acetonitrile, 0.5 ml of CH_3I is added, and the mixture is boiled for 1 h. When cool, the iodomethylate of the corresponding base formed is precipitated by the addition of 20 ml of anhydrous ether; the precipitate is filtered, washed with 20 ml of ether, dried, and identified by comparing the melting point with that of an authentic sample. The filtrate is washed with water and dried over sodium sulfate, and after distillation of the solvent in a water jet pump vacuum, it is purified by chromatography on grade II Al_2O_3 by eluting the corresponding initial α-hydroxyferrocenyl derivative with a hexane–ether mixture (1:1), and then crystallizing from hexane. There was no depression of the melting point of a mixture of the sample of α-hydroxyferrocenyl derivative obtained with the initial sample.

[N,N-Dimethyl-N-(ferrocenylmethyl)-N-(β-ethylpyridinium bromide]ammonium bromide (XXIV). A mixture of 2 mmoles of N,N-dimethylaminomethylferrocene and 1 mmole of N-(β-bromoethyl)pyridinium bromide [9] in 5 ml of methanol is boiled for 5 min. The mixture is then cooled to room temperature, poured into 100 ml of anhydrous diethyl ether, and left to stand for 15 h at 5-8°C. The precipitate of salt XXIV is filtered, washed with water, and dried. The yield of XXIV is 0.85 g (83%). Found, %: Br 31.12; Fe 10.85; N 5.34. $C_{20}H_{26}Br_2FeN_2$. Calculated, %: Br 31.38; Fe 10.91; N 5.49.

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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF HYDROCHLORIDES OF SUBSTITUTED α-AMINOACETOPHENONES

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In continuation of our studies on the synthesis and antiinflammatory activity of amino ketones [1-4], in the present work we obtained substituted α-aminoacetophenones (IIa-p) by the reaction of α-bromoacetophenones (Ia-g) [5, 6] with amines.

$$n\text{-}RC_6H_4COCHBrR^1 \xrightarrow{HAm} n\text{-}RC_6H_4COCHR^1Am$$

Ia-g IIa-p

Ia, IIa: $R = OC_2H_5$; Ib, IIb, e: $R = OCH_3H_7$; Ic, IIc, f, h: $R = OC_4H_9$; Ia, IId, g: $R = OC_5H_{11}$; Ie, IIi, l, o: $R = Cl$; If, IIj, m, p: $R = Br$; Ig, IIe, n: $R = F$; Ia-d, IIa-h $R^1 = H$; Ie-g, IIi-p: $R^1 = C_6H_5$; IIa-d, n-p: $Am = NC_6H_{12}$; IIe-g: $Am = N(C_2H_5)_2$; IIb: $Am = N(CH(CH_3)_2)_2$; IIi, j $Am = NC_4H_8O$; IIk-m: $Am = NC_5H_{10}$.

α-Amino ketones IIa-p were converted into hydrochlorides (IIIa-p) and iodomethylates (IVc, d, g, h).

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TABLE 1. Substituted α-Aminoacetophenones IIa-p

Compound	Yield, %	Found, %			Empirical formula	Calculated, %			R_f
		C	H	N		C	H	N	
IIa	65,0	73,43	8,75	5,32	$C_{16}H_{23}NO_2$	73,52	8,82	5,35	0,68
IIb	95,0	74,28	9,03	5,18	$C_{17}H_{25}NO_2$	74,14	9,15	5,08	0,63
IIc	91,0	74,42	9,56	4,57	$C_{18}H_{27}NO_2$	74,70	9,40	4,84	0,61
IId	97,0	70,37	9,60	4,53	$C_{19}H_{29}NO_2$	70,58	9,66	4,61	0,67
IIe	90,0	71,98	9,23	5,76	$C_{15}H_{23}NO_2$	72,25	9,30	5,62	0,73
IIf	80,0	73,08	9,29	5,12	$C_{16}H_{25}NO_2$	72,96	9,57	5,32	0,64
IIg	93,0	72,17	9,13	3,85	$C_{23}H_{32}NO_2$	72,27	9,09	3,95	0,68
IIh	85,2	74,30	10,20	4,85	$C_{18}H_{29}NO_2$	74,14	10,02	4,79	0,65
IIi	96,4	68,54	5,68	4,31	$C_{18}H_{18}ClNO_2$	68,46	5,74	4,44	0,82
IIj	93,0	59,93	5,13	3,73	$C_{18}H_{18}BrNO_2$	60,01	5,04	3,89	0,74
IIk	87,3	76,94	6,31	4,58	$C_{19}H_{20}FNO$	76,74	6,78	4,71	0,73
IIl	85,0	72,65	6,52	4,31	$C_{19}H_{20}ClNO$	72,71	6,42	4,46	0,65
IIm	92,0	63,50	5,59	3,80	$C_{19}H_{20}BrNO$	63,70	5,63	3,91	0,54
IIn	88,0	77,11	7,34	4,19	$C_{20}H_{22}FNO$	77,14	7,12	4,50	0,64
IIo	96,0	73,12	6,46	4,21	$C_{20}H_{22}ClNO$	73,27	6,76	4,27	0,68
IIp	90,0	64,13	5,83	3,47	$C_{20}H_{22}BrNO$	64,52	5,96	3,76	0,72

TABLE 2. Hydrochlorides and Iodomethylates of Substituted α-Aminoacetophenones IIIa-p and IVc, d, g, h

Compound	mp, °C	Found, %		Empirical formula	Calculated, %		R_f
		N	Cl		N	Cl	
IIIa	163—5	4,83	11,98	$C_{16}H_{23}NO_2 \cdot HCl$	4,70	11,90	0,67
IIIb	131—3	4,45	11,51	$C_{17}H_{25}NO_2 \cdot HCl$	4,49	11,37	0,67
IIIc	157—60	4,14	10,70	$C_{18}H_{27}NO_2 \cdot HCl$	4,30	10,88	0,60
IIId	140—3	4,23	10,51	$C_{19}H_{29}NO_2 \cdot HCl$	4,12	10,43	0,63
IIIe	135—7	4,74	12,38	$C_{15}H_{23}NO_2 \cdot HCl$	4,90	12,40	0,70
IIIf	123—5	4,70	11,90	$C_{16}H_{25}NO_2 \cdot HCl$	4,67	11,83	0,61
IIIg	223—4	3,47	9,11	$C_{23}H_{32}NO_2 \cdot HCl$	3,57	9,06	0,65
IIIh	125—8	4,20	10,62	$C_{18}H_{29}NO_2 \cdot HCl$	4,27	10,81	0,66
IIIi	227—9	4,13	10,34	$C_{18}H_{18}ClNO_2 \cdot HCl$	3,97	10,06	0,85
IIIj	198—200	3,48	8,45	$C_{18}H_{18}BrNO_2 \cdot HCl$	3,53	8,37	0,76
IIIk	240—3	4,20	10,62	$C_{19}H_{20}FNO \cdot HCl$	4,20	10,40	0,74
IIIl	212—5	4,29	10,19	$C_{19}H_{20}ClNO \cdot HCl$	4,00	10,12	0,66
IIIm	208	3,51	8,77	$C_{19}H_{20}BrNO \cdot HCl$	3,55	8,98	0,56
IIIn	199—202	4,30	9,90	$C_{20}H_{22}FNO \cdot HCl$	4,03	10,19	0,65
IIIo	179—80	3,71	9,55	$C_{20}H_{22}ClNO \cdot HCl$	3,84	9,73	0,70
IIIp	150—2	3,54	8,45	$C_{20}H_{22}BrNO \cdot HCl$	3,43	8,67	0,75
IVh	125—6	3,44	28,12	$C_{18}H_{29}NO_2 \cdot CH_3I$	3,72	28,51	0,71
IVe	129—31	3,40	29,50	$C_{18}H_{27}NO_2 \cdot CH_3I$	3,24	29,42	0,58
IVg	133—5	2,53	25,43	$C_{23}H_{32}NO_2 \cdot CH_3I$	2,81	25,56	0,65
IVd	128—30	3,03	28,30	$C_{19}H_{29}NO_2 \cdot CH_3I$	3,12	28,51	0,66

The individuality of the compounds synthesized was confirmed by the data of TLC, PMR and IR spectroscopy, and elemental analysis. In the IR spectra of IIa-p, there are absorption bands of the carbonyl group (1690-1680 cm^{-1}). The PMR spectra of compounds IIa-h contain multiplet signals of aromatic protons in the 6.8-7.9 ppm region, and also a singlet of methylene protons at 3.5 ppm (CCH_2N). In the PMR spectra of compounds IIi-p, a multiplet signal of unsubstituted aromatic ring protons is observed at 7.2 ppm (5 aromatic protons), and also a singlet of the methyl group proton at 4.7 ppm ($CCH(C_6H_5)N$). The PMR spectra of the compounds differ little in the positions of the proton signals of the substituted aromatic ring.

EXPERIMENTAL CHEMISTRY

The TLC was carried out on a fixed silica gel–gypsum layer. The system of solvents used was n-butanol–ethanol–acetic acid–water (8:2:1:3), and the development was carried out by iodine vapors. The IR spectra were run on the UR-20 spectrophotometer (GDR). The PMR spectra were run on the Varian T-60 spectrometer, using carbon tetrachloride as solvent, and tetramethylsilane as standard.

α-Bromo-4-alkoxyacetophenones and α-Bromo-α-phenyl-4-haloacetophenones (Ia-g). These were obtained by the method described in [5, 6].

α-Phenyl-4-haloacetophenones. These were obtained by the method described in [7].

General Method for Preparation of N-Substituted α-Amino-4-alkoxyacetophenones (IIa-h) and α-Amino-α-phenyl-4-haloacetophenones (IIi-p). A 0.2-mole portion of amine is added to an ether solution of 0.1 mole

TABLE 3. Action of Hydrochlorides of Substituted α-Aminoacetophenones IIj, k, m, n, p on Models of Chronic Inflammation in Rats (Pellet granulema)

Compound	Method of administration	Suppression of granulema development, %	
		5 mg/kg	50 mg/kg
IIIj	Per os	33,3	23,5
	P	>0,05	>0,05
	Subcutaneously	60	43,3
	P	0,01	0,01
IIIk	Per os	35	25
	P	<0,05	>0,05
	Subcutaneously	46	39
	P	<0,01	>0,05
IIIm	Per os	46,7	38,5
	P	<0,01	<0,05
IIIn	Per os†	39,3	18,4
	P	0,01	>0,05
IIIp	Per os	44,3	52,3
	P	0,01	<0,01
Indomethacin 3 mg/kg	Per os	60	
	P	<0,01	

*In a dose of 1 mg/kg, a 56% suppression is obtained ($P < 0.01$).
†In a dose of 1 mg/kg, a 33.3% suppression in obtained ($P < 0.01$).

of α-bromo-4-alkoxy- and α-phenyl-α-bromo-4-haloacetophenones. The mixture is stirred and left to stand at room temperature for 3 h. The amine hydrobromide is filtered, and ether is evaporated. The unreacted amine is distilled at reduced pressure. An oily product is obtained which is the amino ketone IIa-p (Table 1).

General Method for Preparation of Hydrochlorides of N-Substituted α-Amino-4-alkoxy- and α-Amino-α-phenyl-4-haloacetophenones (IIIa-p). An ether solution of hydrogen chloride is added dropwise to an ether solution of IIa-p to a weakly acid reaction. The precipitate is filtered, washed with absolute ether, and recrystallized from acetone. The physical constants are listed in Table 2.

General Method for Preparation of Iodomethylates of N-Substituted α-Amino-4-alkoxyacetophenones (IVc, d, g, h). Methyl iodide is added to an ether solution of IIc, d, g, h, and the mixture is left to stand in the dark for 24 h. The precipitate is filtered and recrystallized from absolute alcohol or acetone. The physical constants are listed in Table 2.

EXPERIMENTAL BIOLOGY

The antipyretic, analgesic, and antiinflammatory properties of hydrochlorides IIIa-p were studied on the model of a yeast fever, acute Carrageen inflammation of rat paw, and chronic proliferative inflammation (Pellet granulema) [8-11] in doses of 1, 5, and 50 mg/kg. The determination of acute toxicity in mice showed that all these compounds are slightly toxic. Their maximal endurable dose on oral administration exceeds 1000 mg/kg.

Fluoro- and bromo derivatives of α-amino ketones suppressed the development of granulation tissue during chronic inflammation (Table 3), and the corresponding chlorine derivatives did not exhibit a similar activity. All these compounds did not show antiinflammatory or analgesic action on acute Carrageen inflammation and antipyretic action in yeast fever in rats.

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PYRIMIDINES.

LIX. SYNTHESIS AND BIOLOGICAL PROPERTIES OF N-SUBSTITUTED DIHYDROURACILS AND DIHYDROTHIOURACILS

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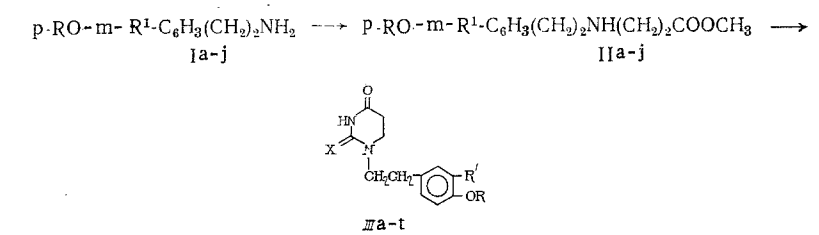
N-substituted pyrimidines with p-alkoxybenzyl groups have been described in earlier reports [1-3]. In continuation of these studies, in order to elucidate the relationship of biological properties to structure, we have synthesized some new dihydrouracils and dihydrothiouracils (IIIa-t), containing N-phenethyl groups, from phenethylamines (Ia-j).



IIIa-t

Ia, g, IIa, g: R = CH_3; Ib, h, IIb, h R = C_2H_5; Ic, i, IIc, i: R = C_3H_7; Id, l, IId, l: R-iso-C_3H_7; Ie, IIe: R = C_4H_9; If, IIf: R-iso-C_3H_7; Ia-f, IIa, f R^1 = H; Ig, j, IIg-j R^1 = CH_3; IIIa: R = CH_3, R^1 = H, X = O; IIIb R = C_2H_5; R^1 = H, X = O; IIIc. R = C_3H_7, R^1 = H, X = O; IIId: R-iso-C_3H_7, R^1 = H, X = O; IIIe. R = C_4H_9, R^1 = H, X = O; IIIf: R-iso-C_4H_9, R^1 = H, X = O; IIIg: R = R^1 = CH_3, X = O; IIIh R = C_2H_5, R^1 = CH_3, X = O; IIIi: R = C_3H_7, R^1 = CH_3, X = O; IIIj: R-iso-C_3H_7, R^1 = CH_3, X = O; IIIk: R = CH_3, R^1 = H, X = S; IIIl: R = C_2H_5, R^1 = H, X = S; IIIm: R = C_3H_7, R^1 = H, X = S; IIIn: R = iso-C_3H_7, R = H, X = S; IIIl: R = C_4H_9, R^1 = H, X = O; IIIp: R = iso-C_4H_9, R^1 = H, X = S; IIIo R = R^1 = CH_3, X = S; IIIr: R = C_2H_5, R^1 = CH_3, X = S; IIIs: R = C_3H_7, R^1 = CH_3, X = S; IIIq: R = iso-C_3H_7, R^1 = CH_3, X = S.

The starting materials (Ia-j) were obtained by reducing p-alkoxy- and m-methyl-p-alkoxybenzyl cyanides over a standard industrial catalyst consisting of nickel on chromium oxide, as described in the literature [4, 5]. Reaction with methyl acrylate in absolute methanol at ambient temperature converted the amines (Ia-j) into the methyl β-(phenethylamino)propionates (IIa-j). Reaction of the latter with urea or ammonium thiocyanate in an acid medium gave the dihydrouracils and dihydrothiouracils (IIIa-t).

The purities of the compounds (IIIa-t) were checked by TLC, and their structures established by mass spectrometry. The mass spectra of (IIIi) and (IIIq) showed peaks for the molecular ions, together with a number of fragment peaks (290, 206, 177, 164, 134, 107, 292, 208, 162, 134, 116, 107), the derivation of which confirmed their structures.

EXPERIMENTAL CHEMISTRY

Mass spectra were obtained on an MX-1303 instrument with direct introduction of the sample into the ionization region at a temperature 40-50°C below the melting point, ionizing electron energy 30 eV. Chromatography

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