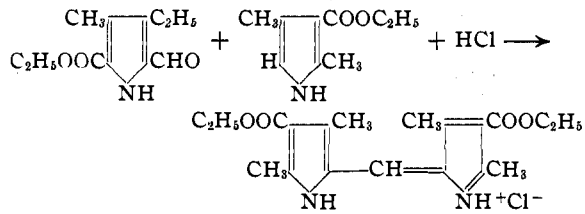
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Studies in the Pyrrole Series. II. The Mechanism of the Aldehyde Synthesis of Dipyrrylmethenes[1]

BY ALSOPH H. CORWIN AND JOHN S. ANDREWS

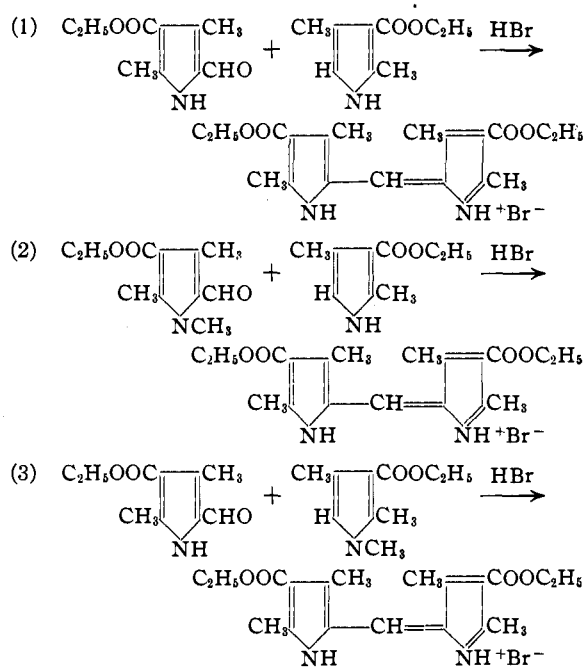
In the preceding paper[2] it was shown that the introduction of N-methyl groups into the pyrrole nucleus causes the aldehyde synthesis of methenes to follow a course different from that usually postulated. Fischer and Ernst[3] have also reported an anomalous aldehyde condensation

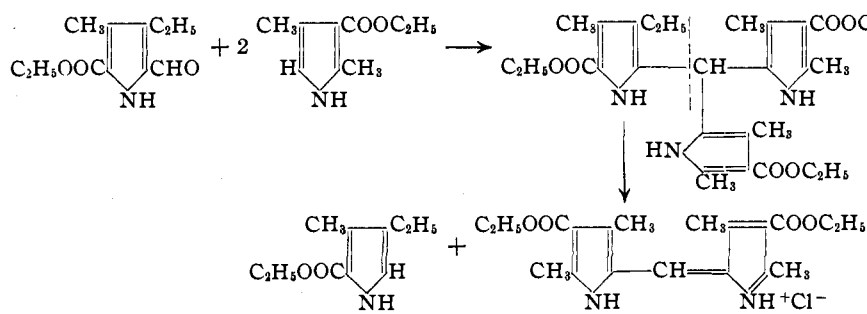


In order to account for the product obtained they assumed that the aldehyde was first hydrolyzed to yield formic acid which subsequently reacted with the 2,4-dimethyl-3-carbethoxypyrrole. This mechanism does not agree, however, with their observation that the best yield of methene resulted when two mols of the pyrrole were used for each mol of the aldehyde. These proportions suggest a tripyrrylmethane intermediate.

The suggestion of a tripyrrylmethane intermediate in the formation of methenes was unwittingly made by Piloty, Krannich and Will[4] who obtained a colorless compound as an intermediate in the synthesis of a methene and assigned to it the formula of a dipyrryl carbinol. Fischer and Ammann[5] proved this substance to be a tripyrrylmethane, substantiated Piloty's observation that hydrochloric acid would convert it into a methene but ignored his intuition that it was truly an intermediate in the reaction. If we assume a tripyrrylmethane as the intermediate in the reaction reported by Fischer and Ernst we have a complete explanation of the "abnormal" reaction by assuming cleavage at the bond which gives the symmetrical methene.

It becomes of interest, therefore, to determine whether or not tripyrryl methanes are actually intermediates in the methene syntheses. To this end we are reporting herewith a study of three reactions





The first of these is well known. The latter two are new examples of anomalous aldehyde syntheses.

The possibility of the existence of a tripyrryl-

(1) From the doctoral dissertation of John S. Andrews, The Johns Hopkins University, 1935.

(2) Corwin and Quattlebaum, THIS JOURNAL, **58**, 1081 (1936).

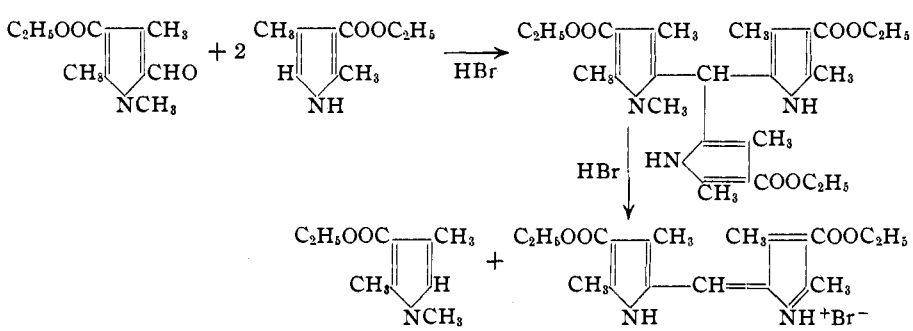
(3) Fischer and Ernst, *Ann.*, **447**, 146, 162 (1926).

(4) Piloty, Krannich and Will, *Ber.*, **47**, 2535 (1914).

(5) Fischer and Ammann, *ibid.*, **56**, 2319 (1923).

methane intermediate in the first reaction was tested by preparing the tripyrrylmethane and comparing its rate of cleavage with the rate of condensation of the aldehyde and the pyrrole. The fact that no appreciable difference in either velocity or yield could be found indicates that the tripyrrylmethane is a possible intermediate in the reaction.

In the second reaction a quantitative yield of methene was obtained when two mols of the pyrrole were used with one mol of the N-methyl aldehyde. In addition, 1,2,4-trimethyl-3-carbethoxypyrrole, predicted on the assumption of the tripyrrylmethane mechanism, was isolated in good yield. With equimolecular proportions the same products were formed but approximately half of the original aldehyde was recovered unchanged, indicating that it was not hydrolyzed to give formic acid under the conditions of the experiment. The tripyrrylmethane postulated as an intermediate was prepared and cleaved with acid under the conditions of the condensation. The same methene and N-methylpyrrole were obtained. We present these three facts as positive evidence of the existence of a tripyrrylmethane intermediate in this reaction as formulated in the following scheme



On the basis of this evidence we should predict that the condensation of the unmethylated aldehyde with the methylated pyrrole, the third reaction, should lead to an N-methyl methene. Actually, however, a new complication appears which upsets this prediction. The third reaction differs from the first two in that it is slow and does not give quantitative yields of the methene. That the postulated tripyrrylmethane is an intermediate in this reaction was proved by its actual isolation from the reaction mixture. Identification was made by comparison with a sample prepared by the Feist fusion method.[6] Cleavage of this material by acid led to the same yield of the methene as was produced in the same time by the condensation. We believe that these facts justify the formulation of the condensation given on the following page.

The three reactions which we have studied represent increasing degrees of complexity in the mechanism of the methene synthesis. They emphasize that the structures of the methenes obtained in the aldehyde condensation cannot in all cases be predicted from the starting products by the formulations previously used. The carbinol which is assumed to be formed first may undergo further condensation to give a tripyrrylmethane. This may cleave to form a second carbinol which may give either a methene or a second tripyrrylmethane. The latter may then yield a third carbinol and a third methene. The number of possible methenes resulting from the aldehyde condensation must be increased from one to three and we envisage the possibility that mixtures of these may occasionally result. The factors which influence the formation and cleavage of tripyrrylmethanes will be the subject of a later communication.

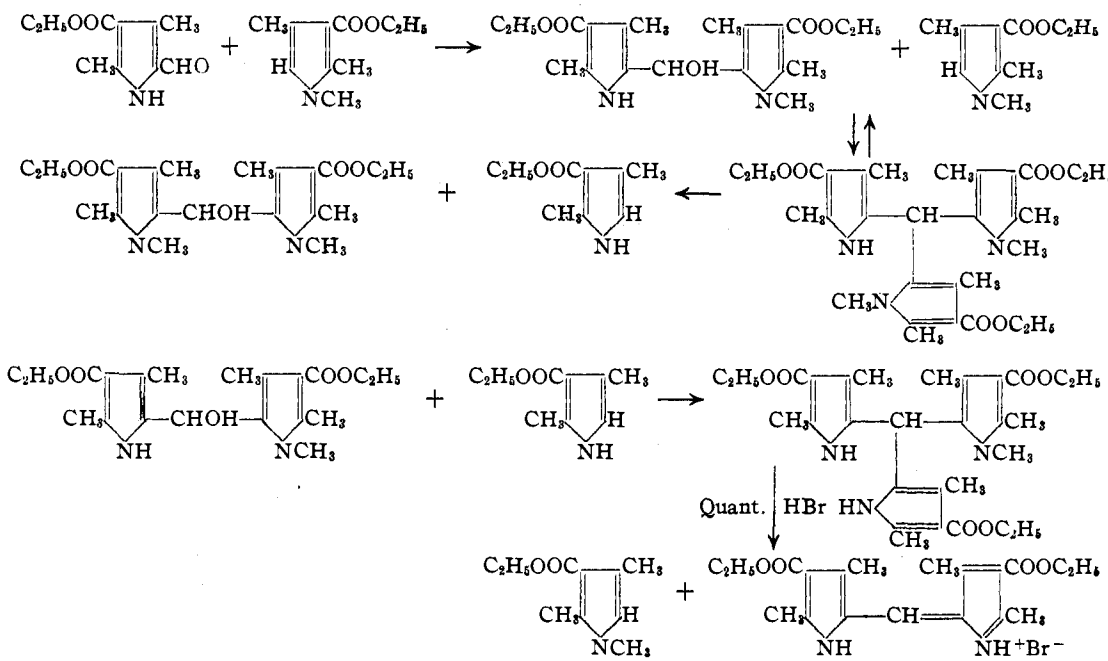
Experimental Part

Identification of 3,5,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethene (Piloty's Methene).—The recorded melting point of the hydrochloride[7] is not a true melting point but an irreversible decomposition point as noted by Fischer and Schubert.[8] Likewise the "melting point" of the free base, 190°, is the point of an irreversible decomposition. Thus the identification of the methene with unknown samples by the method of mixed melting points is theoretically unjustifiable. The method of mixed solubilities cannot be used on solutions of the methene hydrochloride for these darken and decompose on standing even at room temperature, thus precluding long contact of a solution with crystals to obtain a saturated solution. While a solution of the free base in methyl alcohol

(6) Feist, *Ber.*, **35**, 1647 (1902).

(7) (a) Ref. 4, p. 2545; (b) Fischer and Zerweck, *ibid.*, **55**, 1947 (1922); (c) *ibid.*, **56**, 526 (1923); (d) Fischer and Heyse, *Ann.*, **439**, 255 (1924); (e) Fischer, Schormüller and Windecker, *ibid.*, **498**, 289 (1932).

(8) Fischer and Schubert, *Ber.*, **56**, 1209–1210 (1923).



appears to be stable so that the method of mixed solubilities might be used for a comparison of the bases, it was found more convenient to resort to catalytic reduction to the methane. By this method a substance with a true melting point was obtained which was suitable for purposes of identification. The method of Fischer and Ammann[5] (p. 2324) was modified by the substitution of alcohol for glacial acetic acid as a solvent, under which conditions no green by-product was formed. Adams catalyst was used; yield of the methane, 85%; m. p. 230°.

3,5,3',5',3",5" - Hexamethyl - 4,4',4" - tricarbethoxytripyrrylmethane.—The method of Fischer and Heyse[7d] (p. 246) was used. Repeated recrystallizations from alcohol–water alternated with methanol increased the purity of the compound. The substance sintered at 195° and melted with decomposition at 220–225°.

Anal. Calcd. for $C_{28}H_{37}O_6N_3$: C, 65.71; H, 7.29. Found: C, 65.70; H, 7.28.

Parallel Cleavage of Tripyrrylmethane and Aldehyde Condensation.—0.197 g. of hexamethyltricarbethoxytripyrrylmethane and 0.075 g. of 2,4-dimethyl-3-carbethoxy-5-formylpyrrole were dissolved in 20 cc. of methanol. Another solution was prepared by dissolving 0.15 g. of the aldehyde and 0.13 g. of 2,4-dimethyl-3-carbethoxypyrrole in the same amount of methanol. One cc. of hydrobromic acid solution, prepared by adding 3 cc. of saturated aqueous hydrobromic acid to 10 cc. of methanol, was added to each solution. Almost simultaneously and in less than one minute precipitates of the methene were formed in each tube. Filtration and washing with methanol yielded 0.27 g. of the hydrobromide of Piloty's methene in each case.

2,4-Dimethyl-3-carbethoxy-5-formylpyrrole.—The modification of the Gattermann synthesis introduced by Adams[9] is advantageous in this preparation. Fifty grams of 2,4-dimethyl-3-carbethoxypyrrole was dissolved in 500 cc. of anhydrous ether. Seventy-five grams of zinc cyanide was added, the mixture cooled to 10° and dry hydrogen chloride passed in rapidly until the solution was saturated (about three hours). The solution was allowed to warm to room temperature and to remain at this temperature for at least three hours. The supernatant liquid should be only slightly yellow colored. The imide hydrochloride was filtered off and washed with dry ether. It was then dissolved in 3.5 liters of cold water and filtered. Upon heating to 40° the solution deposited 53–54 g. of crystalline aldehyde. This was recrystallized from ethanol; m. p. 164°. Repeated recrystallizations raised the m. p. to 167°.

1,2,4 - Trimethyl - 3 - carbethoxy - 5 - formylpyrrole.—Twenty grams of 2,4-dimethyl-3-carbethoxy-5-formylpyrrole was dissolved in 200 cc. of dry commercial benzene, 7 g. of sodium monoxide was added and the suspension refluxed for one hour. Twelve cc. of freshly distilled dimethyl sulfate was added dropwise with vigorous mechanical stirring. The gelatinous mixture was refluxed for one hour, the sodium sulfate filtered off and washed with benzene and the filtrate allowed to stand overnight. About 3 g. of starting product crystallized out. The filtrate was steam distilled and the residual oil cooled until it solidified, filtered off and recrystallized from 80 cc. of methanol; yield, first crop, 8.5 g.; m. p. 97°. The mother liquor was cooled in dry ice and 6 g. of additional yield obtained.

Anal. Calcd. for $C_{11}H_{15}O_3N$: C, 63.18; H, 7.23. Found: C, 63.19; H, 7.28.

Condensations of 1,2,4-Trimethyl-3-carbethoxy-5-formylpyrrole with 2,4-Dimethyl-3-carbethoxypyrrole.—First experiment, 1:2 ratio: 1 g. of the N-methyl aldehyde and 1.65 g. of 2,4-dimethyl-3-carbethoxypyrrole were dissolved in 100 cc. of warm hexane. After cooling to room temperature dry hydrogen chloride gas was passed in for fifteen seconds and the resulting methene hydrochloride filtered

(9) Adams and Levine, THIS JOURNAL, **45**, 2373 (1923); Adams and Montgomery, *ibid.*, **46**, 1518 (1924).

off and washed with a little hexane; yield, 1.90 g. or 100%; identified by reduction to the methane, m. p. 230°. The faintly yellow filtrate was evaporated on the steam-bath to about 20 cc. Chilling in dry ice–ethanol mixture yielded 0.6 g. of a nearly colorless crystalline solid, m. p. 57°. A mixed m. p. with 1,2,4-trimethyl-3-carbethoxypyrrole, m. p. 57°, gave no depression.

Second experiment, 1:1 ratio: 1 g. of the N-methyl aldehyde and 0.8 g. of the pyrrole were dissolved in 100 cc. of hexane and treated with dry hydrogen chloride for about thirty seconds. The methene was filtered off after five minutes and washed with hexane until the washings were nearly colorless; 0.9 g. of Piloty methene salt was obtained and identified by reduction to the methane. The filtrate was chilled in dry ice–ethanol mixture and 0.6 g. of colorless needles were obtained, m. p. 65–80°. This product was recrystallized by dissolving in ether at room temperature and cooling in dry ice mixture; 0.3 g. of colorless crystals was obtained, m. p. 94°, mixed m. p. with 1,2,-4-trimethyl-3-carbethoxy-5-formylpyrrole, no depression. By evaporation of the hexane filtrate from which the crude N-methyl aldehyde had been removed a nearly colorless residue was obtained. Recrystallization from 3–4 cc. of hexane by chilling in dry ice yielded 0.1 g. of material, m. p. 57°, mixed m. p. with 1,2,4-trimethyl-3-carbethoxypyrrole, no depression.

1,2,4,2′,4′,2″,4″ - Heptamethyl - 3,3′,3″ - tricarbethoxytripyrrylmethane.—The preparation was analogous to that of the hexamethyltricarbethoxytripyrrylmethane above. A preliminary purification was obtained by dissolving the product in chloroform and precipitating with petroleum ether. Crystallization from methanol yielded 1.6 g. of the methane and 0.3 g. additional was obtained from the mother liquor. Three recrystallizations from ethanol–water gave a colorless product, m. p. 177°.

Anal. Calcd. for $C_{29}H_{39}O_6N_3$: C, 66.24; H, 7.48. Found: C, 66.25, 66.29; H, 7.44, 7.44.

Cleavage.—Two-tenths gram of the heptamethyltricarbethoxytripyrrylmethane was dissolved in 50 cc. of hot methanol, cooled to 40°, and to it added 1 cc. of saturated aqueous hydrobromic acid. Within one minute the formation of a red precipitate was observed. This was filtered off after five minutes and washed with methanol; yield 0.16 g. or 95%. The product was identified by reduction to the methane, m. p. 230°.

Condensations of 2,4-Dimethyl-3-carbethoxy-5-formyl Pyrrole with 1,2,4-Trimethyl-3-carbethoxypyrrole.—Five grams of the aldehyde and 4.6 g. of the N-methylpyrrole were dissolved in 150 cc. of hot methanol and 0.5 cc. of saturated aqueous hydrobromic acid was added and the mixture allowed to stand at 70°. The precipitate which formed was reddish-purple even after washing with ether; yield 4.05 g. of methene hydrobromide, melting with decomposition at 213–215°. This was identified as Piloty methene by catalytic reduction to the methane, m. p. 230°, mixed m. p. with an authentic sample, 230°. The yield of methane from the discolored methene was identical with that from pure methene.

Parallel Test of Aldehyde with the N-Methylpyrrole and Aldehyde without the N-Methylpyrrole.—To test the possibility that the formation of Piloty's methene might be due to the cleavage of the aldehyde discovered by Fischer and Zerweck[7d] the course of the reaction of the aldehyde with and without the N-methylpyrrole was studied. Formation of the methene in the presence of the N-methylpyrrole takes place at a lower temperature than the cleavage of the aldehyde in the absence of the pyrrole. At a higher temperature, where both reactions proceed, the methene is formed more rapidly and in greater yield in the presence of the N-methylpyrrole than in its absence. A typical experiment follows.

Two-tenths gram of 2,4-dimethyl-3-carbethoxy-5-formylpyrrole and 10 cc. of methanol were mixed in each of two flasks. To the first, 0.185 g. of 1,2,4-trimethyl-3-carbethoxypyrrole was added. Both flasks were warmed until all the aldehyde dissolved and then held at about 50°; 0.1 cc. of 48% hydrobromic acid was added to each. The flask containing the N-methylpyrrole assumed a deep red color immediately. After about ten minutes it began to deposit colored crystals. A few minutes later the flask containing the aldehyde alone started to deposit similar crystals. After half an hour the crystals from both flasks were filtered off and weighed. From the flask containing aldehyde and pyrrole, 0.075 g. of the methene was obtained. From the flask containing the aldehyde alone, 0.040 g. of the methene was obtained.

Isolation of Tripyrrylmethane Intermediate in the Reaction.—If the flask containing the mixed aldehyde and N-methylpyrrole be cooled soon after the appearance of the deep red color mentioned above, tripyrrylmethane can be isolated as an intermediate. To favor this reaction, however, three mols of N-methylpyrrole was used to one mol of the aldehyde: 1 g. of the aldehyde and 2.75 g. of the N-methylpyrrole were dissolved in 35 cc. of hot methanol and 0.5 cc. of saturated aqueous hydrobromic acid added. The solution instantly became intensely red and, upon chilling in dry-ice and alcohol, deposited a large amount of a colorless precipitate. Upon warming to room temperature this deposit did not dissolve; yield, 2.5 g.; m. p. 146°. This was identified as 2,4,1′,2′,4′,1″,2″,4″-octamethyl-3,3′,3″-tricarbethoxytripyrrylmethane by a mixed m. p. with material made by the Feist fusion method given below. The yield was thus 88%.

2,4,1′,2′,4′,1″,2″,4″ - Octamethyl - 3,3′,3″ - tricarbethoxytripyrrylmethane.—One gram of 2,4-dimethyl-3-carbethoxy-5-formylpyrrole and 1.85 g. of 1,2,4-trimethyl-3-carbethoxypyrrole were fused at a temperature not exceeding 150° with about 0.1 g. of potassium bisulfate as a catalyst according to Feist's method. The product was purified by dissolving in methanol, adding ether and chilling in dry ice; yield, 1.5 g.; m. p. after several recrystallizations from C_2H_5OH–H_2O, 147–148°; mixed m. p. with substance from hydrobromic acid condensation above, no depression.

Anal. Calcd. for $C_{30}H_{41}O_6N_3$: C, 66.75; H, 7.66. Found: C, 66.67; H, 7.61.

Cleavage.—One and forty-five-hundredths grams of the di-N-methyltripyrrylmethane was dissolved in 25 cc. of hot methanol and when cool this solution was diluted with 50 cc. of ether. Five-tenths cc. of saturated aqueous hydrobromic acid was added and the solution allowed to stand at room temperature. A red coloration appeared very slowly and after one hour purple needles began to be deposited. After twenty hours these were filtered off and washed with ether yielding 0.3 g. of red-purple needles.

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'-dicarbethoxydipyrrylmethane, 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 tripyrrylmethanes can be and in two cases are intermediates in the formation of dipyrrylmethenes 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. RECEIVED MARCH 4, 1936

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

Thiobarbiturates. II

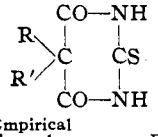
BY ELLIS MILLER, JAMES C. MUNCH, FRANK S. CROSSLEY AND WALTER H. HARTUNG

In an earlier communication[1] 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 further investigation. This is confirmed by a subsequent report of Tabern and Volwiler.[5]

Prior to the publication of their paper, only 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



No.	R =	R' =	M. p., °C.	Empirical formula	Nitrogen, % Found	(Kjeldahl)	Calcd.
1	CH_3CH_2-	CH_3CH_2-	174.5	$C_8H_{12}O_2N_2S$	13.48	13.53	14.0
2	CH_3CH_2-	$CH_3CH_2CH_2$-	174.5	$C_9H_{14}O_2N_2S$	13.01		13.08
3	CH_3CH_2-	$(CH_3)_2CHCH_2$-	170.5	$C_{10}H_{16}O_2N_2S$	12.42	12.48	12.28
4	$CH_3CH_2CH_2$-	$(CH_3)_2CH$-	168.5	$C_{10}H_{16}O_2N_2S$	12.19	12.30	12.28
5	$CH_3CH_2CH_2$-	$CH_2{=}CHCH_2$-	138	$C_{10}H_{14}O_2N_2S$	12.26	12.44	12.39
6	$CH_3CH_2CH_2$-	$CH_3CH_2CH_2CH_2$-	135.5	$C_{11}H_{18}O_2N_2S$	11.20	10.92	11.57
7	$CH_3CH_2CH_2$-	$(CH_3)_2CHCH_2$-	132	$C_{11}H_{18}O_2N_2S$	11.50	11.43	11.57
8	$CH_3CH_2CH_2$-	$CH_3CH_2CH(CH_3)$-	165	$C_{11}H_{18}O_2N_2S$	11.30		11.57
9	$CH_3CH_2CH_2$-	$CH_3(CH_2)_4CH_2$-	114.4	$C_{13}H_{22}O_2N_2S$	10.76		10.40
10	$(CH_3)_2CH$-	$CH_2{=}CHCH_2$-	176.5	$C_{10}H_{14}O_2N_2S$	12.28	12.30	12.39
11	$(CH_3)_2CH$-	$(CH_3)_2CHCH_2$-	115-117	$C_{11}H_{18}O_2N_2S$	10.71		11.67
12	$(CH_3)_2CH$-	$CH_3(CH_2)_3CH_2$-	98.5	$C_{12}H_{20}O_2N_2S$	11.08	10.90	10.93
13	$CH_2{=}CHCH_2$-	$CH_3(CH_2)_2CH_2$-	120-121	$C_{11}H_{16}O_2N_2S$	11.87	11.90	11.66
14	$CH_2{=}CHCH_2$-	$(CH_3)_2CHCH_2$-	147	$C_{11}H_{16}O_2N_2S$	11.61	11.62	11.66
15	$CH_2{=}CHCH_2$-	$CH_3(CH_2)_3CH_2$-	112.5	$C_{12}H_{18}O_2N_2S$	11.15	11.09	11.02

Twenty new thio analogs of known barbituric

(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, **57**, 1961 (1935).
(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.