REACTION OF DIALURIC ACID WITH HYDRAZINE DERIVATIVES

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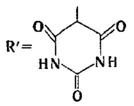
In the condensation of dialuric, thiodialuric, and acetyldialuric acids with hydrazine derivatives, the ketone character of the CO group in the 2 position is manifested only in the case of acetyldialuric acid; the hydroxy or mercapto group in dialuric and thiodialuric acids is substituted to form 5-substituted derivatives of these acids.

Dialuric acid, which is the most important analog of barbituric acid, the compounds of which are widely used in medicine, is of interest from the point of view of its physiological activity [1].

We set out to synthesize a number of derivatives of dialuric acid and to investigate their physiological activity. Since 5-substituted dialuric acids have been sufficiently fully described [2], we were interested in the 2-substituted derivatives, information regarding which is absent in the literature. In our earlier communications [3,4], we have already indicated that the CO group in the 2 position of barbituric acid has ketonic character. If this property is retained in dialuric acid, it should react with hydroxylamine, hydrazine, and hydrazine derivatives to form the corresponding azomethine derivatives.

Dialuric acid quite readily reacts with these compounds in weakly acidic and neutral media. Unlike dialuric acid, the compounds obtained are not acetylated under mild conditions, and more severe conditions lead to resinification of the reaction mixture. This provides a basis for assuming that there is no hydroxyl group in the 5 position of the compounds that we obtained, i.e., the hydroxyl group has undergone substitution. In order to confirm this assumption, we carried out similar condensations with monothiodialuric (5-mercaptobarbituric) acid. This reaction proceeded very readily and was accompanied by vigorous hydrogen sulfide evolution. The compounds obtained in this case did not depress the melting points of the corresponding dialuric acid derivatives.

$R'NHR$ I $\quad R'_2NNHR$ II $\quad R'NHNHR'$ IIa $\quad R'NHNH{-}R{-}NHNHR'$ III



In the case of hydroxylamine, 1,1-diphenylhydrazine, 2,4-dinitrophenyl hydrazine, and isonicotinoylhydrazine, mono derivatives (I) are formed with dialuric acid. Semicarbazide, thiosemicarbazide, phenylhydrazine, benzoylhydrazine, and m-methoxybenzoylhydrazine form 1,1-bis derivatives (II) of hydrazine, hydrazine hydrate forms a 1,2-bis derivative (IIa) of hydrazine, while a compound of the III type is formed in the case of dicarboxylic acid dihydrazide.

Acetyldialuric acid condenses with hydrazine derivatives with somewhat more difficulty. However, in this case the carbon in the 2 position undergoes nucleophilic attack. Hydrazones IV are formed in the case of semicarbazide, thiosemicarbazide, arylhydrazines, and carboxylic acid hydrazides, oxime IV is formed with hydroxylamine, azine V is formed with hydrazine hydrate, and dihydrazones VI are formed with dicarboxylic acid dihydrazides.

The synthesized compounds (Tables 1 and 2) are crystalline substances of acid character that are readily soluble in alkali. The condensation products of dialuric acid are quite resistance to acid hydrolysis,

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TABLE 1. Products of Condensation of Dialuric Acid with Hydrazine Derivatives

Comp.	R	mp, °C	Empirical formula	Found		Calc.		λ_{max}, nm	lg ε	Yield, %
				N, %	M*	N, %	M			
I	OH	208	$C_4H_5N_3O_4$	26,8	—	26,4	—	250	3,71	28
IIa	—	252	$C_8H_8N_6O_6$	30,0	290	29,6	284	248	4,22	33
II	$CONH_2$	300	$C_9H_9N_7O_7$	30,0	316	29,8	325	304	4,25	71
II	$CSNH_2$	225	$C_9H_9N_7O_6S$	28,1	348	28,5	341	238 360	4,15 4,12	56
II	C_6H_5	300	$C_{14}H_{12}N_6O_6$	23,7	350	23,3	360	280 370	3,72 3,77	41
I	$(C_6H_5)_2N$	300	$C_{16}H_{14}N_4O_3$	17,6	—	17,9	—	280 415	3,72 4,16	86
I	2,4-$(NO_2)_2C_6H_3NH$	228†	$C_{10}H_{10}N_6O_7$	25,5	—	25,7	—	395	4,40	52
II	C_6H_5CO	150	$C_{15}H_{12}N_6O_7$	21,1	394	21,6	387	224	4,22	52
II	m-$CH_3OC_6H_4CO$	256†	$C_{16}H_{14}N_6O_8$	20,2	425	20,1	416	240	4,39	75
I	C_5H_4NCONH	238	$C_{10}H_9N_5O_4$	25,7	—	26,1	—	246	4,17	58
III	COCO	280	$C_{10}H_{10}N_8O_8$	29,8	378	30,2	370	265	4,10	54
III	$CO(CH_2)_4CO$	176†	$C_{14}H_{18}N_8O_8$	26,5	434	26,3	426	243	4,25	40

*This is the molecular weight by the Rast method.

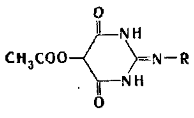
† Melts with decomposition.

TABLE 2. Products of the Condensation of Acetyl Dialuric Acid with Hydrazine Derivatives

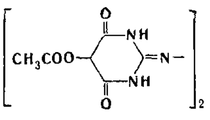
Comp.	R_2	mp, °C	Empirical formula	N, %		λ_{max}, nm	lg ε	Yield, %
				found	calc.			
IV	OH	168	$C_6H_7N_3O_5$	20,8	20,8	264	4,23	9
V	—	185	$C_{12}H_{12}N_6O_8$	23,1	22,8	220	4,25	18
IV	$NHCONH_2$	200	$C_7H_9N_5O_5$	29,2	28,9	260	4,09	25
IV	$NHCSNH_2$	300	$C_7H_9N_5O_4S$	27,5	27,0	241	4,26	11
IV	C_6H_5NH	175	$C_{12}H_{12}N_4O_4$	19,9	20,2	262	4,33	18
IV	$(C_6H_5)_2N$	250*	$C_{18}H_{16}N_4O_4$	16,3	15,9	405	4,05	33
IV	2,4-$(NO_2)_2C_6H_3NH$	170*	$C_{12}H_{10}N_6O_8$	23,4	23,0	386	4,52	23
IV	C_6H_5CONH	162	$C_{13}H_{12}N_4O_5$	18,9	18,5	220	4,38	21
IV	m-$CH_3OC_6H_4CONH$	240	$C_{14}H_{14}N_4O_6$	17,2	16,8	225	4,19	19
IV	C_5H_4NCONH	260*	$C_{12}H_{12}N_5O_5$	23,1	22,9	220	4,10	29
VI	COCO	161	$C_{14}H_{14}N_8O_{10}$	24,4	24,6	248	4,50	8
VI	$CO(CH_2)_4CO$	155	$C_{18}H_{22}N_8O_{10}$	21,9	22,3	223	4,26	11

* Melts with decomposition.

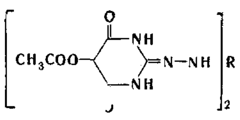
and hydrolysis products are detected only after evaporation with concentrated hydrochloric acid. The derivatives of acetyldialuric acid very readily hydrolyze in the presence of acids, and in this case the corresponding hydrazine, which gives a green color with sodium pentacyanoaminoferroate, forms initially, followed by the production of acetic acid.



IV



V



VI

As compared with the UV spectra of dialuric acid, which does not have a maximum in aqueous and alcohol solutions, primarily two absorption bands at 222-265 and 360-415 nm are observed in the UV spectra of the synthesized compounds. In all likelihood, the short-wave band is due to the presence of an amide chromophore. The semicarbazide, thiosemicarbazide, and phenylhydrazine groupings are responsible for the appearance of intense maxima related to the K band.

Preliminary pharmacological investigations, carried out in the Chair of Pharmacology of the Grodnenskii Medical Institute, have demonstrated that the compounds obtained potentiate the action of narcotics and have a certain antihypoxial and antispasmodic action.

EXPERIMENTAL

Dialuric Acid Derivatives (Table 1). A 0.01-mole sample of the hydrazine derivative in 20-40 ml of water or dilute acetic acid was added to a hot solution of 0.01 mole of dialuric acid in 30-50 ml of water. The mixture was heated on a water bath at 30-50° for 30-45 min, after which 0.005 mole of sodium acetate was added, and the mixture was shaken until a precipitate formed (20-30 min). The precipitate was removed by filtration, washed with water, alcohol, and ether, and dried in vacuo.

Acetyldialuric Acid Derivatives (Table 2). An equimolecular amount of an aqueous or alcoholic (in the case of 2,4-dinitrophenylhydrazine) solution of the hydrazine derivative was added to a solution of 0.01 mole of acetyldialuric acid in 50 ml of 50% ethanol. The mixture was shaken until a precipitate began to form (4-5 h) and was then allowed to stand in the cold for 24-30 h. The precipitate was removed by filtration, washed with water, alcohol, and ether, and dried to constant weight in vacuo. The UV spectra of 1-2 mg % alcohol solutions of the synthesized substances were recorded with an SF-4A spectrophotometer.

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