SYNTHESIS AND BIOLOGICAL ACTIVITY OF HYDROCHLORIDES OF α-AMINO-α-H(PHENYL)-(3-FLUORO-4-METHOXY)ACETOPHENONES

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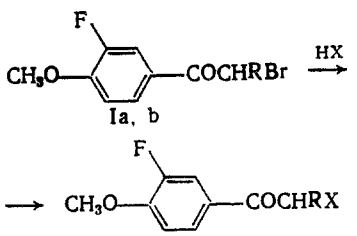
Earlier we published an article on the synthesis and biological activity of hydrochlorides of α-phenyl-β-amino-(3-fluoro-4-methoxy)propiophenones [5].

As a continuation of these investigations and with the purpose of studying the local anesthetic and antiinflammatory activities, we have prepared by the reaction of α-bromo- and α-bromo-α-phenyl-(3-fluoro-4-methoxy)acetophenone (I) with different amines in absolute ether α-amino-α-H(phenyl)-(3-fluoro-4-methoxy)acetophenones (IIa-d, IIIa-c):

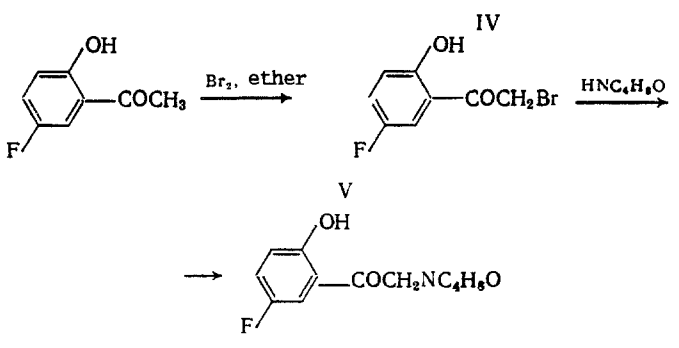


Ia, b

IIa–d, IIIa–c

R = H (Ia, IIa-d), C_6H_5 (Ib, a-c);
X = $N(C_2H_5)_2$ (IIa), $N(iso\text{-}C_3H_7)_2$ (IIb), N-morpholino (IIc, IIIa), N-piperidino (IId, IIIb), N-cylcohexylamino (IIIc)

The substituted acetophenones required for the synthesis of α-bromoketones (I) were prepared by acylation of 2-fluoroanisole with acetyl or phenylacetyl chloride. In the case of acylation of 4-fluoroanisole with acetyl chloride, we isolated, in addition to the 2-methoxy-5-fluoroacetophenone expected, 2-hydroxy-5-fluoroacetophenone (IV), which was subsequently converted to α-bromo-(2-hydroxy-5-fluoro)acetophenone (V) and then to α-morpholino-(2-hydroxy-5-fluoro)acetophenone (VI):



V

VI

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TABLE 1. Physicochemical Constant of α-Aminoketones IIa-d, IIIa-c, and Their Hydrochlorides

Compound	Yield, %	mp., °C	R_f	Empirical formula
IIa	58,6	—	0,67	$C_{13}H_{18}FNO_2$
	—	157—158	0,69	$C_{13}H_{18}FNO_2 \cdot HCl$
IIb	45,3	—	0,68	$C_{15}H_{22}FNO_2$
		173—174	0,69	$C_{15}H_{22}FNO_2 \cdot HCl$
IIc	86,3	81—82	0,70	$C_{13}H_{18}FNO_3$
		183—184	0,69	$C_{13}H_{16}FNO_3 \cdot HCl$
IId	84,4	—	0,70	$C_{14}H_{18}FNO_2$
		186—188	0,71	$C_{14}H_{18}FHO_2 \cdot HCl$
IIIa	87,8	—	0,76	$C_{19}H_{20}FNO_3$
		193—194	0,79	$C_{19}H_{20}FNO_3 \cdot HCl$
IIIb	80,0	—	0,75	$C_{20}H_{22}FNO_2$
		142—144	0,78	$C_{20}H_{22}FNO_2 \cdot HCl$
IIIc	69,0	—	0,70	$C_{21}H_{24}FNO_2$
		176—178	0,71	$C_{21}H_{24}FNO_2 \cdot HCl$

TABLE 2. Antiinflammatory and Analgetic Activities of the Hydrochlorides of Substituted α-Acetophenones

Compound	MED, mg/kg	% Suppression of inflammation on administering carrageenan		% Suppression of inflammation on administering cardboard pieces		% Suppression of pain in case of administering carrageenan at a dose of 5 mg/kg
		5 mg/kg	50 mg/kg	1 mg/kg	5 mg/kg	
IIa	300	0	0	0	0	25
IIc	700	24	34	41,6	41,6	47,7
IId	300	0	0	0	0	35
IIIa	700	0	0	32	0	47
IIIb	700	26	32	24	49,4	38,1
IIIc	700	20	0	48	36	28,6
VI	400	0	0	25	41,7	38

Aminoketones IIa, b, d, and IIIa-c are viscous oily compounds and IIc and VI are crystalline compounds. The individuality and purity of the compounds prepared was checked by means of TLC and data of elemental analyses, and the structure by IR and NMR spectral data, and also by mass spectroscopy.

EXPERIMENTAL (CHEMICAL)

TLC was carried out on a fixed silica gel—gypsum layer. The solvent system was n-butanol—ethanol—acetic acid—water 8:2:1:3. Spots were visualized with iodine vapor. IR spectra were taken on an IK-20 spectrometer (GDR) from dispersions in paraffin oil. PMR spectra were recorded on Varian T-60 (USA), operating at 60 MHz, and XL-200 (USA), operating at 200 MHz, spectrometers; internal standard TMS, solvent carbon tetrachloride.

3-Fluoro-4-methoxyacetophenones were prepared according to [5].

α-Bromo- and α-bromo-α-phenyl-(3-fluoro-4-methoxy)- acetophoneones were prepared according to [7].

α-Phenyl-α-piperidino-(3-fluoro-4-methoxy)acetophenone (IIIb) was prepared according to [4] from 4.5 g (0.014 mole) of α-phenyl-α-bromo-(3-fluoro-4-methoxy)acetophenone in absolute ether and 2.38 g (0.028 mole) of piperidine. IR spectrum, ν, cm^{-1}: 1680 (C=O). PMR spectrum (CCl_4), δ, ppm: 1.4 [6H, m, $(CH_2)_3$]; 2.4 [4H, m, $(CH_2)_2N$]; 3.76 (3H, s, CH_3O); 4.7 (1H, s, -CH-); 6.85-8.05 (8H, m, aromatic protons). Compounds IIa-d and IIIa, c were prepared in the same way; constants are listed in Table 1.

2-Hydroxy-5-fluoroacetophenone (IV) was prepared according to [5] from a mixture of 133.5 g (1 mole) of aluminum trichloride in 150 ml of CCl_4, 126.1 g (1 mole) of 4-fluoroanisole, and 78.5 g (1 mole) of acetyl chloride. Yield 68 g (44.1%) of IV, mp 56-57°C, R_f 0.51. M^+ 154 (mass spectrometry). $C_8H_7FO_2$. PMR spectrum (CCl_4), δ, ppm: 11.96 (1H, s, OH); 6.8-7.3 (3H, m, 3,4,6-H); 2.60 (3H, s, $COCH_3$).

α-Bromo-(2-hydroxy-5-fluoro)acetophenone (V) was prepared according to [5] from 36.5 g (0.024 mole) of 2-hydroxy-5-fluoroacetophenone and 38.4 g (0.024 mole) of bromine in a mixture of ether and dioxane. Yield 41 g (80%) of V, mp 86-87°C, R_f 0.60. $C_8H_6BrFO_2$. PMR spectrum (CCl_4), δ, ppm: 11.53 (1H, s, OH); 6.9-7.7 (3H, m, 3,4,6-H); 4.46 (2H, s, $COCH_2$).

α-Morpholino-(2-hydroxy-5-fluoro)acetophenone (VI) was prepared according to [4] from 14.8 g (0.063 mole) of α-bromo-(2-hydroxy-5-fluoro)acetophenone in absolute ether and 12.2 g (0.014 mole) of morpholine. Yield 9 g (56.4%) of VI, mp 80-82°C, R_f 0.6. $C_{21}H_{14}FNO_3$. IR spectrum, ν, cm^{-1}: 1680 (C=O). PMR spectrum (CCl_4), δ, ppm: 11.76 (1H, s, OH); 6.7-7.8 (3H, m, 3,4,6-H); 3.66 [4H, t, $O(CH_2)_2$]; 3.56 (2H, s, $COCH_2$); 2.6 [4H, t, $N(CH_2)_2$]. Hydrochloride $C_{21}H_{14}FNO_3 \cdot HCl$, mp 199-200°C, R_f 0.61.

EXPERIMENTAL (PHARMACOLOGICAL)

The activation of the compounds were studied with the models of anesthesiometry and analgesiometry, and of antiinflammatory and antidepressive activities.

The local anesthetic activity in case of conduction anesthesia in vitro was determined with isolated frog nerves [3]. Novocaine was used as the control preparation. Surface anesthesia was determined in 1% concentrations with rabbit corneas according to Renier's method [6].

The central anesthetic activity was studied in white mice weighing 18-20 g with the "hot plate" method on intraperitoneal injection of the compounds at a dose of 30 mg/kg [10]. In experiments with rats (mechanical squeezing of the tail [9]) we studied the suppression of the analgetic activity of morphine (opioid antagonism) at a dose of 5 mg/kg (ED_{99}) [9]. The compounds were administered subcutaneously at a dose of 10 mg/kg.

The antiinflammatory and analgetic activities were studied with the models of carrageenan edema of rabbit paws and chronic proliferative inflammation (Pellet's granuloma) [1, 11]. The compounds were administered internally at doses of 1.5 and 50 mg/kg. The acute toxicity of the compounds studied was determined by their maximal tolerant dose in white mice on internal administration.

In studying the antidepressive activity [8] we determined the influence of the compounds on the behavior and the motor activity of the animals, on the effects on hexanal, reserpine and tryptamine, and also on hyperkinesis caused by administration of 5-oxytrytophan (5-OTP). The compounds were administered subcutaneously at doses of 10 and 100 mg/kg, tryptophan at 70 mg/kg, reserpine at 2 mg/kg, tryptamine at 250 mg/kg, and 5-OTP at 50 mg/kg, intraperitoneally. The experiments were carried out with white mice and rats of both sexes weighing 18-22 and 130-160 g, respectively. The obtained data were processed statistically [2] and compared with those of the control drug indopamon (5 mg/kg).

The results obtained from the experiments about surface anesthesia, central anesthesia, and opioid antagonism showed that the compounds have weak activities. In the investigation of the local anesthetic activity (conduction anesthesia) compounds VI and IIIa block the conduction via the nerve by 84 and 71.5%, respectively. The control preparation, Novocaine, blocks the conductivity by 92% under the same conditions.

The results of the experimental data obtained from the investigation of the antiinflammatory and analgetic properties are listed in Table 2. It can be seen from this table that the MED of compounds IIc and IIIa-c is 700 mg/kg, and that those of compounds IIa and IId are considerably lower (300 mg/kg). Compounds IIc, IIIb, and IIIc reduce carrageenan edema of rat paws at doses of 5 and 50 mg/kg and suppress the growth of fibrogranular tissue at doses of 1 and 5 mg/kg. All the compounds studied suppress pain at a dose of 5 mg/kg by 25-45% ($P < 0.01$). The

control preparation voltaren, at a dose of 10 mg/kg, considerably (by 65%) suppresses edema and pain in case of carrageenan inflammation; its MED is 470 mg/kg.

Investigations of the antidepressive properties showed that all the compounds, with the exception of IIc, have a stimulating action on the animals at a dose of 100 mg/kg: they increase the spontaneous motor activity and the tactile sensitivity, and cause exophthalmos and stereotypic movements. Compounds IIc and IId prolong the soporific effect of hexenal by a factor of two ($P < 0.01$), but the others are inactive. When administered 1 h before reserpine, compound IIc counteracts the development of the depressing effects of reserpine: instead of depression, which is characteristic of neurolytics, raising of the motor activity, piloerection, stereotypy, and aggressiveness are observed. Only compound IIc increases the toxicity of tryptamine by 40% ($P < 0.05$) in grouped mice. In experiments with mice, compound IIc, administered before 5-OTP, causes 14-15 episodes of shaking of the head over a period of 30 min, but with indopan this action is considerably more pronounced. All the compounds do not have similar properties at a lower dose (10 mg/kg). Investigation of the acute toxicity of compound IIc in white mice showed that in the case of intraperitoneal administration its LD_{50} is 950 mg/kg.

The experiments have shown that compound IIc is the most active of the compounds investigated, but the properties mentioned above manifest themselves at high doses.

Thus, some derivatives of α-amino- and α-phenyl-α-amino-(3-fluoro-4-methoxy)acetophenones possess local anesthetic, antidepressive, antiinflammatory, and analgetic activities and are of interest for the search for novel medicines in this series.

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