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The Syntheses of Barbituryl-pyrryl-methines. Some Condensation Products of Pyrrole-2-aldehyde with Barbituric Acids and Barbiturates

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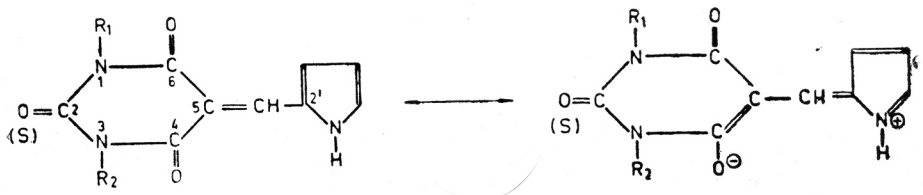
The preparation of condensation products of pyrrole-2--aldehyde with barbituric acids and barbiturates is described. The sodium salts of some barbituryl-pyrryl-methines showed hypnotic and spasmolytic activity.

As known, aldehydes react very easily with compounds containing one methylene group between two carbonyl groups, including barbituric and thiobarbituric acids.[1,2,3] In our previous paper[4] we reported about compounds of helicin (salicylaldehyde-β-D-glucopyranoside) with barbiturates and thiobarbiturates. Apart from that, pyrrole-2-aldehyde gives no condensation product with malonic acid. C. R. Clemo and coworkers[5] obtained only one compound of pyrrole-2-aldehyde with ethyl malonate, by addition of pyridine, but the yield was slight. A. Treibs and R. Zimmer-Galler[6] described recently — at a time when our work was in course of execution — some condensation products of pyrrole aldehydes with barbituric acid and dimethylbarbituric acid.

The pyrrole-2-aldehyde was prepared from pyrrole by the method of G. F. Smith.[7,8] We have condensed pyrrole-2-aldehyde with barbituric acid, *N*-ethylbarbituric acid,[9] *N*-phenylbarbituric acid,[10] *N,N*-diphenylbarbituric acid,[11] *N*-(*p*--tolyl)-barbituric acid[10], thiobarbituric acid and *N,N*-diphenylthiobarbituric acid.[12]

The new synthesized compounds can be formulated as follows according either to (a) or (b):



(a) (b)

R_1 = H or $-C_2H_5$, $-C_6H_5$, $-C_6H_4CH_3$; R_2 = H or $-C_6H_5$

TABLE I

Compound	R_1	R_2
[Barbituryl-(5)]-[pyrryl-(2')]-methine (I)	H	H
[*N*-Ethylbarbituryl-(5)]-[pyrryl-(2')]-methine (II)	$-C_2H_5$	H
[*N*-Phenylbarbituryl-(5)]-[pyrryl-(2')]-methine (III)	$-C_6H_5$	H
[*N*,*N*-Diphenylbarbituryl-(5)]-[pyrryl-(2')]-methine (IV)	$-C_6H_5$	$-C_6H_5$
[*N*-(*p*-Tolyl)-barbituryl-(5)]-[pyrryl-(2')]-methine (V)	$-C_6H_4CH_3$	H
[Thiobarbituryl-(5)]-[pyrryl-(2')]-methine (VI)	H	H
[*N*,*N*-Diphenylthiobarbituryl-(5)]-[pyrryl-(2')]-methine (VII)	$-C_6H_5$	$-C_6H_5$

The substance (I) was prepared by Treibs and Zimmer-Galler.[6]

All of these compounds are slightly soluble in water, easily soluble in sodium hydroxide water-solution and in pyridine, yellow or orange coloured with relatively high melting points.

Some of these compounds were also examined pharmacologically. It is well known that many barbiturates have strong hypnotic activity. In all these substances two hydrogen atoms in C_5-position are substituted by two monovalent radicals. In our compounds both of the hydrogens on the carbon in position 5 of barbituric acid (as can be seen from the structural formula) are substituted by a divalent pyrryl-methine rest. Here no hypnotic activity could be expected, but, contrary to our expectations, these compounds show sedative and hypnotic activity. The pyrrole-2-aldehyde has also sedative and hypnotic properties.

Pharmacological examinations upon experimental mice showed that sodium salts of substance (I) and (II) have hypnotic activity. The hypnotic activity was observed especially on sodium salts of substance (II). 110 mg./kg. were necessery for mice to fall asleep. They slept shortly. After waking them up they moved at once and were entirely awake.

Later on we found that sodium salts of substances (I, II and V) have an evident spasmolytic activity. Preliminary experiments have been done on isolated organs: intestines of guinea pigs with pelvic nerve and Ductus deferens with hypogastric nerve or bladder of rats with pelvic nerve. The spasmolytic activity was most marked on the sodium salts of substances (II) and (V).

Particulars of these pharmacological investigations will be published elsewhere.

EXPERIMENTAL

All melting points were determined with Kofler's heating microscope.

[*Barbituryl*-(5)]-[*pyrryl*-(2')]-*methine* (I)

A mixture of pyrrole-2-aldehyde (0.19 g., 2 mM), ethanol (20 ml.) and barbituric acid (0.26 g., 2 mM) was heated on the steam-bath for 30 min. under reflux. After crystallization the substance weighed 0.40 g. (97.4% yield). For the analyses it was recrystallized from dilute ethanol, giving yellow rod-shaped crystals. Dried *in vacuo* over calcium chloride, m.p. 285° (decomp). Over »Metallblock« mp. 320°.

Anal $C_9H_7N_3O_3$ (205.27) calc'd.: C 52.68; H 3.44%
found : C 52.70; H 3.70%

[N-*Ethylbarbituryl*-(5)]-[*pyrryl*-(2')]-*methine* (II)

Pyrrole-2-aldehyde (0.19 g., 2 mM) dissolved in 10 ml. ethanol was added to *N*-ethylbarbituric acid (0.3 g., 2 mM). The mixture was shortly heated on the steam-bath. After crystallization yellow cluster crystals were obtained. The yield was 0.42 g. (86.7%). The product for the analysis was recrystallized from ethanol and dried *in vacuo* at room temperature m.p. 205°.

Anal. $C_{11}H_{11}N_3O_3.1/2H_2O$ (242.2) calc'd.: C 54.56; H 5.00%
found : C 55.14; H 4.79%

The substance was dried under high vacuum at 60° for 7 hours; m.p. 210°.

Anal. $C_{11}H_{11}N_3O_3$ (233.2) calc'd.: C 56.70; H 4.76%
found : C 56.58; H 5.05%

[N-*Phenylbarbituryl*-(5)]-[*pyrryl*-(2')]-*methine* (III)

N-Monophenyl-barbituric acid (0.4 g., 2 mM) was added to pyrrole-2-aldehyde (0.19 g.) which had been dissolved in ethanol (20 ml.) and the mixture was heated for 15 min. Yellow crystals were obtained in a yield of 0.52 g. (89.6%). Recrystallization from glacial acetic acid-ethanol yielded pale-yellow crystals, m.p. 290° (decomp).

Anal. $C_{15}H_{11}N_3O_3.1/2\ H_2O$ (290.26) calc'd.: C 62.06; H 4.17%
found : C 62.18; H 4.35%

[N,N-*Diphenylbarbituryl*-(5)]-[*pyrryl*-(2')]-*methine* (IV)

Pyrrole-2-aldehyde (0.19 g.) was dissolved in 20 ml. ethanol and *N,N*-diphenyl-barbituric acid (0.56 g., 2 mM) was added. The yellow solution was heated on the steam-bath for 15 min. The product was obtained by crystallization in a refrigerator, 0.64 g. (87.5%). Recrystallization from ethanol, m.p. 262°.

Anal. $C_{21}H_{15}N_3O_3.1/2\ H_2O$ (366.35) calc'd.: C 68.83; H 4.41%
found : C 68.60; H 4.16%

[N-(p-*Tolyl*)-*barbituryl*-(5)]-[*pyrryl*-(2')]-*methine* (V)

A mixture of pyrrole-2-aldehyde (0.19 g.) and *N*-(*p*-tolyl)-barbituric acid (0.42 g., 2 mM) dissolved in 10 ml. ethanol was heated on the steam-bath for 15 min. The mixture was left at room temperature for 24 hours, and yellow crystals were obtained with a yield of 0.49 g. (80.5%). For analysis purposes the product was recrystallized from ethanol and dried at room temperature *in vacuo* over calcium chloride, m.p. 310—312° (decomp.)

Anal. $C_{16}H_{13}N_3O_3.1/2\ H_2O$ (304.28) calc'd.: C 63.17; H 4.64%
found : C 63.32; H 4.49%

[*Thiobarbituryl*-(5)]-[*pyrryl*-(2')]-*methine* (VI)

Pyrrole-2-aldehyde (0.19 g.) was added to thiobarbituric acid (0.28 g.) dissolved in hot ethanol (10 ml.). The orange coloured crystals precipitated immediately. For the microanalysis the crystals washed with ethanol were dried at room temperature *in vacuo* over calcium chloride, red crystals, m.p. 300° (decomp.). The substance is insoluble in water and slightly soluble in warm ethanol.

Anal. $C_9H_7N_3O_2S$ (221.1) calc'd.: C 48.89; H 3.19%
found : C 48.97; H 3.41%

[N,N-*Diphenylthiobarbituryl*-(5)]-[*pyrryl*-(2')]-*methine* (VII)

a) *N,N*-Diphenylthiobarbituric acid (0.59 g., 2 mM) was dissolved in dilute ethanol (10 ml.) and to the hot solution pyrrole-2-aldehyde (0.19 g.) was added. The yellow crystals precipitated immediately. The crystals were washed with dioxane.

Yield: 0.64 g. (83.7%). Dried at room temperature *in vacuo* over calcium chloride, orange crystals were obtained, m.p. 310° (decomp.).

Anal. $C_{21}H_{15}N_3O_2S.1/2\ H_2O$ (382.2) calc'd.: C 65.97; H 4.22%
found : C 65.97; H 4.67%

b) A mixture of pyrrole-2-aldehyde (0.19 g.) and *N,N*-diphenylthiobarbituric acid (0.59 g., 2 mM) in water (10 ml.) was heated for 30 min. on the steam-bath. A yellow voluminous precipitate was obtained, which, when left in the refrigerator, changed into yellow crystals. Yield: 0.72 g. (94.1%). The crystals were washed with ethanol and dried at room temperature *in vacuo* over calcium chloride, m.p. 310° (decomp.).

Anal. $C_{21}H_{15}N_3O_2S.1/2\ H_2O$ (382.2) calc'd.: C 65.97; H 4.22%
found: C 65.78; H 4.02%

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REFERENCES

1. M. Conrad and H. Reinbach, *Ber.* **34** (1901) 1340.
2. R. Jäger and E. Unger, *Ber.* **35** (1902) 4443.
3. S. Acabori, *Ber.* **66** (1933) 139. — M. Ridi and G. Aldo, *Gazz. chim. Ital.* **82** (1952) 13.
4. M. Deželić and A. Repaš, *Glasnik Društva hem. NRBiH (Bull. Soc. Chim., Sarajevo, Yougoslavie)* **8** (1959) 11.
5. G. R. Clemo, N. Fletcher, G. R. Fulton, and R. Raper, *J. Chem. Soc.* **1950**, 1140.
6. A. Treibs and R. Zimmer-Galler, *Ber.* **93** (1960) 2547.
7. G. F. Smith, *J. Chem. Soc.* **1954**, 3842.
8. M. Deželić and K. Grom-Dursun, *Glasnik Društva hem. NRBiH (Bull. Soc. Chim., Sarajevo, Yougoslavie)* **9** (1960) 49.
9. H. Biltz and H. Wittek, *Ber.* **54** (1921) 1035.
10. S. Gabriel and A. Colman, *Ber.* **37** (1904) 3657.
11. M. A. Whiteley, *J. Chem. Soc.* **91** (1907) 1338. *cf. Beilsteins Hdb.* XXIV (1936) 472.
12. P. C. Isherwood, *Chem. N.* **99** (1911) 234. *cf. Beilsteins Hdb.* XXIV (1946) 477.

IZVOD

Sinteze barbituril-piril-metina. O kondenzacionim produktima pirol-2-aldehida sa barbiturnim kiselinama i barbituratima

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Priredili smo kondenzacione produkte pirol-2-aldehida sa barbiturnom i tiobarbiturnom kiselinom, kao i s *N*-etilbarbiturnom kiselinom, *N*-fenilbarbiturnom kiselinom, *N,N*-difenilbarbiturnom kiselinom, *N*-(*p*-tolil)-barbiturnom kiselinom i *N,N*-difeniltiobarbiturnom kiselinom.

Farmakološki smo istražili sam pirol-2-aldehid kao i neke barbituril-piril-metine, pa smo ustanovili, da posjeduju sedativno i hipnotsko djelovanje (kod pokusnih miševa). Natrijeve soli nekih barbituril-piril-metina, napose spojevi (II i V), pokazivali su također izrazito spazmolitičko djelovanje na izoliranim organima pokusnih životinja.

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