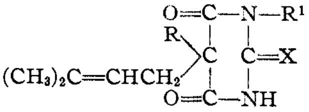
TABLE I

BARBITURIC ACIDS[a]



	R	R¹	X	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	$(CH_3)_2CH—$	H—	O	67	127–128[b,c]	60.50	60.44	7.61	7.23	11.76	11.86
II	$(CH_3)_2CH—$	$CH_2{=}CHCH_2—$	O	47	78–79[c]	64.72	64.84	7.97	7.81	10.07	10.26
III	$(CH_3)_2CH—$	$CH_3—$	O	31	87–88[d]	61.88	62.02	7.99	7.92	11.10	10.89
IV	$CH_2{=}CHCH_2—$	H—	O	71	104–105[d]	61.04	61.02	6.83	6.88	11.86	11.99
V	$C_2H_5—$	H—	O	50	155–156[e]	58.92	59.15	7.19	7.07	12.49	12.33
VI	$(CH_3)_2CH—$	H—	S	26	134–135[e]	56.66	56.57	7.13	7.03	11.02	11.43
VII	H—	H—	O	45	186–188[e]	55.10	54.81	6.12	6.10	14.28	14.22

[a] Although some of the pharmacology of 5-ethyl-5-(3-methyl-2-butenyl)-barbituric acid was reported as early as 1945 (Noble, Associate Committee on Drug Medical Research, 7th Meeting, National Research Council, Ottawa, April, 1945; *cf.* Ballem, Noble and Webster, *Can. Med. Assoc. J.*, **58**, 447 (1948)), there appears to be no description of these dimethylallyl barbiturates in the chemical literature. [b] Potentiometric titration of this acid in 50% alcohol indicated, at half-neutralization, that the pK_a was 9.1. [c] Recrystallized from aqueous alcohol. [d] Recrystallized from aqueous ethylene glycol. [e] Recrystallized from methanol.

isoprenyl malonic ester (11.4 g., 0.05 mole), urea (4.5 g., 0.075 mole; or an appropriate amount of thiourea or methylurea) and sodium ethoxide (3.45 g., 0.15 mole, of sodium in 70 cc. of absolute alcohol; in the case of I, IV and V dry sodium ethoxide was used) was heated for eight hours on the steam-bath in a pressure bottle. The precipitated sodium salt was removed by filtration and dissolved in water, or in case no solvent had been used water was added to the entire reaction mixture, and the crude barbituric acid was precipitated by carbon dioxide.

Isoamylbarbituric Acid.—A solution of 2.0 g. of 5-(3-methyl-2-butenyl)-barbituric acid in 45 cc. of absolute ethanol was hydrogenated over 0.1 g. of Adams catalyst for two hours at 48 p.s.i. Considerable material separated from the solution during the reduction. Additional alcohol (100 cc.) was added to take all the separated solid into solution, the catalyst was removed by filtration and the filtrate was chilled to give 5-isoamylbarbituric acid which, after recrystallization, did not depress the m. p. of an authentic sample[2] of the material, m. p. 238–240°, prepared by alkylation of barbituric acid with isoamyl bromide.

Ethyl 3-Methyl-2-butenylmalonic Ester XI.—To a stirred and cooled (2 to 10°) mixture of ethyl malonic ester (62 g., 0.33 mole, Eastman Kodak Co. redistilled, b. p. 95–97° (12 mm.)), isoprenyl bromide (50 g., 0.33 mole) and alcohol (20 cc.) there was slowly added a solution of sodium (7.6 g., 0.33 mole) in alcohol (150 cc.). After thirty minutes refluxing the no-longer basic mixture was worked up in the usual manner to give 53 g. (62% yield) of product, b. p. 131–138° (10 mm.); n^{25}_D 1.4450.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.62; H, 9.37. Found: C, 65.18; H, 9.40.

5-Isopropyl-5-(3-methyl-2-butenyl)-barbituric Acid, I.—The following is the alternative preparation of this substance. To a cooled (−5°) and stirred mixture of 5-isopropylbarbituric acid[2] (8.5 g., 0.050 mole) and sodium ethoxide (1.15 g. (0.050 mole) of sodium in 20 cc. of alcohol) there was added during one hour a solution of isoprenyl bromide (7.5 g., 0.050 mole) in alcohol (10 cc.). After 30 minutes additional stirring at −5° the mixture was allowed to warm to room temperature and worked up in the usual manner to give 3.3 g. (27% yield) of pure product, m. p. 128–129°. A portion of the isoprenyl bromide was consumed in a side-reaction, and when the isoprenyl bromide was added all at once and the condensation was carried out at room temperature this side-reaction became predominant. After the reaction was carried out at room temperature the mixture was poured into water and the aqueous mixture was extracted with ether. The extract was washed with 10% sodium hydroxide and then with water until the washings were neutral. After the extract was dried the solvent was removed and the residue was distilled to give 2–3 g., which after redistillation boiled at 102° (750 mm.).

Anal. Calcd. for $C_5H_{10}O$: C, 69.76; H, 11.62. Found: C, 68.87; H, 11.97.

The material is possibly dimethylvinylcarbinol, the b. p. of which is reported[7] to be 98–99° and which has been obtained[8] by treatment of 3-methyl-3-butenyl chloride or bromide with aqueous alkali or even with water. The isomeric 3-methyl-2-butenol-1 is reported[9] to boil at 140°.

1-Allyl-5-isopropyl-5-(3-methyl-2-butenyl)-barbituric Acid, II.—A mixture of 5-isopropyl-5-isoprenylbarbituric acid (11.9 g., 0.050 mole), allyl bromide (6.2 g., 0.050 mole) and cupric sulfate pentahydrate (1.25 g., 0.005 mole) in 25 cc. of 2 *N* sodium hydroxide was refluxed seven hours and then allowed to stand overnight, during which time the crude crystalline product precipitated.

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(7) Gadziatzki, *Jahresber.*, 700 (1887).

(8) Claisen, *J. prakt. Chem.*, [2] **105**, 78 (1908).

(9) Courtot, *Bull. soc. chim.*, [3] **35**, 660 (1906); *cf.* also Ultee, *Rec. trav. chim.*, **68**, 483 (1949).

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A Novel Sulfidation Reaction and Its Application to Some Indoles and Pyrroles

BY RICHARD G. WOODBRIDGE 3RD[1] AND GREGG DOUGHERTY

In a recent paper[2] we disclosed a novel reaction whereby 4-substituted-2-aminothiazoles are directly converted to their corresponding bis-(5-thiazolyl) sulfides by making alkaline a solution of the aminothiazole, thiourea and a halogen.

On extending this reaction to other heterocyclic compounds we have found that with certain indoles and pyrroles the corresponding disulfides may be obtained.

In general the procedure was to add to a water–alcohol solution of the compound under investigation, thiourea in amount equivalent to two moles of thiourea per mole of compound, and iodine equivalent to one mole per mole of compound. The solution was then made very alkaline with

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(1) Ethyl Corporation Fellow, 1948.

(2) Woodbridge and Dougherty, THIS JOURNAL, **71**, 1744 (1949).

solid sodium hydroxide. We have found that the above reactant ratios in the aminothiazole series result in increased yields and products of higher purity than the ratios indicated in our previous paper.

The yields of indyl and pyrryl disulfides were greatly increased on exposing the reaction mixture to the air. It was found that by adding an additional mole of halogen to the reaction mixture the disulfide was immediately and completely thrown out.

This indicates that with indoles and pyrroles the reaction proceeds through a mercaptan intermediate, the probable steps in the reaction being (1) halogenation in the β-position, (2) condensation of the β-halo-compound with thiourea to yield a thiuronium compound, (3) dismutation of this to the corresponding β-mercapto compound, followed by oxidation to the disulfide either by unreacted halogen, oxygen from the air or by additional halogen.

With the aminothiazoles the reaction may be considered to be the same with the exception that in step three the mercapto compound presumably reacts as rapidly as it is formed with the thiuronium compound, which has not yet undergone dismutation, to yield a monosulfide.[3]

As evidence for this proposed mechanism, in the case of the aminothiazoles, we have found that 2-amino-4-methyl-5-bromothiazole in a solution containing thiourea yields bis-(2-amino-4-methyl-5-thiazolyl) sulfide immediately as a voluminous crystalline precipitate on making the solution strongly alkaline.

In our previous paper, we pointed out that bis-(4-substituted-2-amino-5-thiazolyl) sulfides could be isolated as a by-product from the 4-substituted-2-aminothiazole preparation developed by Dodson and King.[4] We should like to report at this time that the easily reducible condensation product of monochloroacetone and 2-amino-4-methylthiazole[5] appears to be identical with another by-product formed in the preparation of 2-amino-4-methylthiazole as prepared by the procedure of Dodson and King. We plan to report on this work some time in the future.

Experimental

Bis-(indyl) Disulfide.—A 2-l. flask was charged with 23.4 g. of indole and 45.6 g. of thiourea. To this were added 400 cc. of alcohol and 200 cc. of water. Fifty and eight-tenths grams of iodine was then dissolved in this solution, following which solid sodium hydroxide was added until the solution was very alkaline. The flask was filled with water and the resulting slurry allowed to stand overnight. After filtering, washing and drying, 6.9 g. (23.3%) of product was obtained. The product was dissolved in ether and decolorized with charcoal. It was crystallized from its ether solution by adding petroleum ether until a permanent turbidity was produced and allowing crystallization to proceed overnight. The crystals so obtained were highly electrified, m. p. 227-229.5° (cor.). *Anal.* Calcd. for $C_{16}H_{12}N_2S_2$: S, 21.6. Found: S, 21.4.

Bis-(2-methyl-3-indyl) Disulfide.—A 250-cc. flask was charged with 6.6 g. of 2-methylindole[6] and 7.6 g. of thiourea. This was dissolved in a mixture of 75 cc. of alcohol and 25 cc. of water by warming to 50°. To the clear solution was added 12.7 g. of iodine. The solution was made very alkaline by adding solid sodium hydroxide. After standing for 48 hours the product was filtered off and washed well. On recrystallization from absolute alcohol the bis-(2-methyl-3-indyl) disulfide was obtained in large (1 cm. thick) crystals of a sulfur-yellow color. The yield was 4.4 g. (54.0%), m. p. 236-237° (cor.). *Anal.* Calcd. for $C_{18}H_{16}N_2S_2$: S, 19.8. Found: S, 19.8.

Bis-(2-phenyl-3-indyl) Disulfide.—Nine grams of 2-phenylindole[7] and 7.1 g. of thiourea were charged to a 250-cc. flask. To this were added 75 cc. of alcohol and 25 cc. of water. The slurry was warmed to 50° and 23.7 g. of iodine was added. The resulting, clear, dark solution was made very alkaline with sodium hydroxide. One hundred cc. of water was added and the mixture was allowed to stand overnight. After filtering, washing and drying, 10 g. (95.7%) of golden, yellow crystals were obtained. These were purified by crystallization from alcohol. They had a melting point of 161.8-162.4° (cor.). *Anal.* Calcd. for $C_{28}H_{20}N_2S_2$: S, 14.3. Found: S, 14.2.

Bis-(2,3,5-trimethyl-4-pyrryl) Disulfide.—2,3,5-Trimethyl-4-carbethoxypyrrole[8] was converted to 2,3,5-trimethylpyrrole in one step,[9] as follows: three grams of 2,3,5-trimethyl-4-carbethoxypyrrole in a 250-cc. flask was dissolved in 3 cc. of concentrated C. P. sulfuric acid. As soon as the pyrrole had dissolved, 4.5 cc. of 20% sulfuric acid was added. The mixture was gently heated over a flame until the temperature had reached 105° and all effervescence had ceased. The sulfidation reaction was carried out on this solution of 2,3,5-trimethylpyrrole. To the cooled, dark red solution was added a mixture of 45 cc. of water and 15 cc. of alcohol. Two and one-half grams of thiourea was added and when this had dissolved, 4.2 g. of iodine, which immediately dissolved. The solution was then made very alkaline by adding solid sodium hydroxide. A dark crystalline precipitate immediately formed and was filtered off. To the filtrate was added 4.2 g. more iodine dissolved in 50 cc. of alcohol. This caused the formation, immediately, of a voluminous, creamy precipitate. Combined yield of all solids was 1.9 g. (81.8%). The product was purified by repeated recrystallizations from acetone, and decomposed at 217-218° (cor.). *Anal.* Calcd. for $C_{14}H_{20}N_2S_2$: S, 22.9. Found: S, 22.7.

Bis-(2,5-dimethyl-3-carbethoxy-4-pyrryl) Disulfide.—Five grams of 2,5-dimethyl-3-carbethoxypyrrole[10] and 4.6 g. of thiourea were charged to a 250-cc. flask. To this were added 50 cc. of water and 50 cc. of alcohol. On warming to 55° a clear solution was obtained to which was added 7.6 g. of iodine. This rapidly dissolved. The solution was then made very alkaline with solid sodium hydroxide. The precipitate, after filtering, washing, and drying weighed 5.8 g. (97.8%). It was obtained pure on one recrystallization from glacial acetic acid. It decomposed at 271-272° (cor.). *Anal.* Calcd. for $C_{18}H_{24}O_4N_2S_2$: S, 16.2. Found: S, 16.3. Fisher and Hermann[11] have reported the preparation of this compound from 2,5-dimethyl-3-carbethoxypyrrole and sulfur monochloride.

Bis-(2-amino-4-methyl-5-thiazolyl) Sulfide from 2-Amino-4-methyl-5-bromothiazole.—2-Amino-4-methyl-5-bromothiazole was prepared according to the sulfuric acid solution method of Ochiai and Nagasawa.[12] One

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[3] Surrey and Lindwall, THIS JOURNAL, **62**, 1697 (1940); *cf.* also Talen, *Rec. trav. chim.*, **47**, 782 (1928); Blanksma, *ibid.*, **20**, 408 (1902); Johnson and Edens, THIS JOURNAL, **63**, 1058 (1941).

[4] Dodson and King, *ibid.*, **67**, 2242 (1945).

[5] *Cf.* Kondo and Nagasawa, *J. Pharm. Soc. Japan*, **57**, 308 (1937).

[6] Beilstein, 4th ed., Bd. 20, p. 311, 1935.

[7] Reisenegger, *Ber.*, **16**, 662 (1883).

[8] Treibs, *Ann.*, **524**, 289 (1936).

[9] *Cf.* Hess, Wissing and Sueheim, *Ber.*, **48**, 1871 (1915).

[10] Fischer and Orth, "Die Chemie des Pyrrols," Leipzig, 1934, Bd. I, p. 247.

[11] Fisher and Hermann, *Z. physiol. Chem.*, **122**, 20 (1922).

[12] Ochiai and Nagasawa, *Ber.*, **72**, 1470 (1939).

and nine-tenths grams of 2-amino-4-methyl-5-bromothiazole was suspended in 100 cc. of water. Two grams of thiourea was added and the mixture shaken until all solids had dissolved. The solution was made very alkaline by adding solid sodium hydroxide. In a few seconds, the characteristic glistening crystals of bis-(2-amino-4-methyl-5-thiazolyl) sulfide were thrown out. The yield was 0.3 g. With some bis-(2-amino-4-methyl-5-thiazolyl) sulfide previously prepared there was no melting point depression.

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The Hydroxymethylation of Kojic Acid

BY L. L. WOODS

The reaction of formaldehyde with kojic acid introduces one hydroxymethyl group in either the 3 or the 6 position of the pyrone ring. An earlier report[1] indicates that both of these positions are reactive so that a definite structure cannot be assigned to the derivative herein described. However, the compound is probably 2,6-bis-(hydroxymethyl)-5-hydroxy-4-pyrone since base catalyzed reactions[2] presumably require a mechanism which depends upon the nucleophilic character of the phenolic ion, thus causing the primary substitution to take place at a position ortho to the phenolic hydroxyl, in this instance position 6.

Treatment of the above product with thionyl chloride, followed by recrystallization from boiling water, gives a substance containing only one chlorine atom. The 2-chloromethyl group is assumed to remain intact since Yabuta[3] has shown that 2-chloromethyl-5-hydroxy-4-pyrone resists hydrolysis by hot water.

Attempts to introduce two hydroxymethyl groups into kojic acid under forcing conditions always gave mixtures whose composition approached that of 2,3,6-tri-(hydroxymethyl)-5-hydroxy-4-pyrone, but the analysis of the benzoate indicated that it was contaminated with condensation products with similar physical properties.

Experimental[4]

Two grams of paraformaldehyde was added to a boiling mixture of 10 g. of kojic acid in 100 ml. of absolute ethanol, the solution was cooled slightly and 1 g. of potassium bicarbonate or anhydrous sodium carbonate was added with stirring. After standing for two hours, the solid was filtered and dried in a vacuum desiccator over sulfuric acid. Recrystallization of the crude product (9.8 g.) from absolute ethanol gave very pale yellow needles which melted at 155–156°, following an apparent change in structure above 132°, and which gave a red-purple coloration with ferric chloride solution.

Anal. Calcd. for $C_7H_8O_5$: C, 48.83; H, 4.65. Found: C, 49.20, 49.02; H, 4.37, 4.42.

Two grams of the above compound was refluxed with 7 ml. of thionyl chloride. The product, weighing 0.5 g. after recrystallization from 25 ml. of boiling water, separated either as needles or stout prisms which changed to needles between 120 and 140° and melted at 165°.

Anal. Calcd. for $C_7H_7O_4Cl$: C, 44.38; H, 3.16. Found: C, 44.71, 44.60, 44.68; H, 3.24, 3.08, 3.18.

Benzoylation of 2 g. of the compound by the usual Schotten–Baumann method produced a white solid which was recrystallized three times from absolute ethanol; yield 2.2 g., m. p. 134.5–135.5°.

Anal. Calcd. for $C_{28}H_{20}O_8$: C, 69.42; H, 4.13. Found: C, 69.04; H, 4.08.

In an attempt to introduce two hydroxymethyl groups into the pyrone nucleus, a mixture of 10 g. of kojic acid, 3.8 g. of paraformaldehyde, 1 g. of potassium bicarbonate and 50 ml. of absolute ethanol was heated for seventeen hours at 75°. Two ml. of concentrated hydrochloric acid was then added, the mixture was refluxed for thirty minutes, treated with Norite and filtered. After standing in the refrigerator for two days, the solution deposited 5.4 g. of a brown solid which was not appreciably soluble in alcohol or other organic solvents. Recrystallization from water, followed by digestion with absolute ethanol, gave a yellow powder which decomposed above 233° and gave a red coloration with ferric chloride.

Anal. Calcd. for $C_8H_{10}O_6$: C, 47.52; H, 4.95. Found: C, 47.99; H, 4.70.

Benzoylation of 1.8 g. of the above powder with 12 ml. of benzoyl chloride at 100–110° for one hour, followed by the action of 10% sodium hydroxide, gave a solid which was recrystallized once from benzene and four times from ethanol. The product, a yellow powder melting at 99–101°, failed to give the proper analysis, an indication that the substance from which the benzoate was prepared probably contained significant amounts of condensation products similar to 2,3,6-tri-(hydroxymethyl)-5-hydroxy-4-pyrone.

Anal. Calcd. for $C_{36}H_{26}O_{10}$: C, 69.90; H, 4.20. Found: C, 68.71; H, 4.00.

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(1) Woods, THIS JOURNAL, **68**, 2744 (1946).

(2) Price, "Reactions at Carbon–Carbon Double Bond," Interscience Publishers, New York, N. Y., 1946, p. 46.

(3) Yabuta, *J. Chem. Soc.*, **125**, 575 (1924).

(4) The kojic acid was obtained from the Corn Products Sales Company. Analyses were by Dr. Carl Tiedcke. The Fisher–Johns apparatus was used for all melting points

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Calcium Hydride as a Basic Catalyst in the Perkin Reaction

BY SAVERIO ZUFFANTI AND JOHN J. SARDELLA

Gibb[1,2] and others[3-6] have investigated the use of calcium hydride in the condensations of aldehydes, ketones and esters.

This note reports data on the use of calcium hydride in the Perkin reaction. Benzaldehyde has been treated with acetic, propionic, and *n*-butyric anhydrides.

Experimental

Materials.—The calcium hydride was the commercial gray grade of about 95% purity. The benzaldehyde was purified by keeping it in contact with calcium hydride for several days and then collecting the fraction distilling at 178–180°. The acetic, propionic and *n*-butyric anhydrides were purified by allowing each to stand over metallic sodium for a few days, distilling, then allowing to stand over calcium hydride for a few days, and distilling again before use.

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(1) Gibb and Mann, M. I. T., B.S. Thesis, 1946.

(2) Gibb and Horne, M. I. T., B.S. Thesis, 1946.

(3) Taboury and Godchot, *Compt. rend.*, **169**, 62–64 (1919).

(4) Porlezza and Gatti, *Gazz. chim. ital.*, **54**, 491 (1924); **55**, 224 (1925).

(5) Perkin and Pratt, *J. Chem. Soc.*, **95**, 159 (1909).

(6) Packendorff, *Ber.*, **64B**, 948–949 (1931).