SUBSTITUTION IN BARBITURIC ACIDS

I. Condensation of Barbituric Acid with Oxo Compounds

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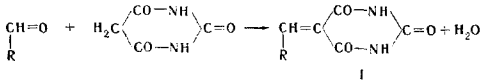
In water or aqueous alcohol, oxo compounds condense with one or two barbituric acid residues. The arylidene derivatives synthesized possess absorption maxima in the 240–260 and 320–440 nm regions, while the products of condensation with aliphatic aldehydes and ketones have only one absorption maximum, at 240–265 nm.

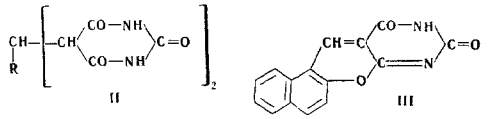
As is well known, the hydrogen atoms in position 5 of the barbituric acid molecule are extremely labile, in consequence of which this acid readily condenses with aldehydes, ketones, formamide, etc. Although the reaction of barbituric acid with oxo compounds was found as early as 1864 [1], no systematic investigations in this field have been performed up to the present time. We have set ourselves the aim of studying the condensation of barbituric acid with various oxo compounds and investigating the UV absorption spectra of the condensation products.

The condensation of barbituric acid with aromatic aldehydes takes place very readily, and in the majority of cases the condensation products precipitate directly when solutions of the components are mixed. The reaction takes place in three different ways. In the case of benzaldehyde and its m-nitro, p-nitro, 2,4-dinitro, p-chloro, p-hydroxy, and p-diethylamino derivatives, the monarylidene derivatives (I) are formed. Cinnamaldehyde and the aldehydes of the furan series react similarly.



I

Resorcylaldehyde, salicylaldehyde, and m-aminosalicylaldehyde form arylidenebis derivatives (II), while in the case of β-hydroxynaphthaldehyde the anhydridization of the mono-β-hydroxynaphthylidene derivative takes place with the formation of the anhydride III:

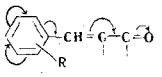


II

III

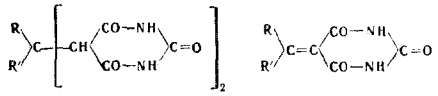
The arylidene derivatives synthesized (Table 1) are crystalline substances with an acid nature and dissolve in NH_4OH and NaOH solutions even in the cold or on gentle warming. The products of the condensation of barbituric acid with aliphatic aldehydes (Table 1) do not have sharp melting points. Of them, methyleneoxybarbituric acid is apparently a polymeric substance, since it is practically insoluable in the usual solvents and solutions of alkalis.

The alkylidene and arylidene derivatives of barbituric acid retain the absorption maximum in the 245–260 nm region that is characteristic for barbituric acid itself [2]. In addition, in the case of the 5-arylidene derivatives, because of the formation of a new, longer, chain of conjugation



a high-intensity absorption maximum appears in the region above 320 nm which may be called a K absorption band. This band is also retained for substances of structure II, which shows the transfer of electrons between the aryl and amide groups.

The condensation of barbituric acid with ketones takes place with considerably more difficulty. The condensation products (Table 2) are, as a rule, bis-(barbituric acid)s of structure IV and are only rarely normal derivatives of structure V.



IV V

The UV absorption spectra have a single absorption maximum in the 243–265 nm region.

Pharmacological studies carried out in the department of pharmacology of the Grodno Medical Institute have shown that the sodium salts of the benzylidene, p-hydroxybenzylidene, and resorcylidene derivatives cause slight and brief hypertension in doses of 10–20 mg/kg. At the same time, the sodium salts of the salicylidene and β-hydroxynaphthylidene derivatives cause an increase in arterial pressure by 48% in 5–20 min.

EXPERIMENTAL

Condensation of barbituric acid with aldehydes. A solution of 0.1 mole of barbituric acid in 100 ml of water was heated, and a solution of 0.1 mole of the appropriate aldehyde in 65 ml of ethanol was added. The mixture was boiled under reflux for 2 min–5 hr and cooled, and the precipitate formed was filtered off, washed with water and ether, and dried. The reactions with benzaldehyde, m-aminosalicylaldehyde, furfurylidene derivatives, formaldehyde, acetaldehyde, and 3-(α-furyl) acrolein were carried out only in an aqueous medium. The rapid formation of precipitates was observed in all cases with the exception of 2,5-dinitrobenzaldehyde, resorcylaldehyde, propionaldehyde, butyraldehyde, and isovaleraldehyde.

Table 1

Products of the Condensation of Barbituric Acid with Various Aldehydes (I, II, III)

Compound	R	Mp,	λ_{max}, nm	log ε	Empirical formula	Found, %			Calculated, %			Yield, %
						N	C	H	N	C	H	
I	C_6H_5	256*	255, 330	4,02, 2,88	$C_{11}H_8N_2O_3$	12,84	61,11	3,51	12,96	61,10	3,73	80,0
I	*m*-$O_2NC_6H_4$	232	260	4,25	$C_{11}H_7N_3O_5$	16,36	50,49	2,78	16,09	50,58	2,70	35,7
I	*p*-$O_2NC_6H_4$	265*	260	4,23	$C_{11}H_7N_3O_5$	16,51	50,64	2,54	16,09	50,58	2,70	70,1
I	2,4-$(NO_2)_2C_6H_3$	230	255	4,57	$C_{11}H_6N_4O_7$	17,92	43,10	2,00	18,29	43,12	1,97	46,8
I	*p*-ClC_6H_4	271*	255, 374	4,33, 3,25	$C_{11}H_7ClN_2O_3$	11,22	52,70	2,60	11,18	52,71	2,82	61,1
I	*p*-$(CH_3)_2NC_6H_4$	264*	255, 340	4,10, 4,39	$C_{13}H_{13}N_3O_3$	16,14	60,38	5,05	16,21	60,22	5,05	88,0
I	*p*-HOC_6H_4	270*	260, 336, 395	4,39, 2,78, 3,11	$C_{11}H_8N_2O_4$	12,12	56,60	3,50	12,03	56,70	3,46	54,9
II	*m*-HOC_6H_4	226	260, 320	4,55, 2,46	$C_{15}H_{12}N_4O_7$	15,25	49,70	3,11	15,55	50,00	3,36	59,6
II	*o*-HOC_6H_4	235	260	4,20	$C_{15}H_{12}N_4O_7$	15,50	50,25	3,26	15,55	50,00	3,36	91,1
II	2-OH-5-$NH_2C_6H_3$	203	245, 325	4,14, 4,26	$C_{15}H_{13}N_5O_7$	18,92	48,21	3,48	19,09	48,00	3,49	41,3
III	—	230	258, 420, 440	4,14, 2,94, 2,94	$C_{15}H_8N_2O_3$	10,44	68,12	3,26	10,60	68,18	3,05	62,1
I	$C_6H_5CH=CH$	270*	250, 375	4,08, 4,60	$C_{13}H_{10}N_2O_3$	11,70	—	—	11,56	—	—	100,0
I	2-C_4H_3O	260*	255, 370	3,58, 3,92	$C_9H_6N_2O_4$	13,54	—	—	13,59	—	—	77,7
I	5-CH_3-2-C_4H_2O	250*	256, 380	3,87, 4,39	$C_{10}H_8N_2O_4$	12,91	—	—	12,70	—	—	77,3
I	2-C_4H_3O—CH=CH	260*	245, 368	3,47, 4,43	$C_{11}H_8N_2O_4$	12,06	—	—	12,06	—	—	89,5
II	H	290*	255	4,00	$C_9H_8N_4O_6$	20,83	—	—	20,89	—	—	83,6
I	CH_3	223	260	3,88	$C_6H_6N_2O_3$	18,02	—	—	18,17	—	—	47,4
I	CH_3CH_2	180	255	3,91	$C_7H_8N_2O_3$	16,50	—	—	16,66	—	—	47,6
I	$CH_3CH_2CH_2$	115	260	4,09	$C_8H_{10}N_2O_3$	15,29	—	—	15,37	—	—	43,5
I	$(CH_3)_2CH$	172	240	3,95	$C_8H_{10}N_2O_3$	15,30	—	—	15,37	—	—	39,5
I	$(CH_3)_2CHCH_2$	180	253	3,99	$C_9H_{12}N_2O_3$	14,61	—	—	14,28	—	—	65,3

*Melts with decomposition.

Table 2

Products of the Condensation of Barbituric Acid with the Ketones IV and V.

Compound	R	R′	Mp, °C	λ_{max}, nm	log ε	Empirical formula	N, % found	N, % calculated	Yield, %
IV	CH_3	CH_3	275	255	4.30	$C_{11}H_{12}N_6O_2$	18.88	18.90	50.0
IV	CH_3	C_2H_5	275	255	4.35	$C_{16}H_{14}N_4O_6$	17.84	18.05	31.4
IV	C_2H_5	C_2H_5	250	255	4.39	$C_{13}H_{16}N_4O_6$	17.00	17.27	37.0
IV	CH_3	n-C_6H_{13}	250	255	4.21	$C_{16}H_{22}N_4O_6$	15.72	15.50	30.8
IV	CH_3	CH_3COCH_2	250	260	4.48	$C_{13}H_{14}N_4O_7$	16.78	16.56	20.0
IV	$-CH_2CH_2CH_2CH_2CH_2-$		245	263	4.32	$C_{13}H_{14}N_4O_6$	17.04	17.38	50.0
IV	$-CH_2CH_2CH_2CH_2-$		255	255	4.55	$C_{14}H_{16}N_4O_6$	16.92	16.66	37.0
IV	$-(CH_2)_2-CH(CH_3)-(CH_2)_2-$		248	255	4.46	$C_{15}H_{18}N_4O_6$	16.02	15.98	34.5
IV	CH_3	C_6H_5	250	277	4.46	$C_{16}H_{14}N_4O_6$	16.10	15.92	33.3
V	CH_3	$C_6H_5CH{:}CH$	250	265	3.95	$C_{14}H_{12}N_2O_3$	11.96	12.06	86.2
IV	p-$(CH_3)_2NC_6H_4$	p-$(CH_3)_2NC_6H_4$	167	243, 360	4.29, 4.51	$C_{25}H_{26}N_6O_6$	14.52	14.61	50.0
IV	CH_3	β-$C_{10}H_7$	257	257	4.28	$C_{20}H_{16}N_4O_6$	13.51	13.72	37.2

Condensation of barbituric acid with ketones. A mixture of 0.025 mole of barbituric acid and 0.025–0.05 mole of ketone was boiled in 50 ml of dilute ethanol (1:1) for 5 hr. The precipitate formed during the boiling process only in the case of cyclopentanone. After cooling, the precipitate was filtered off and was washed with water and ether. In the case of the reaction with Michler's ketone, the barbituric acid was dissolved in aqueous ethanol and the ketone was dissolved in a mixture of 20 ml of ethanol, 20 ml of water, and 20 ml of benzene.

The UV absorption spectra of the substances synthesized were recorded by means of an SF-4 spectrophotometer using $2.5 \times 10^{-6} - 10^{-5}$ M solutions prepared from double-distilled ethanol.

REFERENCES

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