2,3-Bis(acetoxymethyl)-6,7-dimethylquinoxaline (XV). A solution of (XIV) (1 g, 4.5 mmole) [4] in acetic anhydride (5 ml) and acetic acid (7.5 ml) was refluxed with stirring for 15 min and then evaporated to dryness under vacuum. The residue was crystallized from ether to give (XV) (0.59 g, 43.5%), mp 90°C. Found, %: N 9.3. $C_{16}H_{18}N_2O_4$. Calculated, %: N 9.29.

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α-CYCLOHEXYL-β-AMINO-4-SUBSTITUTED PROPIOPHENONES

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Among β- and α-amino ketones many compounds have analgestic, anesthetic, and antiinflammatory properties. Replacement of the α-hydrogen of amino ketones by various substituents can modify the biological activity [1].

We have already described [2, 3] the synthesis and a study of the antiinflammatory activity of β-amino ketones with an α-phenyl substituent. Our intention in the work described here was to synthesize and examine the antiinflammatory and anesthetic properties of α-cyclohexyl-β-amino-4-substituted propiophenones (I).

$$RC_6H_4COCH(C_6H_{11})CH_2NR'$$
I

R = H, HO, CH_3O,..., C_4H_9O, F, iso-C_3H_7O; R′ = NC_5H_{10}, NC_6H_{12}

We synthesized (I) by Mannich condensation of 4-substituted phenyl cyclohexylmethyl ketones with paraformaldehyde and amines in ethanol or dioxane.

Examination of the aminomethylation reaction revealed that the yield of the final product increases with reduction in solution pH. Thus, when equimolar quantities of phenyl cyclohexylmethyl ketone, paraformaldehyde and hexamethylenimine were heated for 15 h at pH 1.0 in dioxane, the yield was 83%, whereas it was only 25-30% at pH 7.0-8.0.

We prepared the 4-substituted phenyl cyclohexylmethyl ketones (III), which were needed for the synthesis of amino ketones (I), in high yield by Friedel–Crafts reaction of cyclohexylacetyl chloride (II) with benzene or substituted benzenes in the presence of aluminum chloride in ligroin (80-100°C) or carbon disulfide. Their properties are summarized in Table 1.

$$\underset{\text{II}}{C_6H_{11}CH_2COCl} + C_6H_5R \xrightarrow[\text{ligroin}]{AlCl_3} \underset{\text{III}}{C_6H_{11}CH_2COC_6H_4R}$$

R = H, HO, CH_3O,..., C_4H_9O, iso-C_3H_7O, F

We prepared the starting cyclohexylacetyl chloride (II) by the route

$$C_6H_{11}OH \rightarrow C_6H_{11}Br + CH_2(COOC_2H_5)_2 \rightarrow C_6H_{11}CH(COOC_2H_5)_2 \rightarrow C_6H_{11}CH(COOH)_2 \xrightarrow[-CO_2]{} C_6H_{11}CH_2COOH \xrightarrow{SOCl_2} \text{II}$$

We verified the purity and homogeneity of compounds (I), (II), and (III) by gas-liquid (GLC) and thin-layer chromatography (TLC), IR spectroscopy, and elemental analysis. All the ketones were characterized as the oximes (Table 2). The IR spectra of the ketones have the carbonyl bands in the 1680 cm^{-1} region.

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TABLE 1. 4-Substituted Phenyl Cyclohexylmethyl Ketones (III)

R	Yield, %	Boiling point, °C (mm)	n_d^{20}	d_4^{20}	Found, %		Formula	Calculated, %		R_f	Oxime		
					C	H		C	H		mp., °C	found, %	calculated, %
H*	56,0	145—50 (8)	1,5312	1,0016	83,82	8,99	$C_{14}H_{18}O$	83,10	8,91	0,42	98—9	6,41	6,47
HO	60,0	158—61 (1)	—	—	77,75	9,25	$C_{14}H_{18}O_2$	77,03	8,31	0,43	109—110	6,03	6,00
CH_3O*	82,5	—	—	—	77,82	8,76	$C_{15}H_{20}O_2$	77,60	8,62	0,30	92—3	5,68	5,65
C_2H_5O*	95,5	200—210 (10)	—	—	78,35	9,50	$C_{16}H_{22}O_2$	78,00	9,00	0,44	87—8	4,40	5,36
C_3H_7O	55,6	190—95 (10)	1,5332	1,0391	78,01	9,31	$C_{17}H_{24}O_2$	78,47	9,22	0,44	113—4	5,43	5,08
iso-C_3H_7O	53,4	165—70 (1)	1,5238	1,0316	78,21	9,12	$C_{17}H_{24}O_2$	78,47	9,22	0,42	72—3	5,21	5,08
C_4H_9O	63,0	225—30 (10)	—	—	78,56	9,06	$C_{18}H_{26}O_2$	78,77	9,55	0,43	145—6	5,23	4,84
F	86,0	130—35 (1)	1,5230	0,9809	76,48	7,35	$C_{14}H_{17}OF$	76,36	7,72	0,36	42—3	6,01	6,09

*Described in [6, 7].

TABLE 2. α-Cyclohexyl-β-amino-4-substituted Propiophenone Hydroxides

R	R'	Yield, %	Melting point, °C	Found, %				Formula	Calculated, %				R_f
				C	H	N	Cl		C	H	N	Cl	
H	NC_6H_{12}	89,0	156—158	72,32	9,83	8,32	10,06	$C_{21}H_{32}NOCl$	72,07	9,21	8,58	10,14	0,76
HO	NC_6H_{12}	83,0	65—67	68,25	8,91	3,75	9,70	$C_{21}H_{32}NO_2Cl$	68,64	8,81	3,81	9,68	0,80
CH_3O	NC_6H_{12}	47,0	90—92	70,03	9,86	8,13	9,08	$C_{22}H_{34}NO_2Cl$	69,47	8,42	3,67	9,34	0,72
C_3H_7O	NC_6H_{12}	43,4	89—90	70—89	9,40	3,64	8,89	$C_{24}H_{38}NO_2Cl$	70,82	9,24	3,43	8,71	0,53
iso-C_3H_7O	NC_6H_{12}	91,0	85—87	70—57	9,50	3,50	8,50	$C_{24}H_{38}NO_2Cl$	70,82	9,24	3,43	8,71	0,81
C_4H_9O	NC_6H_{12}	64,1	51—52	71—45	9,89	3,80	8,96	$C_{25}H_{40}NO_2Cl$	71,15	9,55	3,32	8,40	0,42
F	NC_6H_{12}	59,8	147—8	73—50	9,00	3,40	11,00	$C_{21}H_{31}NOCl$	73,76	9,14	4,09	10,37	0,75
H	iso-HNC_3H_7	12,0	171—72	69,73	9,10	4,52	11,54	$C_{18}H_{28}NOCl$	69,76	9,01	4,52	11,44	0,33
CH_3O	iso-HNC_3H_7	11,0	138,41	72,43	9,53	4,30	11,02	$C_{18}H_{30}NO_2Cl$	70,45	9,33	4,31	10,95	0,24
C_3H_7O	iso-HNC_3H_7	14,0	221—22	65,31	8,23	3,90	9,21	$C_{21}H_{34}NO_2Cl$	65,82	8,21	3,85	9,08	0,15
F	iso-HNC_3H_7	8,0	193—4	64—62	8,45	4,04	11,02	$C_{18}H_{27}NOCl$	64,65	8,53	4,38	11,12	0,23
C_2H_5O	NC_5H_{10}	75,0	104—105	69,90	9,02	3,79	9,58	$C_{22}H_{34}NO_2Cl$	69,18	8,97	3,66	9,28	0,48
C_3H_7O	NC_5H_{10}	49,6	73—74	71—13	9,53	3,72	8,99	$C_{23}H_{36}NO_2Cl$	70,64	9,38	3,43	8,69	0,44

TABLE 3. Antiinflammatory and Antipyretic Activity of α-Cyclohexyl-β-hexamethylenimino-4-substituted Propiophenone Hydrochlorides (HCl)

R	Min. antiinflammatory dose, mg/kg	Reduction in temperature (°C) after administration of HCl in a dose of 25 mg/kg	Carrageenan edema (%) after administration of HCl		
			50 mg/kg	25 mg/kg	10 mg/kg
H	150	1,5±0,2 (>0,02)	66,7 (>0,01)	67 (0,02)*	99,8
CH_3O	170	No reduction	66,7 (<0,01)	75 (0,1)	
C_3H_7O	150	" "	75 (0,1)	91	
OH	200	" "	77,8 (>0,05)	94,4	
F	200	" "	55,6 (<0,02)	75 (0,02)	109

Brackets enclose the value of P.

Introduction of an alkoxy group or fluorine atom into the para position of the benzene ring of ketones (III) and amino ketones (I) is accompanied by a bathochromic shift of the UV absorption maximum (R = H, λ_{max} = 243 nm; R = F, λ_{max} = 255 nm; R = alkoxy, λ_{max} = 272 nm).

For work on the biological activity we converted (I) to the hydrochlorides (HCl), whose properties are summarized in Table 2.

EXPERIMENTAL PHARMACOLOGY

We assayed the antiinflammatory activity of the HCl from their effect on carrageenan-induced rat paw edema and evaluated the antipyretic properties against yeast fever in rats by the methods described earlier [3].

Compounds were administrated intraperitoneally in doses of 10, 25, and 50 mg/kg. Four to seven animals received the compound at each dose level. A comparative examination of the HCl revealed that the entire group of compounds is capable of 45-25% suppression of carrageenan edema in a dose of 50 mg/kg.

The HCl (R = H) and its fluoro derivative are active in lower doses (25 mg/kg). However, their antiinflammatory activity is reduced on peroral administration; they produce 25% reduction of carrageenan edema in higher doses (100 mg/kg) (Table 3). These compounds are far inferior to indomethacin, which is capable of 70% suppression of carrageenan edema in a dose of 3 mg/kg.

On intraperitoneal administration in a dose of 25 mg/kg, this HCl suppresses yeast fever. The other compounds have no antipyretic properties in doses of 10, 25, and 50 mg/kg.

All the compounds have a slight anesthetic effect (conduction anesthesia test). We determined the average effective concentration (EC_{50}) in isolated frog nerves by indirect recording of the action potential. The most active compound is HCl (R = CH_3O) with EC_{50} 46.9 mg/kg. However, its activity is inferior to that novocain (EC_{50} 5.0 mg/kg). We examined the surface anesthesia on rabbit cornea. All preparations were inactive.

We have previously established [2] that α-phenyl-β-hexamethylenimino-4-alkoxypropiophenone hydrochlorides have no antiinflammatory properties. However, antiinflammatory activity appears when halogen (F, Cl) is introduced into position 4 of the propiophenone benzene ring. As our present work reveals, this activity persists when the α-phenyl substituent is replaced by cyclohexyl. In addition (I) (R = H) has antipyretic properties.

Thus our experimental results demonstrate that in the propiophenones the replacement of the α-phenyl substituent by cyclohexyl does not affect their antiinflammatory activity while individual compounds acquire antipyretic properties.

EXPERIMENTAL CHEMISTRY

The GLC analyses were carried out on a Khrom-4 chromatograph (Czechoslovakia) fitted with a flame-ionization detector. The stationary phase was 6% polyethylene glycol on Chromaton (0.2-0.25 mm) treated with 1% sodium hydroxide solution; column oven temperature 160-180°C, column length 1.2 m, diameter 3 mm, carrier gas nitrogen (flow rate 30-40 ml/min), sensitivity 1 : 50.

The IR spectra were recorded on a UR-20 spectrophotometer in Vaseline oil; UV spectra were recorded on a Specord spectrophotometer. Thin-layer chromatography was carried out on silica gel–gypsum (with binder), elution by butanol–ethanol–acetic acid–water (8 : 2 : 1 : 3), and visualization with iodine vapor.

α-Cyclohexyl-β-amino-4-substituted Propiophenone Hydrochlorides (I). An equimolar mixture of 4- (III), paraformaldehyde, and the amine in ethanol or dioxane at pH 1.0 was refluxed on a water bath for 10-15 h. The solvent was stripped off and the mixture was dissolved in a small quantity of water and extracted with ether; 50% sodium hydroxide solution was added to the aqueous layer until alkaline. The amino ketone was extracted with ether. The ethereal extracts were dried over anhydrous sodium sulfate. After removal of ether and unreacted amine, the residue was converted to the hydrochloride.

The starting compounds (II) and (III) were prepared by the procedures described in [4] and [5], respectively.

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