

The material was identified as Piloty's methene salt by catalytic reduction to the methane, m. p. 230°. The yield was therefore 53%; mixed m. p. with 3,5,3',5'-tetramethyl-4,4'-dicarbethoxydipyrrolylmethane, 230°. A parallel test using 1 g. of aldehyde and 1.85 g. of N-methylpyrrole under these conditions yielded 0.57 g. of methene or 52%.

Condensation of 1,2,4-Trimethyl-3-carbethoxy-5-formylpyrrole with 1,2,4-Trimethyl-3-carbethoxypyrrole.—When this condensation was carried out in acid media, highly colored tars resulted from which no crystalline compound could be isolated.

Summary

1. It has been demonstrated that tripyrryl-

methanes can be and in two cases are intermediates in the formation of dipyrrolylmethenes by Piloty's aldehyde synthesis.

2. As a result of the three possibilities for cleavage of a tripyrrylmethane of this type, the number of normally expected methenes from this reaction must be increased from one to three.

3. Experiments have been performed in which the substituent groups were so modified as to give each of the three possibilities.

BALTIMORE, MD.

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[CONTRIBUTION FROM THE TECHNICAL DIVISION OF SHARP AND DOHME, INC.]

Thiobarbiturates. II

BY ELLIS MILLER, JAMES C. MUNCH, FRANK S. CROSSLEY AND WALTER H. HARTUNG

In an earlier communication¹ it was pointed out that in spite of the unfavorable indications obtained with diethyl thiobarbituric acid,²⁻⁴ the sulfur analogs of the well-known barbituric acids gave promise of therapeutic value and merited

a few thiobarbituric acid derivatives were described in the literature, namely, the unsubstituted acid itself,^{6,7} 5-methyl,⁹ 5-ethyl,^{8,9} 5-trimethylene,¹⁰ 5,5-diethyl,^{11,12} and 5,5-dipropyl thiobarbituric acids.¹³

TABLE I

5,5-DISUBSTITUTED THIOBARBITURIC ACIDS							
				$\begin{array}{c} \text{CO-NH} \\ \\ \text{R} \text{---} \text{C} \text{---} \text{CS} \\ \\ \text{R}' \text{---} \text{C} \text{---} \text{CO-NH} \end{array}$			
No.	R =	R' =	M. p., °C.	Empirical formula	Found (Kjeldahl)	Nitrogen, %	Calcd.
1	CH ₃ CH ₂ -	CH ₃ CH ₂ -	174.5	C ₉ H ₁₂ O ₂ N ₂ S	13.48	13.53	14.0
2	CH ₃ CH ₂ -	CH ₃ CH ₂ CH ₂ -	174.5	C ₉ H ₁₄ O ₂ N ₂ S	13.01		13.08
3	CH ₃ CH ₂ -	(CH ₃) ₂ CHCH ₂ -	170.5	C ₁₀ H ₁₆ O ₂ N ₂ S	12.42	12.48	12.28
4	CH ₃ CH ₂ CH ₂ -	(CH ₃) ₂ CH-	168.5	C ₁₀ H ₁₆ O ₂ N ₂ S	12.19	12.30	12.28
5	CH ₃ CH ₂ CH ₂ -	CH ₂ =CHCH ₂ -	138	C ₁₀ H ₁₄ O ₂ N ₂ S	12.26	12.44	12.39
6	CH ₃ CH ₂ CH ₂ -	CH ₃ CH ₂ CH ₂ CH ₂ -	135.5	C ₁₁ H ₁₈ O ₂ N ₂ S	11.20	10.92	11.57
7	CH ₃ CH ₂ CH ₂ -	(CH ₃) ₂ CHCH ₂ -	132	C ₁₁ H ₁₈ O ₂ N ₂ S	11.50	11.43	11.57
8	CH ₃ CH ₂ CH ₂ -	CH ₃ CH ₂ CH- CH ₃	165	C ₁₁ H ₁₈ O ₂ N ₂ S	11.30		11.57
9	CH ₃ CH ₂ CH ₂ -	CH ₃ (CH ₂) ₄ CH ₂ -	114.4	C ₁₃ H ₂₂ O ₂ N ₂ S	10.76		10.40
10	(CH ₃) ₂ CH-	CH ₂ =CHCH ₂ -	176.5	C ₁₀ H ₁₄ O ₂ N ₂ S	12.28	12.30	12.39
11	(CH ₃) ₂ CH-	(CH ₃) ₂ CHCH ₂ -	115-117	C ₁₁ H ₁₈ O ₂ N ₂ S	10.71		11.67
12	(CH ₃) ₂ CH-	CH ₃ (CH ₂) ₃ CH ₂ -	98.5	C ₁₂ H ₂₀ O ₂ N ₂ S	11.08	10.90	10.93
13	CH ₂ =CHCH ₂ -	CH ₃ (CH ₂) ₂ CH ₂ -	120-121	C ₁₁ H ₁₆ O ₂ N ₂ S	11.87	11.90	11.66
14	CH ₂ =CHCH ₂ -	(CH ₃) ₂ CHCH ₂ -	147	C ₁₁ H ₁₆ O ₂ N ₂ S	11.61	11.62	11.66
15	CH ₂ =CHCH ₂ -	CH ₃ (CH ₂) ₃ CH ₂ -	112.5	C ₁₂ H ₁₈ O ₂ N ₂ S	11.15	11.09	11.02

further investigation. This is confirmed by a subsequent report of Tabern and Volwiler.⁵

Prior to the publication of their paper, only

- (1) Miller, Munch and Crossley, *Science*, **81**, 615 (1935).
- (2) Fischer and v. Mering, *Therapie der Gegenwart*, **101**, 97 (1903).
- (3) Fraenkel, "Die Arzneimittelsynthese," 6th ed., 1927, p. 510.
- (4) Ostwald, "Chemische Konstitution und pharmakologischer Wirkung," Gebrüder Borntraeger, Berlin, 1924, p. 130.
- (5) Tabern and Volwiler, *THIS JOURNAL*, **67**, 1961 (1935).

Twenty new thio analogs of known barbituric

- (6) Johnson and Johns, *ibid.*, **36**, 973 (1914).
- (7) Dox and Plaisance, *ibid.*, **38**, 2156, 2164 (1916).
- (8) Wheeler and Jamieson, *Am. Chem. J.*, **32**, 352 (1904).
- (9) Einhorn, *Ann.*, **359**, 171 (1908).
- (10) Dox and Yoder, *THIS JOURNAL*, **43**, 683 (1921).
- (11) Fischer and Dilthey, *Ann.*, **335**, 350 (1904); *Chem. Centr.*, **75**, II, 1381 (1904).
- (12) German Patents 162,219, 171,292, 182,764, 234,012, 235,801.
- (13) German Patents 182,764, 234,012, 235,801; ref. 9, p. 177.

acid derivatives have been prepared in our laboratories. Six of these (the ethyl isopropyl, ethyl allyl, ethyl *n*-butyl, ethyl isoamyl, ethyl phenyl and allyl *s*-butyl thiobarbituric acids) are included in the list given by Tabern and Volwiler, and since their properties agree substantially with those already described, they need not be repeated here.

The synthesis of these compounds follows a single pattern, and one example will illustrate the method.

Ethyl *n*-Propyl Thiobarbituric Acid.—In a 1-liter, 3-necked round-bottomed flask, equipped with a mechanical stirrer and reflux condenser, is placed 276 ml. of anhydrous ethanol, and in it is dissolved 13.8 g. (0.6 mole) of metallic sodium. 24.3 g. (0.32 mole) of thiourea is added, while stirring. With continued stirring, 46 g. (0.2 mole) of ethyl *n*-propyl malonic ester is added quickly. Stirring is continued and the mixture is gently heated to incipient refluxing over a period of six to seven hours. After standing overnight the reaction mixture is concentrated on a steam-bath to about 150 ml. and diluted with 75 ml. of water. Concentrated hydrochloric acid is now added until the mixture is strongly acid to litmus paper, whereupon the desired ethyl *n*-propyl thiobarbituric acid precipitates out.

The crystals, after drying and recrystallizing from toluene, melt at 174–174.5° (uncorr.).

By substituting an equimolar amount of the appropriate malonic ester in the above reaction, other desired 5,5-disubstituted thiobarbituric acids have been obtained. In general the yield is somewhat higher than that obtained for the oxygen analogs.

The thiobarbituric acid derivatives are listed in Table I.

The intermediate dialkyl malonic esters have all been described in the literature. They were purchased where possible, or synthesized by well-known procedures. Of the esters synthesized, it may be said that in general the yields are satisfactory, except when a second alkyl group is being introduced into secondary-alkylmalonic ester.

Summary

Twenty 5,5-disubstituted thiobarbituric acids have been prepared and their chemical characteristics determined. Of these, six have recently been described by others. The method of preparation corresponds to that used for the oxygen analogs, but the yields are generally somewhat higher. A pharmacological study of these compounds has been completed and will be presented elsewhere.

GLENOLDEN, PENNA.

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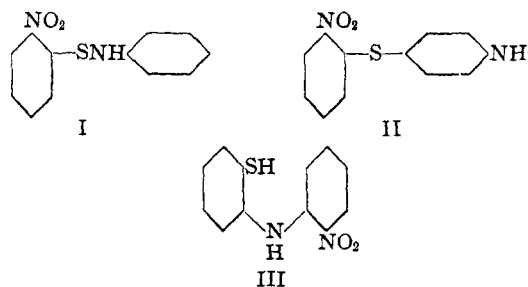
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Molecular Rearrangement of Sulfenylanilides.¹ III

By MAURICE L. MOORE² AND TREAT B. JOHNSON

In previous communications³ from this Laboratory, the authors have discussed the rearrangement of certain aromatic sulfenylanilide compounds of Type I. They have shown that on heating these alone or in the presence of an excess of the corresponding amine, they undergo rearrangement to *p*-aminophenyl sulfides II, whereas by digestion in alcoholic sodium hydroxide solution they give the corresponding *o*-mercaptodiphenylamines III. We have now extended the study of these molecular rearrangements to other compounds of similar structure, and in this paper we shall discuss the results of some new experi-

ments in which we have accomplished molecular rearrangements under the influence of heat.



In addition to the compounds of Type I, previously studied by the authors, many others examined give the same type of change upon heating. Thus, 2,4-nitrochlorobenzene-sulfenylanilide, prepared by the action of 2,4-nitrochlorobenzene-sulfonyl chloride upon aniline, gave 2,4-nitrochlorophenyl-4'-aminophenyl sulfide when heated at a temperature of 150–160° or when heated with an excess of aniline at a temperature of 180–190°. The corresponding *o*-toluidide underwent

(1) In our previous papers we have observed the nomenclature of the earlier workers in related fields in naming these sulfur compounds, but we have noticed that the abstractors for the *Chemical Abstracts* prefer and have applied another nomenclature. In order to be consistent and to maintain uniformity of spelling, in our Journals, we are, therefore, now following their system, as indicated in the Abstracts of our previous papers, and also in the last edition of "Organic Syntheses," Vol. XV, 1935, p. 45.

(2) A. Homer Smith Research Fellow in Organic Chemistry, 1935–1936.

(3) Moore and Johnson, *THIS JOURNAL*, **57**, 1517, 2234 (1935); see also *Science*, **81**, 643 (1935).