semiautomatic instrument supplied by IITC Inc (USA). The compounds, dissolved in distilled water, were administered internally to the animals in doses of 50 and 100 mg/kg. The animals in the control groups received the same volume of distilled water.

The standard used was Captopryl in a dose of 10 mg/kg (internally).

The acute toxicities of the compounds were determined in female mice weighing 16-17 g by the intragastric route. The LD_{50} values were calculated as described in [10]. The animals were observed for a period of 48 h.

The results shown in Table 3 show that (IX), (Xb), and (Xc) are all of low toxicity, and reduce the AP in rats with birenal renovascular hypertension. The radical in the 6-position of the piperidine ring has a considerable influence on antihypertensive activity. For example, the clearest reduction in AP was obtained with (Xc), which has the dichlorophenyl residue. The presence of a cyclohexyl residue reduces the degree of activity (compound IX).

The test compounds were inferior to Captopryl in activity, but they were also somewhat less toxic than the latter. The duration of the reduction in AP brought about by (Xc) was around 60 min when given in a dose of 50 mg/kg, and 150 min in a dose of 100 mg/kg.

LITERATURE CITED

1. A. J. Gordon and R. Ford, Chemist's Companion [Russian translation], Moscow (1976), p. 302.
2. A. Kh. Kogan, Byull. Éksp. Biol., No. 1, 112-114 (1961).
3. L. I. Mastafanova, K. F. Turchin, M. I. Evstratova, et al., Khim. Geterotsikl. Soedin., No. 3, 367-371 (1985).
4. M. V. Rubtsov, E. S. Mikitskaya, and V. S. Usovskaya, Zh. Obshch. Khim., 26, 130-134 (1956).
5. L. N. Yakhonotv, L. I. Mastafavona, M. I. Evstratova, et al., Khim.-farm. Zh., No. 10, 1185-1190 (1984).
6. D. G. Brenner, W. Halczenko, and K. Shepard, J. Het. Chem., 19, 897-900 (1982).
7. H. U. Daeniker and J. Drney, Helv. Chim. Acta, 40, 2148-2156 (1957).
8. Drugs of the Future, 8, 953-956 (1983).
9. Y. Honma, K. Hanamoto, T. Hishiyama, et al., J. Med. Chem., 27, 125-128 (1984).
10. J. Litchfield and F. Wilcoxon, J. Pharmacol. Exp. Ther., 96, 99-113 (1949).
11. B. Rubin and M. J. Antonaccio, Pharmacology of Antihypertensive Drugs, New York (1980), pp. 21-42.

SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 5-SUBSTITUTED COUMARANS

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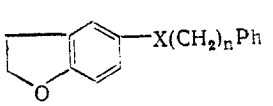
012.1

Certain 6-(ω-phenylacyl)chromans have anti-inflammatory activity [2] and 6-(amino-ω-phenylalkyl)chromans — a local anesthetic one [3]. Therefore, as our aim was to search for new drugs, we synthesized and studied coumarin analogs of the above compounds.

5-(ω-Phenylacyl)coumarans (Ia-d) were synthesized by acylating coumaran with acid chlorides in the presence of anhydrous $AlCl_3$, while 5-(α-amino-ω-phenylalkyl)coumarans (IIIa-d) were obtained by reducing oximes (IIa-d), synthesized by the reaction of ketones Ia-d with $H_2NOH \cdot HCl$ in a pyridine solution, by sodium in a butanol solution



Ia-d; IIa-d; IIIa-d

a-d X = CO; IIa-d: X = —CH=NOH; IIIa-d X = $CHNH_2$; a: n = 0, b: n = 1, c: n = 2, d: n = 3.

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TABLE 1. Characteristics of Compounds Ic, d, IIa-d and IIIa-d

Compound	Yield, %	mp, °C (ethanol)	UV spectrum λ, nm	lg ε	IR spectrum, ν_{OH}, cm^{-1}	Found, %				Empirical formula	Calculated, %			
						C	H	Cl	N		C	H	Cl	N
Ic*	88	57—8	209 229 291	4,25 4,06 4,13	—	81,2	6,3	—	—	$C_{17}H_{16}O_2$	80,9	6,4	—	—
Id*	85	52—3	209 228 289	4,34 4,20 4,20	—	81,0	6,7	—	—	$C_{18}H_{18}O_2$	81,2	6,8	—	—
IIa	80	151—2	210 245 284	4,37 4,19 shoulder	3200	75,2	5,5	—	5,7	$C_{15}H_{13}NO_2$	75,3	5,5	—	5,8
IIb	76	103—4	212 270	4,43 4,12	3230	75,7	6,1	—	5,5	$C_{16}H_{15}NO_2$	75,9	6,0	—	5,5
IIc	90	81—2	215 271	4,34 4,16	3260	76,4	6,4	—	5,4	$C_{17}H_{17}NO_2$	76,4	6,4	—	5,2
IId	85	72—3**	213 267	4,38 4,08	3290	76,7	7,0	—	5,0	$C_{18}H_{19}NO_2$	76,8	6,8	—	5,0
IIIa	92	220—1	209 239 289	4,29 3,91 3,88	—	60,0	6,4	13,3	5,4	$C_{15}H_{15}NO \cdot HCl$	68,8	6,2	13,5	5,4
IIIb	90	215—6	210 234 288	4,39 3,98 3,50	—	69,9	6,9	12,8	5,2	$C_{16}H_{17}NO \cdot HCl$	69,7	6,6	12,8	5,1
IIIc	85	191—2	209 235 288	4,22 3,95 3,50	—	70,5	7,0	12,0	4,8	$C_{17}H_{19}NO \cdot HCl$	70,5	7,0	12,2	4,8
IIId	90	202—3	208 234 288	4,27 3,99 3,56	—	70,9	7,2	11,9	4,5	$C_{18}H_{21}NO \cdot HCl$	71,2	7,3	11,7	4,6

*ν_{C-O} 1670 cm^{-1}.
**Cyclohexane.

TABLE 2. Data of PMR Spectra (δ, ppm) of Compounds Ic, d, II-a-d and IIIa-d

Compound	CH	$ArCH_2$	XCH_2	$CH_2CH_2CH_2$	NH_2	OH	2-H	3-H	4-H	6-H	7-H	C_6H_5
Ic	—	2,92—3,32m		—	—	—	4,56t [a]	— [b]	7,71 ee [c]	7,66 ee [c,d]	6,65 ee [c,d]	7,05 s
I	—	2,70t [a]	2,57t [a]	1,92q [a]	—	—	4,47t [a]	3,07t [a]	7,60 e [c]	7,55 ee [c,d]	6,60 e [d]	7,05 s
IIa	—	—		—	—	9,22s	4,46t [a]	3,08t [a]	7,08—7,32m		6,64 e [d]	7,37 s
IIb	—	4,15s		—	—	9,00s	4,47t [a]	3,07t [a]	7,22—7,47m		6,67 e [d]	7,17 s
IIc	—	2,77—3,00m		—	—	9,95s	4,47t [a]	3,07t [a]	7,09—7,35m		6,62 ed	7,07
IId	—	2,75t [a]	2,62t [a]	1,82q [a]	—	9,42s	4,47t [a]	3,12t [a]	7,07—7,32		6,62 ed	7,07 s
III a [e]	4,85	—	—	—	1,47s	—	4,20t [a]	3,82t [a]	6,77—7,30m		6,50 ed	— [f]
III b [e]	3,92t [a]	2,69e [a]		—	2,17	—	4,37t [a]	3,02t [a]	6,74—7,20m		6,52 ed	7,05 s
III c [e]	3,61t [a]	2,43t [a]	1,75q [a]	—	1,60	—	4,32t [a]	2,97t [a]	6,71—7,15m		6,49 ed	6,98 s
III d [e]	3,50—3,77m	2,32—2,62m	1,37—1,75m			—	4,37t [a]	3,00t [a]	6,72—7,17m		6,50 ed	7,04 s

[a] J 708 Hz.
[b] Overlaps with $ArCH_2$ and XCH_2 signals.
[c] J 3 Hz.
[d] J 9 Hz.
[e] Free base.
[f] Overlaps with 4-H and 6-H signals.

The structure of the compounds synthesized was confirmed by the data of PMR spectra. Ketones Ia [11] and 1B [6] have already been described. The frequency of the stretching vibrations of the hydroxyl group in the IR spectra of oximes IIa-d increases with increase in the number of methylene groups (n) in their side chain. The UV spectrum of oxime IIa shows a bathochromic shift of the long-wave absorption band and thus differs from the spectra of the remaining oximes (IIb-d), in which the aromatic rings in their molecules are not conjugated through the C=N bond. The UV spectra of hydrochlorides of amines IIIa-d differ inappreciably (Table 1).

Coumaran was synthesized in a 36% yield by heating 1-(2-hydroxyethyl)-2-methoxybenzene with a mixture of hydrobromic and acetic acids by the method in [8]. Thus, 2-(2-bromoethyl)-phenol was obtained in 46% yield as a by-product. When this compound was heated with ROH in ethanol solution, coumaran was also obtained in an overall yield of 76%.

EXPERIMENTAL CHEMICAL

The UV spectra were run on a Specord UV-VIS spectrophotometer (GDR) in ethanol, IR spectra on a UR-20 spectrophotometer (GDR) in mineral oil, and the PMR spectra on a Tesla BS 487C spectrometer (CSSR) with a working frequency of 80 MHz in CCl_4 (compounds Ic, d, IIIa-d) or $CDCl_3$ (oximes IIa-d). The internal standard was TMS.

The characteristics and yields of the compounds studied are given in Tables 1 and 2.

5-(ω-phenylacyl)coumarans (Ia-d). A 6.4 g portion (49 mmoles) of anhydrous $AlCl_3$ is added in the course of 30 min at −10°C to a mixture of 25 ml of anhydrous CH_2Cl_2, 4.8 g (40 mmoles) of coumaran and 44 mmoles of the corresponding acid chloride. The mixture is stirred for 1 h at 15°C, poured onto ice, acidified with HCl, and extracted by CH_2Cl_2. The extract is washed with water, dried and concentrated. The yield of ketones Ia, b are 90 and 85%, respectively.

Oximes IIa-d. A mixture of 0.04 mole of ketones Ia-d, 11.6 g (0.16 mole) of $H_2NOH \cdot HCl$ and 120 ml of pyridine is heated for 4 h at 100°C, then cooled to 20°C, poured into water, and extracted by ether, and the extract is dried and concentrated.

Hydrochlorides of 5-(α-amino-ω-phenylalkyl)coumarans (IIIa-d). Metallic sodium (4.6 g, 0.2 mole) is added in portions to a solution of 25 mmoles of oximes IIa-d in 70 ml of butanol at the boiling point of the solution. After the sodium has dissolved, the mixture is cooled to 20°C, acidified by HCl, concentrated in vacuo, and the residue is made alkaline by an aqueous solution of NaOH, and the mixture is extracted by ether. Anhydrous gaseous HCl is passed into the dry extract to precipitate the amine hydrochlorides IIIa-d.

Coumaran. A solution of 6.6 g (0.1 mole) of KOH in 80 ml ethanol is added at 100°C, with stirring, to 20.1 g (0.1 mole) of 2-(2-bromoethyl)phenol. The mixture is boiled with stirring for 3 h, cooled, poured into water, and extracted by ether. The extract is washed with water, dried and distilled to yield 10.3 g (86%) of coumaran, bp 74-75°C (15 mm Hg).

EXPERIMENTAL PHARMACOLOGICAL

Ketones Ia-d were introduced orally in the form of a suspension in a 1% solution of carboxymethylcellulose to which Tween-80 has been added, and the hydrochlorides of amines IIIa-c were introduced subcutaneously in the form of a 1% aqueous solution. The hydrochloride of IIId was not tested because it was not sufficiently soluble in water. For the investigation we used both sexes of nonpedigree white mice, each weighing 18-25 g, and white rats weighing 150-230 g. The acute toxicity for mice was determined by the method of Leachfield and Wilcoxon, modified by Roth [1].

The anti-inflammatory activity of ketones Ia-d was studied by using experimental models of edemas of a rat paw, induced by carraghenin [13] and bentonite [12]. Table 3 gives the mean arithmetic indexes of percent decrease in edema, measured 1, 2, 3 and 5 h after the introduction of the compounds studied. In the anti-inflammatory activity, ketones Ia-c surpass their chroman analogs [2]. In their convenient combination of low toxicity and high anti-inflammatory activity, ketones Ia, b are superior to acetylsalicylic acid, ibuprofen, and are not inferior to voltaren and indomethacin. The anti-inflammatory activity of ketones Ia-d decreases with increase in the number of methylene groups in their side chain.

The infiltration anesthesia of hydrochlorides of amines IIIa-c was studied on guinea pigs by the method in [5], topical anesthesia was studied on the cornea of an eye of a rabbit by the method in [4], and nerve-block anesthesia by recording motor paralysis [9]. The local

TABLE 3. Acute Toxicity and Anti-inflammatory Activity of Ketones Ia-d

Compound	LD_{50}, mg/kg	Dose, mg/kg	Percent of depression of inflammation	
			corraghenin induced	bentonite induced
Ia	1040 (835—1230)	50	48,7	36,2
Ib	3420 (2854—3672)	50	17,3	23,4
Ic	...	50	8,6	12,2
Id	...	50	6,4	12,4
Acetylsalicyclic acid	1020 (742—1387)	100	16,1	27,3
Ibuprofen	810 (714—917)	80	39,6	24,7
Voltaren	256 (242—276)	25	41,5	36,1
Indomethacine	35 (25—42)	5	26,7	37,1

Note. Here and in Table 4, the fluctuation limits are indicated in brackets; the data are statistically reliable ($P < 0.05$).

TABLE 4. Acute Toxicity, Local Anesthetic Activity and Local Irritating Action of Hydrochlorides of Amines IIIa-c

Compound	LD_{50}, mg/kg	Infiltration anesthesia	Nerve-block anesthesia		Local irritating action		
			minimal effective concentration, mmole	half-survival time, min	degree of irritation by 1% solution	mean tissue irritating concentration, %	threshold tissue irritating concentration, %
IIIa	235 (197—280)	1,4	3,5	14,9	2,0	1,0	0,1
IIIb	200 (143—260)	1,9	2,7	19,6	1,7	1,2	0,2
IIIc	120 (102—142)	3,5	1,0	23,2	1,5	1,6	0.2
Novocaine	570 (539—602)	1,0	7,1	9,3	0,0	6,6	1,8
Trimecaine	390 (372—410)	2,9	5.0	10,8	1,2	3,6	0.1
Lidocaine	270 (204—356)	1,9	7.4	16,4	0,3	6,9	0,7
Pyromecaine	300 (187—313)	2,5	2.0	14,4	1,9	1,2	0,6
Dicain	44 (35—55)	5,6	0.3	13,4	2,6	0,6	0,1

irritating action was studied on white rats by the method in [7], modified in [10]. It was found that the coumaran derivatives IIIa-c (Table 4) differ in acute toxicity and local irritating action from the chroman derivatives with the corresponding structure, but are somewhat inferior in the strength and duration of the local anesthetizing action [3]. The compounds are slightly active under the conditions of topical anesthesia. Their activity under the conditions of the infiltration and nerve-block anesthesia and the acute toxicity increase, and the local irritating action decreases when the number of methylene groups in the side chain is increased. The parameters of the hydrochloride of compound IIIb are close to those of local anesthetics used in medicine (see Table 4).

The investitagions carried out show prospects for the search for new drugs among compounds of the type under consideration.

LITERATURE CITED

1. M. L. Belen'kii, Elements of Quantitative Evaluation of Pharmacological Effect [in Russian], 2nd edition, Leningrad (1963), pp. 81-106.
2. V. K. Daukshas, P. G. Gaidyalis, E. B. Udrenaite, et al. Khim.-farm. Zh., 19, No. 9, 1069-1071 (1985).
3. V. K. Daukshas, O. Ya. Pyatrauskas and Yu. Yu. Ramanauskas, et al., Khim.-farm. Zh., No. 2, 170 (1987).
4. V. V. Zakusov, Pharmacology of the Nervous System [in Russian], Leningrad (1953), pp. 178-191.
5. E. Bülbring and J. Wajda, J. Pharmacol. Exp. Ther., 85, 78-84 (1945).
6. G. Chatelus and P. Cagniat, C. R. Acad. Sci. (Paris), 224, 1777-1779 (1947).
7. J. O. Hoppe, E. B. Alexander, L. C. Miller, J. Am. pharm. Ass. sci. Ed., 39, 147-151 (1950).
8. G. Illuminati, L. Mandolini, and B. Masci, J. Am. Chem. Soc., 97, 4960-5966 (1975).
9. W. R. Jones, T. L. Kerley, and L. E. Wearer, J. Pharm. Sci, 54, 1680-1681 (1965).
10. P. P. Koelzer and K. H. Wehr, Arzneim.-Forsch., 8, 181-190 (1958).
11. S. V. Kostanecki, V. Lampe, and Ch. Marchalk, Ber. dtch. chem. Ges., 40, 3660-3669 (1907).
12. J. Marek, Pharmazie, 36, 46-49 (1981).
13. C. A. Winter, E. A. Richley, and G. W. Nuss, Proc. Exp. Biol. (N.Y.), 111, 544-547 (1962).

SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF 21-THIO DERIVATIVES OF CORTICOSTEROIDS

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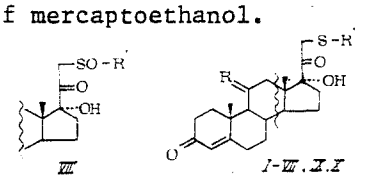
Among the derivatives of corticosteroids in which the primary alcoholic group at the 21-position is substituted by sulfur, the 21-thioaliphatic derivatives are known best [5-8, 10, 14]. Of these, tixocortol pivalate, which has a local anti-inflammatory activity equal to that of cortisol acetate, when there is no glucocorticoid or mineralocorticoid activity [11], is of considerable interest. The 21-sulfide derivatives of corticosteroids [9, 12, 13] have been much less studied.

In our search for new biologically active compounds, we synthesized 21-thio-derivatives of corticosteroids (I-X) that were not yet known, and studied their anti-inflammatory activity.

21-Thioalkanoic acids of corticosteroids I-V are obtained by the reaction of corticosteroid 21-tosylates with the disodium salts of mercaptoalkanoic acids, and acid VI from cortisol 21-tosylate and β-mercaptopropionic acid in the presence of triethylamine. The sodium salt IIIa is obtained from acid III and sodium methylate; the methyl ester VIII is obtained from cortisol 21-tosylate and the sodium salt of mercaptoacetic acid methyl ester, followed by oxidation to sulfoxide. Amide IX is obtained from acid III and diethylamine in the presence of dicyclohexylcarbodiimide. Alcohol X was synthesized by the reaction of cortexolone 21-tosylate with the sodium salt of mercaptoethanol.



III I-III, IX

I: $R = H_2$, $R^1 = CH_2COOH$; II: R = O, $R^1 = CH_2COOH$; III: R = H, β-OH, $R^1 = CH_2COOH$; IIIa: R = H, β-OH, $R^1 = CH_2COONa$; IV: $R = H_2$, $R^1 = CH_3(CH_2)COOH$; V: $R = H_2$; $R^1 = (CH_2)_2COOH$; VI: R = H, β-OH, $R^1 = (CH_2)_2COOH$; VII: R = H, β-OH, $R^1 = CH_2COOCH_3$; VIII: R = H, β-OH, $R^1 = CH_2COOCH_3$; IX: R = H, β-OH, $R^1 = CH_2CON(C_2H_5)_2$; X: $R = H_2$, $R^1 = (CH_2)_2OH$.

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