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Preparation of Some New Substituted 5-(2'-Furfuryl)-barbituric and -thiobarbituric Acids*

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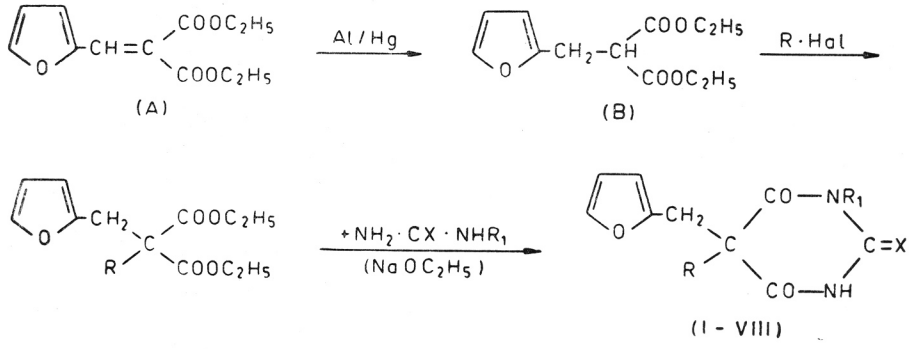
Starting with diethyl (2-furfuryl)-malonate, obtained by reduction of diethyl (2-furfurylidene)-malonate with aluminum amalgam in wet ether, several new or hitherto insufficiently characterized 1- or/and 5-substituted 5-(2-furfuryl)-barbituric and -thiobarbituric acids, have been prepared.

Among the very numerous known barbituric and thiobarbituric acid derivatives which are of interest for their pharmacodynamical properties, only a limited number (about fifteen), containing a 2-furfuryl group, have been described or mentioned in literature,[1] and only one of them, *i. e.* 5-isopropyl-5--(2-furfuryl)-barbituric acid, is in clinical use.[2]

The aim of the present work was to prepare several new or hitherto insufficiently characterized 1- or/and 5-substituted 5-(2-furfuryl)-barbituric and -thiobarbituric acids, in order to make them available for pharmacological testing.

The synthesis of these compounds has been accomplished in the following way:



* Studies in the Furan Series. XII. Part XI. D. Bilović and V. Hahn, *Croat. Chem. Acta* **37** (1965) 185.

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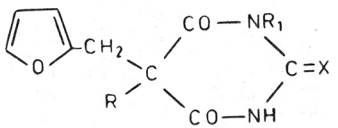
TABLE 1

Derivatives of 5-(2-Furfuryl)--barbituric and -thiobarbituric Acids



No.	R	R_1	X	Yield of crude prod. %	Mp, °C [a]	Formula	Calc'd., %			Found, %		
							C	H	N	C	H	N
I	C_2H_5	H	O	65	160—161[b,c]	$C_{11}H_{12}N_2O_4$	55.93	5.12	11.86	55.76	5.03	11.95
II	H	CH_3	O	75	95—96[d]	$C_{10}H_{10}N_2O_4$	54.05	4.54	12.61	53.99	4.42	12.38
III	C_2H_5	CH_3	O	68	115—116[b]	$C_{12}H_{14}N_2O_4$	57.59	5.64	11.20	57.66	5.68	11.48
IV	*i*-C_3H_7	CH_3	O	8	86—87[e,f]	$C_{13}H_{16}N_2O_4$	59.08	6.10	10.60	59.40	6.14	10.89
V	$CH_2CH = CH_2$	CH_3	O	83	80—81[g]	$C_{13}H_{14}N_2O_4$	59.53	5.38	10.68	59.44	5.12	10.93
VI	C_2H_5	H	S	67	180—181[h]	$C_{11}H_{12}N_2O_3S$	52.36	4.79	11.11	52.26	4.51	11.03
VII	*i*-C_3H_7	H	S	60	178—179[e]	$C_{12}H_{14}N_2O_3S$	54.12	5.30	10.52	54.43	5.06	10.62
VIII	$CH_2CH = CH_2$	H	S	43	152—153[e]	$C_{12}H_{12}N_2O_3S$	54.53	4.58	10.60	54.67	4.56	10.78

[a] After crystallization
[b] Recrystallized from ethanol
[c] Reported[5] m. p. 144.5—145° C
[d] Recrystallized first from ethanol and then from isopropanol
[e] Recrystallized from dilute ethanol (1 : 1)
[f] Reported[10] m. p. 73—75° C
[g] Recrystallized from dilute ethanol (1 : 2)
[h] Recrystallized first from ethanol and then from *n*-butanol

Reduction of diethyl (2-furfurylidene)-malonate (A)[3] with amalgamated aluminum in wet ether[4] yielded an oily product, from which by fractionation 35—40% of diethyl (2-furfuryl)-malonate (B)[5] could be isolated. The rest was a high boiling viscous oil, which proved to be the product of reductive dimerization (»hydrodimerization«[6]) of A. The reduction of A and of related compounds with aluminum amalgam has been studied in detail in our laboratories[7]; the results of this work will be published later.

Diethyl (2-furfuryl)-malonate (B) was alkylated in the usual way[8] to yield the corresponding diethyl alkyl- (or allyl) 2-furfuryl-malonates. Condensation of the disubstituted malonic esters with urea, *N*-methylurea or thiourea, was carried out according to the procedure described by Inman and Bitler,[9] the solution of sodium ethoxide beeing added gradually to the mixture of the reactants in order to minimize formation of by-products. In this manner the barbituric and thiobarbituric acid derivatives I—VIII, listed in Table 1, have been prepared.

The yields were satisfactory in most cases. The crude products could be purified by recrystallization from appropriate solvents, except IV and V, which were obtained in pure form after reprecipitation from aqueous ammonium hydroxide solutions with carbon dioxide.[11]

Two of the prepared barbituric acid derivatives (I and IV) have been prepared earlier in a somewhat different way[5,10]; nevertheless, they are included in this paper because the reported melting points differ sensibly from those found in our experiments.

The prepared compounds have been tested on mice for hypnotic activity.* All the compounds, except I, caused toxic effects (convulsions, tremor), although in several cases hypnotic activity could be established. A detailed report on pharmacological investigations will* be published elsewhere.

EXPERIMENTAL**

Materials

Diethyl (2-furfuryl)-malonate (B), b. p. 148—152°/12 mm., n_D^{20} 1.4610 (lit.[5] b. p. 125—127°/4 mm., n_D^{20} 1.4591), has been prepared by reduction of diethyl (2-furfurylidene)-malonate (A), b. p. 170—172°/12 mm., m. p. 40—41° (lit.[3] b. p. 173—175°/15 mm., m. p. 43°), with aluminum amalgam in wet ether.[4] Details of the preparation will be reported in one of the following papers of this series.

Alkylation of diethyl (2-furfuryl)-malonate (B) was carried out in the usual way,[8] using freshly dehydrated absolute ethanol and a slight (10%) excess of sodium and of the appropriate alkyl (or allyl) bromide. In this manner the following esters have been obtained: diethyl ethyl-(2-furfuryl)-malonate, b. p. 153—156°/16 mm., n_D^{20} 1.4620 (lit.[5] b. p. 135—136°/5 mm.), yield 84%; diethyl isopropyl-(2-furfuryl)-malonate, b. p. 151—156°/11 mm., n_D^{20} 1.4635 (lit.[12] b. p. 157—160°/10 mm.), yield 77%; diethyl allyl-(2-furfuryl)-malonate, b. p. 161—162°/12 mm., n_D^{20} 1.4705, yield 85%.

Preparation of the substituted 5-(2-furfuryl)-barbituric and -thiobarbituric acids (Table 1)

General procedure

To the boiling mixture of 30 mmoles of the freshly distilled substituted malonic ester, 45 mmoles of the corresponding urea, and 20 ml. of dehydrated abs. ethanol,

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* Experiments by Dr. H. Krnjević

** Melting points are uncorrected

the solution of sodium ethoxide prepared from 1.5 g. (65 mgatoms) of sodium and 35 ml. of dehydrated abs. ethanol was gradually added during 4—5 hours. Thereafter, boiling was continued for 6—8 hrs., the solvent evaporated *in vacuo*, the residue dissolved in 40 ml. of water, the resulting solution extracted with 2 × 10 ml. of ether, and then acidified with diluted hydrochloric acid (1 : 1). After cooling and standing for several hrs., the crude barbituric (or thiobarbituric) acid was filtered off. In the case of compounds IV and V, a partially crystallized oily product was obtained. After dissolution in about 10 ml. of 10% aqueous ammonium hydroxide the impurities were extracted with two 10 ml. portions of ether and the product precipitated by introduction of gaseous carbon dioxide into the aqueous layer.

The crude products were crystallized from appropriate solvents. In the pure form they are obtained as colorless crystals with sharp melting points.

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REFERENCES

1. *Cf.* W. J. Doran in »*Medicinal Chemistry*«, Vol. IV., J. Wiley and Sons, Inc., New York, **1959**, pp. 104, 164, 206, 212, 213.
2. B. Helwig, »*Moderne Arzneimittel*«, 2. Aufl., Wissenschaftliche Verlagsgesellschaft, Stuttgart, **1961**. S. 145.
3. A. Hintz, G. Meyer, and G. Schüking, *Ber.* **76 B** (1943) 676.
4. A. I. Vogel, *J. Chem. Soc.* **1927**, 594, 1985; id. *ibid.* **1928**, 1019.
5. W. R. Kirner and G. H. Richter, *J. Am. Chem. Soc.* **51** (1929) 3131.
6. The term »hydrodimerization« was used by I. L. Knunjanc and N. P. Gambarjan, *Uspehi Him.* **23** (1954) 781.
7. B. Glunčić, *Thesis*, Zagreb, **1964**.
8. *Cf.* E. Fourneau, »*Préparation des médicaments organiques*«, Librairie J.-B. Baillière et Fils, Paris, **1921**, p. 301.
9. N. T. Inman and W. P. Bitler, *U. S.* 2,358,072 (1944): *cf. Chem. Abstr.* **39** (1945) 1020.[1]
10. Chem. Fabrik Dr. J. Wiernik & Co. A. G., *Brit.* 468, 503 (1935); *cf. Chem. Zentr.* **1937 II** 3039.
11. E. H. Volwiler and D. L. Tabern, *U. S.* 2,153,729 (1939).
12. G. Heilner, *F.* 797,152 (1936) and *U. S.* 2,035,317 (1936); *cf. Chem. Zentr.* **1936 II** 1579.

IZVOD

Priprava nekih novih supstituiranih 5-(2-furfuril)-barbiturnih i -tiobarbiturnih kiselina

B. Glunčić, K. Jakopčić, N. Krvavica i V. Hahn

Polazeći od dietil-estera 2-furfuril-malonske kiseline, koji je dobiven redukcijom dietil-estera 2-furfuriliden-malonske kiseline pomoću aluminijeva amalgama u vlažnom eteru,[4,7] pripravljeno je više novih ili ranije nedovoljno karakteriziranih derivata 5-(2-furfuril)-barbiturne, odnosno -tiobarbiturne kiseline (I—VIII, vidi tabelu 1).

Pripravljeni spojevi bili su podvrgnuti farmakološkom ispitivanju na bijelim miševima (pokusi dr H. Krnjevića). U više je slučajeva ustanovljeno hipnotsko djelovanje, no svi su spojevi, osim 5-etil-5-(2-furfuril)-barbiturne kiseline (I), pokazali toksične efekte kod pokusnih životinja (konvulzije, tremor).

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