β-AMINO KETONES — SUBSTITUTED α-AMINO ACIDS.

II. N-[β-(p-SUBSTITUTED BENZOYL)ETHYL]-D-α-ALANINES, GLYCINES AND THEIR ETHYL ESTERS

A. G. Agababyan, G. A. Gevorgyan,
L. P. Podol'skaya, T. O. Asatryan,
N. A. Apoyan, R. A. Aleksanyan,
and O. L. Mndzhoyan

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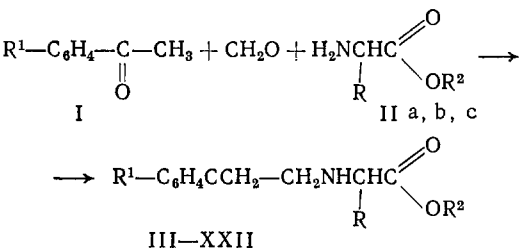
We have continued our work on the biological activity of β-amino ketones containing an α-amino acid residue [1] by synthesizing N-β-10-benzoylethyl- and N-[β-(p-substituted benzoyl) ethyl]alanines, glycines, their hydrochlorides, and some of their ethyl esters (III-XXIII):



I II a, b, c

III—XXII

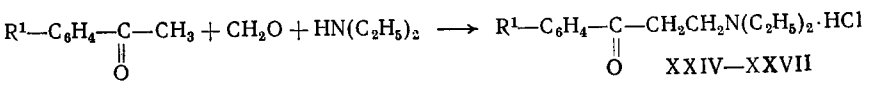
IIa: $R = CH_3$; $R^2 = H$;
IIb: $R = CH_3$; $R^2 = C_2H_5$;
IIc: $R = H$; $R^2 = C_2H_5$;
III—XIV: $R = CH_3$; $R^1 = H$, AlkO ; $R^2 = H$;
XV, XVI: $R = H$; $R^1 = Hal$; $R^2 = C_2H_5$;
XVII—XX: $R = CH_3$; $R^1 = Hal$; $R^2 = H$;
XXI, XXII: $R = CH_3$; $R^1 = C_3H_7O$; $R^2 = C_2H_5$.

We synthesized III-XXII by aminomethylation of the 4-substituted acetophenones I. We have previously found [1] that the condensation of glycine with formaldehyde and I gives low yields. Replacement of the free amino acid by its ethyl ester considerably facilitated the condensation.

In the work described here we have examined the aminomethylation of 4-substituted acetophenones with alanine (IIa) with the ethyl alaninate (IIb) and glycinate (IIc).

Work on the condensation of alanine with acetophenone and paraformaldehyde revealed that the yields of the amino ketones III-XXII vary considerably depending on the reaction conditions and the reactant ratio. Thus after 10 h heating in ethanol (reactant ratio (1:1:1) at pH 6.0-7.0 the yield did not exceed 10-12%, whereas at pH 1.0-2.0 after the same heating time it increased to 28-30%. Change in the reactant ratio to a twofold excess of acetophenone and formaldehyde over alanine raised the yield to 30% (pH 6.0-7.0) and to 50% (pH 1.0-2.0). Replacement of ethanol by dioxane and use of iron trichloride as catalyst did not increase the yield.

We also prepared amino ketones III, XI, XIII, and XIX by transamination [2]:



XXIV—XXVII

XXIV: $R^1 = H$; XXV: $R^1 = Iso\text{-}C_3H_7O$; XXVI: $R^1 = C_4H_9O$; XXVII: $R^1 = Br$.

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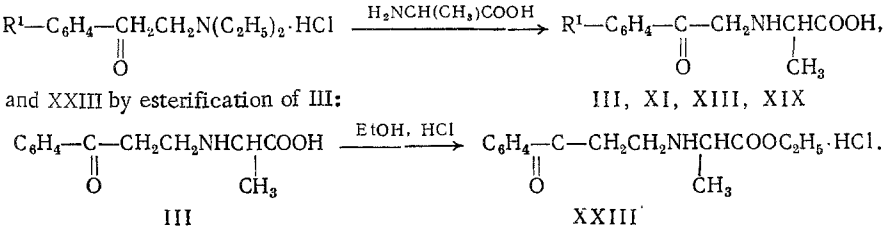

and XXIII by esterification of III:

The IR spectra of amino ketones III-XIV and XVII-XX have keto (ν_{CO} 1690 cm^{-1}) and carboxyl bands (ν_{COO} 1610 cm^{-1}), and also the amino band (ν_{NH_2} 3060 cm^{-1}) typical of amino acids. In the IR spectra of XV, XVI, XXII, and XXIII the carboxyl band is replaced by the ester carbonyl band (ν_{CO} 1755 cm^{-1}).

EXPERIMENTAL PHARMACOLOGICAL PART

We screened the synthetic compounds for antipyretic and antiinflammatory properties against yeast fever and carrageenen inflammation in rats [3]. A preliminary evaluation of their toxicity in mice revealed that all the compounds are relatively nontoxic — their maximum tolerable dose is more than 500 mg/kg.

We examined the activity of the preparations in doses of 5, 50, and 100 kg/kg. In all the tests the compounds were administered perorally in 0.5% collodion solution. Each dose level was tested in four or five animals. The tests revealed that none of the compounds have antiinflammatory or antipyretic properties in these doses.

We also examined the effect of the synthetic compounds on the coronary circulation by Moravitz and Zahn's method [4] in Kaverina's modification [5]. The essence of this method is the measurement of the volume of blood passing through the coronary sinus in unit time (10 sec) in cats narcotized with urethane and chloralose (1 g of urethane and 60 mg of chloralose per 1 kg weight) before and after administration of the test compound. The favorable effect of the compounds on the myocardial blood supply was assessed from the increase in the coronary blood flow. Tests were carried out on 22 animals. The majority of compounds were poorly soluble in water and were injected into the femoral vein as a suspension in doses of 0.1 and 1 mg per 1 kg weight.

We compared the coronary dilating activity of the compounds with the effect of the coronary dilator intensain under the same test conditions. The tests revealed that these preparations did not affect the coronary blood flow.

EXPERIMENTAL CHEMICAL PART

Thin-layer chromatography was carried out on silica gel-gypsum. The solvent system was n-butanol—acetic acid—ethanol—water (8:1:2:3); chromatograms were visualized with iodine and 1% aqueous ninhydrin. The IR spectra were recorded on a UR-20 spectrophotometer.

4-Substituted acetophenones I were prepared by the procedure of [6].

Ethyl glycinate and alaninate hydrochlorides IIb and IIc were prepared by the procedure of [7].

N-(β-Benzoylethyl)-D-alanine III was prepared by the procedure of [2].

N-[β-(p-Substituted benzoyl)ethyl]-D-α-alanines III-XIV and XVII-XX, Method A, Aminomethylation Reaction. A mixture of the p-substituted acetophenone (I) (0.1 mole), paraformaldehyde (3.3 g, 0.11 mole), and D-α-alanine (4.5 g, 0.05 mole) in ethanol (50 ml) acidified with concentrated hydrochloric acid to pH 1.0-2.0 was refluxed for about 15 h. After cooling of the reaction mixture to room temperature the product was filtered off and washed with ether. The solvent was stripped from the filtrate under vacuum and the residue was treated with ether to remove unreacted ketone I. The aqueous layer was made alkaline with 25% ammonia and extracted with ether to isolate the product. Their physical constants are summarized in Tables 1 and 2.

Method B. Transamination Reaction (III, XI, XIII, and XIX). A mixture of D-α-alanine (0.9 g, 0.01 mole) and XXIV-XXVII (0.01 mole) in water (20 ml) was heated on the water bath

TABLE 1. N-[β-(Alkoxybenzoyl)ethyl]-D-α-alanines and Their Hydrochlorides

Compound	R^1	Yield, %	Melting point, °C	R_f	Found, %				Formula	Calculated, %			
					C	H	N	Cl		C	H	N	Cl
III	H	38,7	214—7	0,46	65,31	6,90	6,42	—	$C_{12}H_{15}NO_3$	65,14	6,83	6,33	—
IV	H	—	hygroscopic	0,56	54,07	6,41	5,49	13,48	$C_{12}H_{16}ClNO_3$	55,93	6,26	5,44	13,76
V	CH_3O	25,0	oil	0,67	61,97	6,74	5,48	—	$C_{13}H_{17}NO_4$	62,14	6,82	5,57	—
VI	CH_3O		hygroscopic	0,72	54,31	6,47	4,51	12,40	$C_{13}H_{18}ClNO_4$	54,26	6,31	4,87	12,32
VII	C_2H_5O	33,7	oil	0,61	63,49	7,35	5,18	—	$C_{14}H_{19}NO_4$	63,38	7,22	5,28	—
VIII	C_2H_5O		hygroscopic	0,63	55,61	6,49	4,75	11,29	$C_{14}H_{20}ClNO_4$	55,72	6,68	4,64	11,75
IX	C_3H_7O	35,7	185—7	0,67	64,91	7,99	4,85	—	$C_{14}H_{21}NO_4$	64,50	7,58	5,02	—
X	C_3H_7O		hygroscopic	0,63	57,30	7,15	4,31	11,21	$C_{15}H_{22}ClNO_4$	57,05	7,02	4,44	11,23
XI	iso-C_3H_7O	27,0	201—5	0,68	64,60	7,38	5,24	—	$C_{15}H_{21}NO_4$	64,50	7,58	5,02	—
XII	iso-C_3H_7O		hygroscopic	0,66	57,21	7,18	4,35	11,30	$C_{15}H_{22}ClNO_4$	57,05	7,02	4,44	11,23
XIII	C_4H_9O	28,5	195—8	0,73	65,38	8,04	4,42	—	$C_{16}H_{23}NO_4$	65,51	7,90	4,77	—
XIV	C_4H_9O		hygroscopic	0,62	58,48	7,49	4,39	10,94	$C_{16}H_{24}ClNO_4$	58,26	7,33	4,25	10,75

TABLE 2. N-[β-(p-Halobenzoyl)ethyl]-D-α-alanines, Ethyl N-[β-(p-Halobenzoyl)ethyl]glycinates, N-[β-(p-Propoxybenzoyl)ethyl]-D-α-alanine, and Their Hydrochlorides

Compound	R	R^1	R^2	Yield, %	Melting point, °C	R_f	Found, %					Formula	Calculated, %				
							C	H	N	Hal	Cl		C	H	N	Hal	Cl
XV	H	Cl	C_2H_5	25,5	164—5,5	0,69	50,55	5,47	4,91	22,90	11,94	$C_{13}H_{17}Cl_2NO_3$	50,34	5,60	4,57	23,16	11,58
XVI	H	Br	C_2H_5	28,0	173—4,5	0,70	44,61	4,81	4,40	22,09	10,44	$C_{13}H_{17}BrClNO_3$	44,53	4,89	3,99	22,79	10,11
XVII	CH_3	Cl	H	26,6	129—32 (hygroscopic)	0,62	56,19	5,38	5,21	14,20	—	$C_{12}H_{13}ClNO_3$	56,37	5,52	5,48	13,87	—
XVIII	CH_3	Cl	H	—	(hygroscopic)	0,54	49,54	5,23	4,38	23,91	11,94	$C_{12}H_{15}Cl_2NO_3$	49,33	5,17	4,79	24,27	12,14
XIX	CH_3	Br	H	29,5	203—4,5	0,70	48,60	4,59	5,00	26,29	—	$C_{12}H_{14}BrNO_3$	48,02	4,70	4,67	26,62	—
XX	CH_3	Br	H	—	205—8 (decomp.)	0,68	42,74	4,61	4,31	23,49	10,48	$C_{12}H_{15}BrClNO_3$	42,82	4,49	4,16	23,74	10,53
XXI	CH_3	C_3H_7O	C_2H_5	—	(hygroscopic)	0,76	66,46	8,16	5,01	—	—	$C_{17}H_{25}NO_4$	66,42	8,20	4,56	—	—
XXII	CH_3	C_3H_7O	C_2H_5	32,5	103—5	0,68	59,14	5,17	4,10	—	10,09	$C_{17}H_{26}ClNO_4$	59,38	5,28	4,07	—	10,31

Here Hal is the percentage of Br (R = Br) or the total percentage of Cl (R = Cl) determined by combustion.

for 2 h and then cooled. The crystalline product was filtered off and washed on the filter with acetone. The yields were 69.0, 31.5, 43.6, and 30.6% respectively.

Ethyl N-(β-Benzoylethyl)-D-α-alaninate Hydrochloride XXIII. To N-(β-benzoylethyl)-D-α-alanine (3.5 g, 0.016 mole) was added dropwise 4.6% alcoholic hydrogen chloride (25 ml). The mixture was stirred for 30 min and cooled with ice–salt mixture. After 2 h XXIII (3.2 g, 90.9%) was filtered off, mp 131-133°C (from ethanol). The mother liquor gave more product (0.8 g), mp 129-130°C. Found, %: N 4.80, Cl 11.99. $C_{14}H_{20}ClNO_3$. Calculated, %: N 4.90, Cl 12.41, R_f 0.73.

p-Substituted diethylaminopropiophenone hydrochlorides XXIV-XXVII were synthesized by the procedure of [8].

Ethyl N-[β-(p-Halobenzoyl)ethyl]glycinate and N-[β-(p-Propoxybenzoyl)ethyl]-D-α-alaninate hydrochlorides XV, XVI, XXII were prepared by the procedure of [1]. Their physical constants are summarized in Table 2.

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