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# SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-ARYLIMINOBARBITURIC ACIDS

A. S. Zaks, S. B. Goncharenko,
V. G. Voronin, E. A. Usachev,
Yu. V. Portnov, Yu. M. Rabotnikov,
and L. E. Pchelintseva

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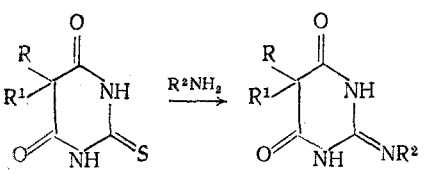
Derivatives of 2-thiobarbituric acid with their clearly marked soporific action occupy an important place among synthetic medicinal agents. The substitution of the thione group by the protected amino group leads to the appearance of new types of biological action [6]. We previously [1] accomplished the synthesis of a series of unknown 4-aryl(aralkyl)iminobarbituric acids among which compounds possessing antiphlogistic activity were found [2]. The aim of the present work was the synthesis and investigation of the anti-inflammatory and analgesic activity of the 2-aryliminobarbituric acids (II*a*-m) which are isomeric with them. Several methods for the synthesis of such compounds are known; these utilize both the methods of cycilization of malonic esters or the acid chlorides of malonic acids with substituted guanidines [8, 10] and the direct substitution of the thio, methylthio, or imino group by the substituted imino group [6, 7, 9]. The synthesis of the compounds II*a*-m was accomplished by us in the reaction of the 2-thiobarbituric acids (I*a*, b) with amines according to [1].




I*a*, b II*a*-m

I*a*, II*a*-h: R = R¹ = Et; Ib, III-m: E = Et, R¹ = Am-sec; II*a*, i: R² = Ph; IIb: R² = $CH_2Ph$; IIc, j: R² = $C_6H_4Me$-p; IId,k: R² = $C_6H_4Me$-m; IIe: R² = $C_6H_4Cl$-m; IIf,l: R² = $C_6H_4OMe$-p; IIg: R² = $C_6H_4OMe$-m; IIh,m: R² = $C_6H_4OMe$-o.

Heating the 2-thiobarbituric acids I*a*, b with an excess of the amine without a solvent at 160-180°C in the course of 6-12 h leads to the formation of the iminobarbituric acids IIa-m. The compounds obtained are white, high-melting, and crystalline substances. Their IR spectra contain absorption bands corresponding to the vibrations of the NH and the C=O, C=N, and C=C groups in the region of 3300-3000 and 1700-1500 $cm^{-1}$ respectively.

## EXPERIMENTAL (CHEMICAL)

The IR spectra were taken on a Perkin-Elmer 577 spectrophotometer for the suspensions in mineral oil. The control of the course of the reactions and the purity of the compounds obtained was performed using thin layer chromatography on plates of Silufol UV-254 in the

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TABLE 1. 5,5-Dialkyl-2-aryliminobarbituric Acids (II*a*-m)

| Compound | Yield, % | mp, °C | IR spectrum, $\nu_{max}$, cm$^{-1}$ | | Found, % | | | Empirical formula | Calculated, % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | NH | C=O, C=N, C=C | C | H | N | | C | H | N |
| IIg | 65 | 194—6 | 3185 | 1682 (w), 1591 | 61,98 | 7,03 | 14,84 | $C_{15}H_{19}N_3O_3$ | 62,27 | 6,62 | 14,52 |
| IIh | 66 | 234—6 | 3300—3000 | 1724, 1623 (*w*) 1566 (w) | 62,34 | 6,83 | 14,12 | $C_{15}H_{19}N_3O_3$ | 62,27 | 6,62 | 14,52 |
| IIi | 56 | 174—5 | 3310 3185 3050 | 1724, 1680 1638, 1600 1576, 1520 | 68,30 | 7,30 | 13,84 | $C_{17}H_{23}N_3O_2$ | 67,75 | 7,69 | 13,94 |
| IIj | 75 | 181—2 | 3300—3000 | 1722, 1635 1616, 1578, 1515 | 68,41 | 8,30 | 13,46 | $C_{18}H_{25}N_3O_2$ | 68,55 | 7,99 | 13,32 |
| IIk | 67 | 191—2 | 3300—3000 | 1721, 1652 1638, 1605 1578, 1530 | 68,48 | 7,89 | 13,22 | $C_{18}H_{25}N_3O_2$ | 68,55 | 7,99 | 13,32 |
| IIℓ | 83 | 199—200 | 3300—3000 | 1725, 1659 1635, 1593 1575, 1535 1518 | 65,18 | 7,84 | 12,22 | $C_{18}H_{25}N_3O_3$ | 65,24 | 7,60 | 12,68 |
| IIm | 67 | 120—3 | 3200 | 1722, 1676 1647, 1618 1579, 1552 | 65,50 | 7,96 | 12,19 | $C_{18}H_{25}N_3O_3$ | 65,24 | 7,60 | 12,68 |

Note. For the mps of IIa and IIc-f, see [1]. The mp of IIb is 165-166°C (see [9]). The yields of II*a*-f are 83, 85, 68, 70, 83, and 70% correspondingly.

TABLE 2. 5,5-Dialkyl-2-aryliminobarbituric Acids and Their Anti-inflammatory Properties

| Compound | $LD_{50}$, mg/kg | Dose, mg/kg (ip) | Inhibition of inflammation, % after 3 h | Inhibition of inflammation, % after 5 h |
|---|---|---|---|---|
| IIa | >1000 | 100 | 0 | 0 |
| IIb | 62 | 6 | 11 | 23 |
| IIc | >1000 | 100 | 37* | 37* |
| | | 50 | 17 | 17 |
| IId | 150 | 50 | 1 | 0 |
| IIe | >1000 | 100 | 23 | 23 |
| IIf | >1000 | 100 | 17 | 23 |
| IIg | >1000 | 100 | 19 | 18 |
| IIh | >1000 | 100 | 23 | 19 |
| IIi | >1000 | 100 | 0 | 0 |
| IIj | 500 | 100 | 0 | 0 |
| IIk | 450 | 100 | 33* | 36* |
| IIl | >1000 | 100 | 0 | 0 |
| IIm | 515 | 50 | 20 | 21 |

*Reliable difference from the control at $P \leq 0.05$.

10:1 system of $CHCl_3$—MeOH and the 3:1 system of benzene—ethyl acetate with the development in UV light or with iodine vapor.

5,5-Diethyl- and 5-Ethyl-5-sec.-amyl-2-thiobarbituric Acids (Ia, b). These compounds were obtained according to the method of [5].

5,5-Dialkyl-2-aryliminobarbituric Acids (IIa-m). The mixture of 0.01 moles of I and 0.015 moles of the corresponding amine is heated without a solvent at 160-180°C in the course of 6-12 h; the mixture is suspended in ether after cooling it. The residue is filtered off and recrystallized from aqueous ethanol.

The characteristics of the compounds obtained are presented in Table 1.

## EXPERIMENTAL (PHARMACOLOGICAL)

The acute toxicity of the compounds was studied in white mice with the determination of the $LD_{50}$ by the method of G. N. Pershin [4] on ip injection.

Compound IIb is the most toxic; it induced tremor, ataxia, short-lived clonic convulsions, and mortality in the animals in the course of the first hour in doses close to the $LD_{50}$.

Compound IId is half as toxic. The picture of its general action appears as the increasing depression, disturbance of coordination, curtailed respiration, and the mortality of the animals after several hours.

The compounds IIj,k,m have approximately equal toxicity, whereby their general action does not differ from that of IId.

None of the remaining substances changed the behavior of the animals in the maximal doses tested (1000 mg/kg).

The analgesic activity was investigated by the "hot plate" test on white mice [11]. Not one of the compounds tested showed it in doses amounting to 0.1 $LD_{50}$ or in the conditionally selected dose of 100 mg/kg.

We determined the anti-inflammatory activity using an agar model produced by the subplantar introduction of 1% DIFKO agar into the hind paws of rats [3]. Substances were given ip at 1 h before the experiment in the dose range of 0.05-0.3 $LD_{50}$. Inhibition of the inflammation (in %) was calculated from the formula $[(K - O)/K] \cdot 100$, where K is the result of the control and O is the result of the experiment.

As can be seen from Table 2, the compounds IIc and IIk possess antiinflammatory properties at a dose of 100 mg/kg, whereby the halving of this dose is accompanied by the loss of these properties.

None of the substances tested showed anti-inflammatory activity on peroral application.

It should be noted that the substances, in these doses, did not influence the control coordinational mechanisms and the tonicity of the skeletal muscles of the animals, which were studied in experiments on the "horizontal wire."

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