added at least 5 moles of the alkyl halide (where methyl chloride was used, the reaction mixture was saturated with the gas). The flask was stoppered and allowed to stand (1.5 hr. for compound XIII, 2–3 days for X and XII, and 2 weeks for IV). The reaction mixture was diluted with ether. The solid which formed was collected on a filter. Compound IV was recrystallized from acetone–ether, compound X from acetone–alcohol, and compounds XII and XIII from alcohol–ether.

A solid which had formed before dilution with ether in the preparation of IV was removed by filtration and shown to be 1-(1-piperidyl)-3-phenyl-3-heptanol hydrochloride by halogen determination and mixed m. p. The filtrate, however, yielded the quaternary salt on dilution with ether.

Acknowledgments.—The authors are indebted to Dr. R. W. Cunningham, Dr. B. K. Harned and their assistants of the Pharmacology Department of the Lederle Laboratories Division for the determination of the antispasmodic activities of these compounds. The microanalytical services of Mr. O. E. Sundberg, Mrs. M. E. Nielson, and Miss I. H. Prokul are greatly appreciated.

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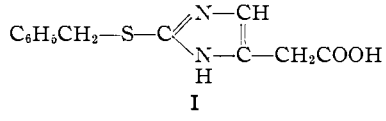
RECEIVED FEBRUARY 9, 1950

The Reaction of Ethyl α- and γ-Bromoacetoacetates with S-Alkylisothioureas

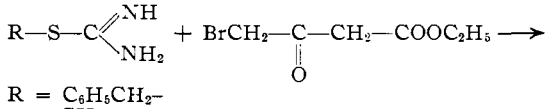
BY R. M. DODSON, ELWOOD R. PETERSON[1] AND JAY K. SEYLER

The preparation of substituted imidazoles by the reaction of α-haloketones with S-alkylisothioureas recently has been reported.[2] The reaction of ethyl γ-bromoacetoacetate with S-benzylisothiourea was studied with the hope of obtaining the substituted imidazolylacetic acid, I, which could then be converted to histamine. However,

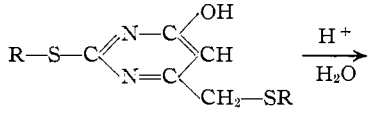


I

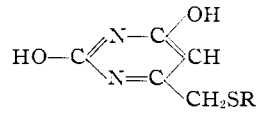
it is well known that ethyl acetoacetate reacts with S-alkylisothioureas to yield substituted pyrimidines.[3] The reaction of S-benzylisothiourea with ethyl γ-bromoacetoacetate, under a variety of conditions, including those used in the previous preparation of imidazoles (sodium bicarbonate and dilute alcohol),[2] yielded 2-benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine (II); no imidazole was obtained from the reaction.



R = $C_6H_5CH_2$–
CH₃–



II, R = $C_6H_5CH_2$–
IV, R = CH₃–



III, R = $C_6H_5CH_2$–
V, R = CH₃–

The structure of II was assigned on the basis of (1) analogy with known reactions, (2) analysis, (3) acid hydrolysis of II to 2,6-dihydroxy-4-benzylthiomethylpyrimidine (III),[4] and (4) desulfurization of II with Raney nickel[5] to the known 4-methyl-6-hydroxypyrimidine.

S-Methylisothiourea reacted with ethyl γ-bromoacetoacetate in an analogous manner to yield 2-methylthio-4-methylthiomethyl-6-hydroxypyrimidine (IV). This in turn was readily hydrolyzed to 2,6-dihydroxy-4-methylthiomethylpyrimidine (V).

Ethyl α-bromoacetoacetate and S-benzylisothiourea failed to give either 2-benzylthio-4-methyl-5-bromo-6-hydroxypyrimidine or 2,5-dibenzylthio-4-methyl-6-hydroxypyrimidine under the conditions used to prepare compound II. Rather, the ethyl α-bromoacetoacetate oxidized the benzyl mercaptan (from the decomposition of S-benzylisothiourea) to dibenzyl disulfide and was itself reduced, at least in part, to ethyl acetoacetate. The ethyl acetoacetate so formed then reacted with S-benzylisothiourea to form 2-benzylthio-4-methyl-6-hydroxypyrimidine. This oxidation of benzyl mercaptan with ethyl α-bromoacetoacetate was not unexpected. Finger and Hemmeter[6] have shown that equal molecular quantities of sodium phenylmercaptide and ethyl α-chloroacetoacetate react to form diphenyl disulfide and diethyl α,α′-diacetylsuccinate.

Experimental[7]

Ethyl γ-Bromoacetoacetate and Ethyl α-Bromoacetoacetate.—Ethyl γ-bromoacetoacetate was prepared by the bromination of ethyl acetoacetate in anhydrous ether.[8] Since Burger and Ullyot reported that attempts to distil the bromoester resulted in considerable decomposition, the crude material was used in the following experiments. Ethyl α-bromoacetoacetate was prepared either by the method of Smith[9] or by the method of Conrad.[9] It was not distilled but was used immediately after preparation.

2-Benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine (II).—To a solution of 26.2 g. (0.125 mole) of ethyl γ-bromoacetoacetate and 50.6 g. (0.250 mole) of S-benzyl-

(1) From the M.S. Thesis of Elwood R. Peterson, September, 1949.

(2) R. M. Dodson, THIS JOURNAL, **70**, 2753 (1948); R. M. Dodson and F. Ross, *ibid.*, **72**, 1478 (1950).

(3) Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(4) The 2-alkylthioimidazoles are not hydrolyzed under these conditions. This is probably due to the great difference in electronegativity of imidazolyl and pyrimidyl groups.

(5) Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943); Howard, Lythgoe and Todd, *J. Chem. Soc.*, 556 (1945).

(6) Finger and Hemmeter, *J. prakt. Chem.*, [2] **79**, 449 (1909).

(7) Microanalyses by Messrs. R. Amidon, J. Buckley, W. Cummings, R. Kelly and H. Turner.

(8) Burger and Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

(9) L. I. Smith, THIS JOURNAL, **44**, 216 (1922); M. Conrad, *Ber.*, **29**, 1042 (1896).

isothiourea hydrochloride in 300 ml. of 95% ethyl alcohol was added 28 g. (0.50 mole) of potassium hydroxide in approximately 50 ml. of water. The resulting mixture was allowed to stand for twenty-four hours at room temperature. Then the solvent was removed under reduced pressure on the steam-bath and water was added to dissolve the inorganic salts. On acidification of this solution with dilute hydrochloric acid, a semi-solid precipitate was formed. When this suspension was shaken with ether, the precipitate became crystalline. It was separated by filtration and was washed with water and ether. This product, m. p. 130–135°, weighed 23 g. but contained an insoluble impurity (which we could not recrystallize). The 2-benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine was dissolved in hot ethyl alcohol and separated from the insoluble material by filtration. When cooled, the alcoholic filtrate deposited 17.5 g. of the pyrimidine, II, m. p. 140–144°. An additional 2 g. of product, m. p. 140–145°, was obtained by extraction of the preceding ether solution with 10% aqueous sodium hydroxide and acidification of the basic extract. Crystallization of the combined 19.5 g. (44.6%) of product from ethyl alcohol gave 18.2 g. (41.1%) of the pyrimidine, m. p. 144–147°. Further crystallization of the compound readily raised the melting point to 146–147°.

Anal. Calcd. for $C_{19}H_{18}N_2OS_2$: C, 64.40; H, 5.12; N, 7.97. Found: C, 64.46; H, 5.31; N, 7.99.

A small quantity (3.1 g.) of crude dibenzyl disulfide, m. p. 63–66°, was isolated from the ether extract.

2,6-Dihydroxy-4-benzylthiomethylpyrimidine (III).—A solution of 9.7 g. (0.027 mole) of 2-benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine in 138.5 ml. of glacial acetic acid and 41.5 ml. of 20% hydrochloric acid was heated on the steam-bath for two and one-half hours, then cooled and neutralized with dilute ammonium hydroxide. The fine white crystals were separated by filtration; they weighed 6.8 g. (100%), m. p. 174–177°. Two crystallizations from ethyl alcohol gave 6.7 g. (98.7%) of 2,6-dihydroxy-4-benzylthiomethylpyrimidine, m. p. 182–183°. Further crystallization of the compound raised the melting point to 183–184°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.06; H, 4.88; N, 11.28. Found: C, 58.42; H, 5.18; N, 10.83.

4-Methyl-6-hydroxypyrimidine.—To a solution of 4 g. of 2-benzylthio-4-benzylthiomethyl-6-hydroxypyrimidine dissolved in 60 ml. of water containing 0.60 g. of sodium hydroxide was added 55 ml. of Raney nickel suspension containing 55 g. of Raney nickel. The suspension was heated at 70–80° with vigorous stirring for one hour. The suspension was filtered and the residue washed with water. The filtrate was made neutral with dilute hydrochloric acid and the solution was evaporated on the steam-bath. The residue, after vacuum sublimation and crystallization of the sublimate from ethyl acetate, yielded 0.60 g. (48%) of 4-methyl-6-hydroxypyrimidine, m. p. 141–146°. Two crystallizations of the product from ethyl acetate raised its melting point to 148–149°. The compound is reported[10] to melt at 149–150°.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.45; N, 25.45. Found: C, 54.51; H, 5.74; N, 25.45.

2-Methylthio-4-methylthiomethyl-6-hydroxypyrimidine (IV).—To a suspension of 92.3 g. (0.333 mole) of S-methylisothiourea sulfate in 750 ml. of ethyl alcohol was added 69.7 g. (0.333 mole) of ethyl γ-bromoacetoacetate. Then 74.5 g. (1.33 mole) of potassium hydroxide in 200 ml. of water was added slowly with vigorous stirring; the stirring was continued at room temperature for three hours. The resulting suspension was allowed to stand for sixteen hours. The product was isolated in a manner similar to that described for compound II. Crystallization of the crude material from ethyl acetate yielded 14.2 g. (21.3%) of 2-methylthio-4-methylthiomethyl-6-hydroxypyrimidine, m. p. 147–149°. Several crystallizations of the product from ethyl acetate raised the melting point to 149.5–150.5°.

(10) Gabriel and Colman, *Ber.*, **32**, 2921 (1899).

Anal. Calcd. for $C_7H_{10}N_2OS_2$: C, 41.55; H, 4.98; N, 13.85. Found: C, 41.93, 41.69; H, 5.15, 4.84; N, 13.74.

2,6-Dihydroxy-4-methylthiomethylpyrimidine (V).—Hydrolysis of compound IV with 20% hydrochloric acid with or without the addition of glacial acetic acid gave 2,6-dihydroxy-4-methylthiomethylpyrimidine, m. p. 221–222°, in 65–70% yield. The product is easily crystallized from water.

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27. Found: C, 41.71, 41.57; H, 4.90, 5.06; N, 16.57.

2-Benzylthio-4-methyl-6-hydroxypyrimidine was prepared from 25.2 g. (0.125 mole) of S-benzylisothiourea hydrochloride and 16.25 g. (0.125 mole) of acetoacetic ester by a procedure similar to that used by Johns[11] for the preparation of 2-ethylthio-4-methyl-6-hydroxypyrimidine. After crystallization of the compound from alcohol, 8.0 g. (28%) of white, needle-like crystals, m. p. 176–178°, was obtained. A second crystallization from alcohol gave 7.0 g. (24%) of the pyrimidine, m. p. 176–178°.

Anal. Calcd. for $C_{12}H_{12}N_2OS$: C, 62.06; H, 5.17; N, 12.06. Found: C, 62.36; H, 5.35; N, 12.35.

The Reaction of Ethyl α-Bromoacetoacetate with S-Benzylisothiourea.—A solution of 26.2 g. (0.125 mole) of ethyl α-bromoacetoacetate and 50.6 g. (0.250 mole) of S-benzylisothiourea hydrochloride in 300 ml. of alcohol was treated with a solution of 28 g. (0.5 mole) of potassium hydroxide in 20 ml. of water. The resulting mixture was allowed to stand overnight. The precipitate which formed during this time was separated by filtration and washed well with water. Crystallization of this precipitate from dilute alcohol gave 20 g. (68%) of dibenzyl disulfide, m. p. 71°. A mixture with an authentic sample of dibenzyl disulfide[2] showed no depression in melting point.

The alcohol was distilled from the filtrate of the reaction mixture and the solution remaining was acidified with two normal hydrochloric acid. The oil which separated solidified on standing. It was crystallized from ethyl acetate to yield 8.0 g. (28%) of crude 2-benzylthio-4-methyl-6-hydroxypyrimidine, m. p. 160–170°. Several recrystallizations from dilute alcohol and from benzene gave 3.0 g. (10%) of the pure pyrimidine, m. p. 176–178°. A mixture with the 2-benzylthio-4-methyl-6-hydroxypyrimidine prepared above showed no depression in melting point.

(11) C. O. Johns, *Am. Chem. J.*, **40**, 348 (1908).

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MINNEAPOLIS, MINN. RECEIVED JANUARY 14, 1950

Derivatives of 6-Methyl-5,6-dihydrophenanthridine

BY JACOB FINKELSTEIN AND SEYMOUR LINDER

During a study of synthetic anti-histaminics in 1945, recognizing the structural relationship between Antergan and 5,6-dihydrophenanthridine, it was decided to prepare N-substituted derivatives of the latter. Since the compounds were devoid of the desired pharmacological action, no further interest was developed. In view of the recent note by Huttrer[1] describing the 5,6-dihydrophenanthridine compound analogous to Antergan, we wish to record the preparation of 6-methyl-5,6-dihydrophenanthridine and a few N-derivatives (as well as a few chemical reactions of 6-methylphenanthridine).

Prior to Huttrer's note,[1] no catalytic reduction studies on the phenanthridine ring were reported.

(1) Huttrer, THIS JOURNAL, **71**, 4147 (1949).