19	$C_{15}H_{31}NO_3$	65,87	11,47	5,12	0,65	184
IX	26,0	105—8 (2)	1,5170	1,0635	84,03	84,45	69,62	9,57	4,40	$C_{17}H_{29}NO_3$	69,62	9,89	4,74	0,69	132
X	47,4	140—2 (4)	1,5200	1,0620	96,03	97,52	71,21	9,40	3,95	$C_{20}H_{33}NO_3$	71,60	9,91	4,17	0,86	82—3
XI	44,5	109	—	—	—	—	70,01	8,67	3,95	$C_{20}H_{31}NO_4$	69,25	8,94	4,01	0,80	154—5
XII	49,4	117	—	—	—	—	73,32	9,38	3,85	$C_{22}H_{35}NO_3$	73,09	9,79	3,88	0,84	214—5
XIII	42,5	152—3 (4)	1,5080	1,0234	100,72	99,93	72,63	8,99	4,11	$C_{21}H_{33}NO_3$	72,58	9,57	4,03	0,79	126—7
XIV	31,9	150—2 (4)	1,5200	1,0912	93,45	94,97	71,13	10,05	4,53	$C_{20}H_{33}NO_3$	71,61	9,91	4,18	0,64	152—3
XV	40,0	103—5 (4)	1,4460	0,9053	77,01	76,87	60,01	9,95	5,77	$C_{13}H_{27}NO_2S_2$	59,73	10,41	5,35	0,60	164

Note. The melting points are given for compounds XI and XII.

into ether, and the extract was dried with magnesium sulfate. Yields and constants of the amines obtained are given in Table 4.

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ISOLATION AND PHYSIOLOGICAL ACTIVITY OF TRITERPENE COMPOUNDS FOUND IN RESIDUES OF INDUSTRIAL THYME EXTRACTION

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In traditional folk medicine the plants of the thyme family have long been used for treating various illnesses (neuritis, radiculitis, disorders of the upper respiratory system, atherosclerosis, etc.) [1, 2]. Under the general commercial name *Thymus serpyllum* these plants are widely used for the preparation of a liquid extract which is then used in various other preparations (pertussin and others) [3, 4].

In most cases these plants are rich in biologically active compounds (essential oils, carbolic acids, flavins, triterpenes). We found that in these plants the major carbolic acid compound is usually caffeic acid; flavins are represented mainly by flavone glycosides; and triterpenes, apart from the neutral compounds, are present mainly as ursolic acid.

At present, the use of these plants in medical practice is limited to using the corresponding essential oils and liquid extracts. In this manner, many of the biologically active compounds present are utilized.

As a part of our studies aimed at developing fuller exploitation of natural resources, we obtained the industrial waste products from the extraction of thyme. It was found that this industrial waste (the pulp after extraction) contained 4.5% of triterpene compounds, mainly as ursolic and oleanolic acids.

The industrial treatment of thyme does not result in utilization of these triterpenes and these compounds, for the most part, remain in the pulp. It has been known, however, that triterpenes are biologically active; they often increase enzymatic activity (for example that of estrone and testosterone propionate [5]), they also decrease the brittleness of blood vessels, and prevent swelling [6], and also show some cardiac-stimulating activity [7], etc.

These facts led us to try to obtain the total mixture of triterpenes from the industrial thyme extraction waste. We used a selective extraction of triterpenes followed by their purification. The product obtained was an amorphous light-yellow powder, insoluble in water, and readily soluble in chloroform, ether, alcohol, and vegetable oils.

The composition of the product was studied by reacting it with concentrated sulfuric acid followed by determining the optical density of the reaction mixture at 310 nm. The results showed that the product contained 59.2% of triterpene acids, 32.3% of neutral triterpenes, not more than 3.5% of residual moisture, and 5% of chlorophyll.

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