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I. K. Korobitsyna, I. G. Zhukova, V. V. Voronkova, and Yu. K. Yur’ ev

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Abstract

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Synthesis of 4-Hydroxy-2,2,5,5-tetraalkylfuranidones-3 by Reduction of 4-Isonitroso-2,2,5,5-tetraalkylfuranidones-3

(Presented by Academician A. N. Nesmeyanov, June 28, 1957)

From the literature it is known that attempts to synthesize oxy ketones of the furanidine series—4-hydroxyfuranidones-3—have not given a positive result ([1,2]).

Since it does not appear possible to apply, for the synthesis of 4-hydroxy-2,2,5,5-tetraalkylfuranidones-3, the usual methods employed for obtaining acyloins ([3]), we were compelled to seek other routes. It is known that the action of reducing agents, including zinc dust in acetic acid ([4,5,6]), on isonitroso ketones of both the aliphatic and alicyclic series usually leads either to aminoketones or to products of their condensation. However, in 1941 Stodola noted an interesting case of an anomalous course of the reaction, when the product of reduction of isonitrosodehydroisoandrosterone with zinc dust in 90% acetic acid proved to be oxydehydroisoandrosterone ([7]).

We have established that upon 6-7-hour heating of 4-isonitroso-2,2,5,5-tetraalkylfuranidones-3 with zinc dust in 50% acetic acid, not aminoketones but oxy ketones—4-hydroxy-2,2,5,5-tetraalkylfuranidones-3—are obtained in yields of 64–78%:

$$\text{4-isonitroso-2,2,5,5-tetraalkylfuranidone-3} \xrightarrow[\mathrm{CH_3COOH}]{\mathrm{Zn}} \text{4-hydroxy-2,2,5,5-tetraalkylfuranidone-3}$$

$\mathrm{R} = \mathrm{R'} = \mathrm{CH_3}$ (I)
$\mathrm{R} = \mathrm{CH_3};\quad \mathrm{R'} = \mathrm{C_2H_5}$ (II)

$\mathrm{R}\bigvee_{\mathrm{R'}}\mathrm{C}$=cyclobutylidene (III)
$\mathrm{R}\bigvee_{\mathrm{R'}}\mathrm{C}$=cyclohexylidene (IV)

In determining the number of labile hydrogen atoms ([8]), we established the presence in 4-hydroxy-2,2,5,5-tetraalkylfuranidones-3 of two labile hydrogen atoms, which should be explained by the participation in the reaction with an excess of methylmagnesium iodide of the enediol form of 4-hydroxy-2,2,5,5-tetraalkylfuranidones-3:

$$\text{4-hydroxy-2,2,5,5-tetraalkylfuranidone-3} \longrightarrow \text{[enediol form]} \xrightarrow{2\,CH_3MgJ} \text{dimagnesium derivative} + 2\,CH_4$$

This is also confirmed by the fact that in 2,2,5,5-tetramethylfuranidone-3 we detected only one labile hydrogen atom. Upon interaction of 4-hydroxy-2,2,5,5-tetramethylfuranidone-3 (I) with phenylhydrazine in alcoholic—

in aqueous solution phenylhydrazone of 4-hydroxy-2,2,5,5-tetramethylfuranidone-3 (V) is formed, whereas in acetic acid medium monophenylhydrazone of 2,2,5,5-tetramethylfuranidindione-3,4 (VI) was obtained, identical with that obtained from 2,2,5,5-tetramethylfuranidindione-3,4 (VII). This reaction—the oxidation by phenylhydrazine of a hydroxyl group adjacent to a carbonyl group —also confirms the structure of the hydroxy ketones obtained by us.

$$\text{(V)} \xleftarrow[C_2H_5OH]{C_6H_5NHNH_2} \text{(I)} \xrightarrow[CH_3COOH]{C_6H_5NHNH_2} \text{(VI)} \xleftarrow{C_6H_5NHNH_2} \text{(VII)}$$

It should be noted that the impossibility of obtaining diphenylhydrazones (osazones) of α-diketones of the furanidine series was noted earlier by T. I. Temnikova and P. A. Tikhomolov (^{9}). We obtained the starting 4-isonitroso-2,2,5,5-tetraalkylfuranidones-3 (VIII—XI) by the action of isoamyl nitrite on a mixture of 2,2,5,5-tetraalkylfuranidone-3, acetyl chloride, and hydrochloric acid in the cold, in yields of 49—89%.

$$\text{2,2,5,5-tetraalkylfuranidone-3} \xrightarrow[HCl,\ CH_3COCl]{C_5H_{11}ONO} \text{4-isonitroso-2,2,5,5-tetraalkylfuranidone-3} \xrightarrow{NH_2OH} \text{dioxime of}$$

$R = R' = CH_3$ (VIII)
$R = CH_3;\ R' = C_2H_5$ (IX)
$R, R' =$ cyclobutane ring fragment (X)
$R, R' =$ cyclohexane ring fragment (XI)

$R = R' = CH_3;$ (XII)
$R = CH_3;\ R' = C_2H_5$ (XIII)
$R, R' =$ cyclobutane ring fragment (XIV)

On treatment with hydroxylamine, the dioximes of the corresponding furanidindiones-3,4 (XII—XIV) were obtained; they were identical with those described in the literature (^{10,11}). We also confirmed the structure of 4-isonitroso-2,2,5,5-tetramethylfuranidone-3 (VIII) by a counter synthesis of it from 2,2,5,5-tetramethylfuranidindione-3,4 (VII) and an equivalent amount of hydroxylamine.

It is necessary to note that 4-isonitroso-2,2,5,5-tetraalkylfuranidones-3 immediately after isolation have a higher melting point than after recrystallization or prolonged standing. The changes in the melting point of 4-isonitroso-2,2,5,5-tetramethylfuranidone-3 are given below.

Standing time, hr	0	8	24	74	146	212	260	300
M.p., °C	129	122	118	107	100	97	97	97

Cases of changes in the melting temperature of isonitroso compounds are known from the literature ([12,13]). Without deciding the question of the spatial configuration of the 4-isonitrosofuranidones-3 obtained by us, we believe that the change in their melting point is due to the transition of one form into another, energetically more favorable one. This, undoubtedly, also explains the fact that the melting point of the 4-isonitroso-2,2,5,5-tetramethylfuranidone-3 (VIII) obtained by us differs from the melting point of the only representative of this class of compounds described in the literature—4-isonitroso-2,2,5,5-tetramethylfuranidone-3 ([1]).

The 4-hydroxy-2,2,5,5-tetraalkylfuranidones-3 and 4-isonitroso-2,2,5,5-tetraalkylfuranidones-3 obtained have not been described in the literature.

Experimental Part

4-Isonitroso-2,2,5,5-tetraalkylfuranidones-3 (VIII–XI). To a mixture of 0.14 g-mol of 2,2,5,5-tetraalkylfuranidone-3 ([10,11]), 5 ml of concentrated hydrochloric acid, and 4 ml of acetyl chloride ···

acetyl was added, with stirring, 0.22 gram-mole of isoamyl nitrite at a rate of 0.5 ml/min*. The last 2–3 ml of isoamyl nitrite were added more slowly and with cooling of the reaction mixture by water with ice; stirring was continued for another 30 min and for 1 hr with cooling by ice and salt**. The precipitate was filtered off and recrystallized. The constants and yields of 4-isonitroso-2,2,5,5-tetraalkylfuranidones-3 and their derivatives are given in Table 1.

Counter synthesis of 4-isonitroso-2,2,5,5-tetramethylfuranidone-3. 3.1 g (0.02 gram-mole) of 2,2,5,5-tetramethylfuranidindione-3,4 (VII) and 1.4 g (0.02 gram-mole) of hydroxylamine hydrochloride were boiled for 2 hr in a mixture of 10 ml of pyridine and 5 ml of absolute alcohol. The precipitate that separated when the mixture was poured into 150 ml of cold water was boiled with benzene; the substance not dissolved in benzene, with m.p. 223–224° (from alcohol), was the dioxime of 2,2,5,5-tetramethylfuranidindione-3,4. From the benzene solution, on cooling, crystals of 4-isonitroso-2,2,5,5-tetramethylfuranidone-3 separated, m.p. 96–97° (from benzene). A mixed-melting test with 4-isonitroso-2,2,5,5-tetramethylfuranidone-3 obtained by nitrosation of 2,2,5,5-tetramethylfuranidone-3 showed no depression.

Table 1

Substance	M.p., °C, experimental	M.p., °C, from the literature	Found, %, C	Found, %, H	Found, %, N	Calculated, %, C	Calculated, %, H	Calculated, %, N
4-Isonitroso-2,2,5,5-tetramethylfuranidone-3 (VIII) (yield 79%)	105–106 (from CCl_4) 96–97 (from C_6H_6)	167–170(1)	56.37 56.47	[illegible]	[illegible]	[illegible]	7.65 7.65	8.18 8.18
2,4-Dinitrophenylhydrazone VIII (from aqueous alcohol)	236–237	–			19.88 19.77			19.94
Dioxime of 2,2,5,5-tetramethylfuranidindione-3,4 (XII) (from alcohol)	223–224	223–224(10)						

Substance	M.p., °C, experimental	M.p., °C, from the literature	Found, %, C	Found, %, H	Found, %, N	Calculated, %, C	Calculated, %, H	Calculated, %, N
4-Isonitroso-2,5-dimethyl-2,5-diethylfuranidone-3 (IX)* (yield 49%) (from petroleum ether)	72–73	–	55.10 55.18	8.81 8.70	6.48 6.49	55.28	8.81	6.40
Dioxime of 2,5-dimethyl-2,5-diethylfuranidindione-3,4 (XIII) (from aqueous alcohol)	192–193	193(10)						
4-Isonitroso-2,2,5,5-bistetramethylenefuranidone-3 (X)** (yield 89%) (from petroleum ether)	97–100	–			6.04 6.19			6.28

Substance	M.p., °C, experimental	M.p., °C, from the literature	Found, %, C	Found, %, H	Found, %, N	Calculated, %, C	Calculated, %, H	Calculated, %, N
Dioxime of 2,2,5,5-bistetramethylenefuranidindione-3,4 (XIV) (from aqueous alcohol)	198	198–199(11)						
4-Isonitroso-2,2,5,5-bispentamethylenefuranidone-3 (XI) (yield 66%) (from cyclohexane)	137–140	–	66.59 66.62	8.55 8.49	5.78 5.93	66.90	8.42	5.57

* The compound was isolated as the monohydrate $-C_{10}H_{17}O_3N \cdot H_2O$.
** The nitrosation was carried out in isoamyl alcohol.

4-Hydroxy-2,2,5,5-tetraalkylfuranidones-3 (I–IV). Into a flask equipped with a reflux condenser and a stirrer were placed 0.05 gram-mole of 4-isonitroso-2,2,5,5-tetraalkylfuranidone-3 and 100 ml of 50% acetic acid. After addition of the first portion of zinc dust, the reaction mixture was ···

was heated until the reaction began, and the remaining portion of the zinc dust was gradually added (0.28 g-at. in all). Boiling and stirring were continued for another 6–7 hr, after which the reaction mixture was diluted with 120 ml of water, neutralized to pH 6, and extracted with ether. After removal of the ether from the ethereal extract dried over anhydrous sodium sulfate, 4-hydroxy-2,2,5,5-tetraalkylfuranidone-3 was isolated. The constants and yields of 4-hydroxy-2,2,5,5-tetraalkylfuranidones-3 are given in Table 2.

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Table 2

Substance	B.p., °C/mm Hg	M.p., °C	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Number of mobile H atoms
4-Hydroxy-2,2,5,5-tetramethylfuranidone-3 (I) (yield 78%) (from petroleum ether)	–	98.5–99	60.80 60.74	8.99 9.03	—	60.74	8.92	–	2.162 2.204
2,4-Dinitrophenylhydrazone I (from aqueous alcohol)	–	187–188	49.49 49.63	5.57 5.44	16.34 16.38	49.70	5.38	16.56	–
Phenylhydrazone I (from *n*-octane)	–	136–137			11.47 11.50	–	–	11.28	–

Substance	B.p., °C/mm Hg	M.p., °C	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Number of mobile H atoms
Monophenylhydrazone 2,2,5,5-tetramethylfuranidinedione-3,4 (VI) (from alcohol)	–	96–97	68.35 68.71	7.56 7.47	11.39 11.45	68.28	7.37	11.35	–
4-Hydroxy-2,5-dimethyl-2,5-diethylfuranidone-3 (II)* (yield 64%)	75–76/3 mm	–	64.60 64.70	10.11 10.02	–	64.48	9.74	–	2.176 2.091
2,4-Dinitrophenylhydrazone II (from alcohol)	–	145–146.5	52.83	5.95	15.70 15.66	52.60	5.79	15.34	–
4-Hydroxy-2,2,5,5-bistetramethylenefuranidone-3 (III) (yield 73%)	112–113/3 mm	47–48	68.54 68.46	8.63 8.67	–	68.54	8.63	–	1.989 2.090

Substance	B.p., °C/mm Hg	M.p., °C	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Number of mobile H atoms
2,4-Dinitrophenylhydrazone III (from aqueous alcohol)	–	177			14.33 14.31			14.35	–
4-Hydroxy-2,2,5,5-bispentamethylenefuranidone-3 (IV) (yield 73%) (from *n*-hexane)	–	75-76	70.81 70.78	9.48 9.52		70.55	9.30		
2,4-Dinitrophenylhydrazone IV (from alcohol)	–	211	57.72 57.71	6.44 6.30	12.98 13.18	57.40	6.26	13.39	–

* n_D^{20} 1.4531; d_4^{20} 1.0221; MR_D 49.28; $C_{10}H_{18}O_3$. Calculated MR_D 49.51.

* Nitration of 2,2,5,5-tetramethylfuranidone-3 may be carried out at a rate of 2.5 ml/min.

** Good yields of isonitrosoketones are achieved with careful observance of the rate of addition of isoamyl nitrite and of the temperature conditions.

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