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Academician of the Academy of Sciences of the Latvian SSR G. Ya. VANAG and Yu. E. PELCHER

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Abstract

Full Text

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5-HYDROXY-5-INDANDIONE-1,3-YL(2)-BARBITURIC ACID

Derivatives of indandione-1,3 have proved to be physiologically active compounds. Thus, for example, many 2-aryl- and 2-acylindandiones-1,3 are valuable blood anticoagulants and have found practical application both in medicine (2-phenyl-, 2-anisyl-, 2-naphthylindandiones-1,3, etc.) and in the control of harmful rodents (2-diphenylacetyl-, 2-trimethylacetylindandiones, etc.). Some 2-amino derivatives of 2-arylindandiones exhibit narcotic, anticonvulsant, and analgesic properties, and 2 of them are already undergoing clinical testing. Their action in many respects resembles that of barbiturates; they act somewhat more weakly than the latter, but are less toxic, and habituation to them develops more slowly than to barbiturates ([1]).

From what has been said it is clear that it is of interest to combine indandiones-1,3 with barbituric acid and to study the properties of the products obtained. This task seemed easily feasible. Ionescu ([2]) had already shown that malonic ester adds to benzalindandione-1,3 with formation of I, which, by condensation with urea, it was hoped could be cyclized to the corresponding barbituric acid (II):

$$C_6H_4<\begin{matrix}CO\\CO\end{matrix}>C{=}CHC_6H_5 \xrightarrow{CH_2(COOC_2H_5)_2} C_6H_4<\begin{matrix}CO\\CO\end{matrix}>CH-CH(C_6H_5)-CH(COOC_2H_5)_2 \rightarrow \quad \text{(I)}$$

$$\xrightarrow{(NH_2)_2CO} C_6H_4<\begin{matrix}CO\\CO\end{matrix}>CH-CH(C_6H_5)-CH<\begin{matrix}CO-NH\\CO-NH\end{matrix}>CO \quad \text{(II)}$$

However, under no conditions could the malonic ester (I) be condensed with urea. Under the action of the usual condensing agent—sodium ethylate—there occurs facile saponification of the ester and lactonization of the free acid with

the enolic form of the indandione group, as Ionescu already pointed out ([2]). Other condensing agents likewise did not give positive results.

It is known that alloxan in the form of the monohydrate readily interacts with substances containing mobile hydrogen atoms, for example, with phenols ([3]), acetophenone, dibenzyl ketone, and others, in the presence of various catalysts ([4]). It turned out that alloxan monohydrate (VI) also reacts readily with indandione-1,3 (III) in dilute acetic acid without any catalysts and gives 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid (V) in a yield above 90%.

$$C_6H_4 <\begin{matrix}CO\\CO\end{matrix}> CH_2 + (HO)_2C <\begin{matrix}CO-NH\\CO-NH\end{matrix}> CO \rightarrow C_6H_4 <\begin{matrix}CO\\CO\end{matrix}> CH-C(OH) <\begin{matrix}CO-NH\\CO-NH\end{matrix}> CO$$

(III, IV, V)

5-Hydroxy-5-indandione-1,3-yl(2)-barbituric acid is a white or slightly yellowish crystalline substance with m.p. 205–206° (decomp.). Since one active hydrogen atom in the indandione group is still retained in it, it dissolves in alkalis and amines with formation of more intensely colored salts. A number of these salts have been prepared in crystalline form. They dissolve fairly well in water and, upon acidification, give back acid V.

Under the action of bromine on 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid, cleavage of its molecule occurs with formation of 2,2-dibromoindandione-1,3, which is characteristic of many derivatives of indandione-1,3. The second product of the cleavage reaction is a mixture of alloxan and alloxanthin.

Cleavage of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid also occurs under the action of hydroxylamine on it. The reaction product is the dioxime of indandione-1,3.

Experimental Part

5-Hydroxy-5-indandione-1,3-yl(2)-barbituric acid. To 10 g (0.69 mole) of indandione dissolved in 50 ml of glacial acetic acid, 11 g (0.69 mole) of alloxan monohydrate in 50 ml of water is added, and the mixture is heated to 50°. The red solution becomes lighter, and a precipitate begins to separate.

On the next day the precipitate is separated and washed with a small amount of cold water. Yield 18.8 g (95%) of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid, m.p. 202–204° (decomp.). The substance is insoluble in benzene and ether, sparingly soluble in water and alcohol. After crystallization from glacial acetic acid—slightly yellowish crystals with m.p. 205–206° (decomp.).

Found, %:	N 9.70; 9.57; C 54.26; H 2.98
$C_{13}H_8O_6N_2$. Calculated, %:	N 9.73; C 54.20; H 2.78

Potassium salt. 2 g of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid is suspended in 20 ml of methanol, 1 ml of a saturated methanolic solution of caustic potash is added dropwise, and the mixture is slightly heated. A yellow precipitate of the potassium salt separates. Yield 1.8 g (82%), m.p. above 250°.

Found, %:	N 8.59
$C_{13}H_7N_2K$. Calculated, %:	N 8.84

Diethylamine salt. 2 g of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid is suspended in 20 ml of methanol and 1 ml of diethylamine (1.8-fold excess) in methanol is added. The acid passes into solution, and orange crystals of the salt separate from the dark-red solution. Yield 1.8 g; from the filtrate, another 0.5 g of salt can be precipitated with ether. The total yield is 92% of theory. After crystallization from methanol with addition of ether, orange crystals with m.p. 190–192° (decomp.) are obtained.

Found, %:	N 11.54
$C_{17}H_{19}O_6N_3$. Calculated, %:	N 11.62

Piperidine salt. Obtained analogously to the diethylamine salt. From 5 g of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid and 2.5 ml of piperidine (2.5-fold excess), 5.6 g of the piperidine salt (85%) is obtained, with m.p. 173–175° (decomp.). It dissolves well in alcohol and acetone, less readily in water, and is insoluble in ether. After crystallization from methanol with addition of ether, orange crystals, m.p. 175–177° (decomp.), are obtained.

Found, %:	N 11.19
$C_{18}H_{19}O_6N_3$. Calculated, %:	N 11.29

Pyridine salt. As above. From 2 g of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid and 1 ml of pyridine, 2.3 g of the salt was obtained (89% of theory). After crystallization from methanol, yellow crystals, m.p. 197–199° (decomp.); darkens at 180°.

Found, %:	N 11.09
$C_{18}H_{13}O_6N_3$. Calculated, %:	N 11.33

Bromination. 2 g of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid is suspended in 30 ml of glacial acetic acid, and 1.5 g of bromine is added dropwise. The liquid becomes decolorized and hydrogen bromide is evolved; to complete the reaction it is heated and the hot solution is filtered. On cooling, 1.5 g of dibromoindandione, m.p. 176–178°, precipitates. Dilution of the filtrate with water gives a further 0.4 g of 2,2-dibromoindandione. Total yield 1.9 g (90%). After crystallization from glacial acetic acid, colorless crystals of

2,2-dibromoindandione-1,3 are obtained, m.p. 178–179°. With an authentic 2,2-dibromoindandione-1,3 sample it gives no depression of the melting point. Evaporation of the filtrate gave a precipitate with m.p. 238–143° (decomp.). Alloxan and alloxanthin were identified in it.

Oximation. 1 g of 5-hydroxy-5-indandione-1,3-yl(2)-barbituric acid in 50 ml of methanol, 2 g of hydroxylamine hydrochloride, and 1 g of sodium acetate are heated on a water bath. The red solution becomes decolorized and a flocculent precipitate forms. After crystallization from alcohol, white felt-like crystals with m.p. 232–234° (decomp.) are obtained; with an authentic dioxime of indandione-1,3 it gives no depression of the melting point.

Found, %: N 15.90; 16.20

$C_9H_8N_2O_2$. Calculated, %: N 15.91

Oximation in pyridine solution gave the same results.

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Note: Figure translations are in progress. See original paper for figures.