[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

The Reaction of S-Benzylisothiourea with Phenacyl Bromide

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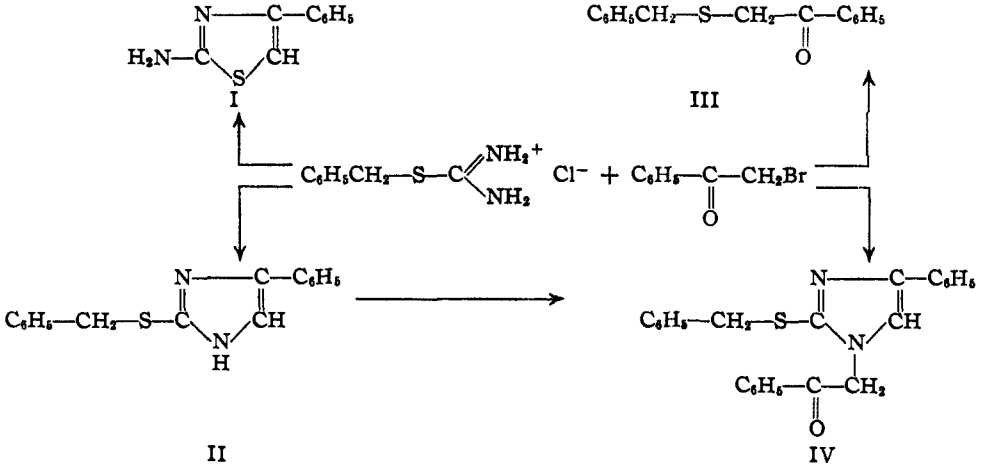
Although thiourea[1] has been used very extensively in the synthesis of heterocyclic compounds the use of S-alkylisothioureas for this purpose has been rather limited. Wheeler[2] and co-workers have used S-methyl- and S-ethylisothioureas in the synthesis of 2-alkylthiopyrimidines. Deck and Dains[3] have used a number of substituted S-methylisothioureas in the synthesis of various heterocyclic rings, but in their syntheses the methylthio group was eliminated. The purpose of this investigation was to extend the use of S-alkylisothioureas to the preparation of alkylthioimidazoles.

It is well known that thiourea reacts with α-haloketones to form 2-aminothiazoles.[1a] This reaction illustrates the preferential alkylation of the thio group in thiourea with alkyl halides. If, however, the thio group is first protected by alkylation, reaction of the S-alkylisothiourea with an α-haloketone should lead to the formation of an alkylthioimidazole. Kunckell[4] has demonstrated that α-haloketones will react with amidines to form imidazoles, and S-alkylisothioureas are merely readily available amidines.



The first attempted preparation of 2-benzylthio-4(5)-phenylimidazole (II) was made by heating equivalent amounts of S-benzylisothiourea hydrochloride and phenacyl bromide over a free flame until a clear melt was obtained. From this reaction 2-amino-4-phenylthiazole (I) rather than the expected imidazole was isolated. The benzyl group was eliminated, and the product was identical with that obtained from the reaction of thiourea with phenacyl bromide.

Condensation of equivalent amounts of S-benzylisothiourea hydrochloride and phenacyl bromide in alcohol in the presence of sodium bicarbonate formed 2-benzylthio-4(5)-phenylimidazole (II) in moderate yield (38%). The product was accompanied by smaller amounts of benzyl phenacyl sulfide (III) and 1-phenacyl-2-benzylthio-4-phenylimidazole (IV). The benzyl phenacyl sulfide (III) was formed concurrently with 2-benzylthio-4(5)-phenylimidazole (II) by the cleavage of the S-benzylisothiourea to benzyl mercaptan, followed by condensation of the mercaptan with phenacyl bromide. The 1-phenacyl-2-benzylthio-4-phenylimidazole (IV)[5,6] was formed by the further reaction of the 2-benzylthio-4(5)-phenylimidazole with phenacyl bromide. The relative quantities of these substances produced in the reaction depended on the conditions. Thus, in 50% aqueous alcohol, cleavage of the S-benzylisothiourea led to the formation of much (50%) benzyl phenacyl sulfide (III), but the 2-benzylthio-4(5)-phenylimidazole (II) (33%) was not alkylated. In absolute alcohol, on the other hand, most of the imidazole was alkylated to 1-phenacyl-2-benzylthio-4-phenylimidazole (IV). When potassium hydroxide was substituted for sodium bicarbonate, cleavage of the S-benzylisothiourea predominated and benzyl phenacyl sulfide (III) was formed in very good yield (81%). The 1-

(1) (a) V. Traumann, *Ann.*, **249**, 31 (1888); (b) M. Jackman, A. J. Bergman and S. Archer, THIS JOURNAL, **70**, 497 (1948); (c) R. Anschütz and H. Geldermann, *Ann.*, **261**, 129 (1891).

(2) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(3) J. F. Deck and F. B. Dains, THIS JOURNAL, **55**, 4986 (1933).

(4) F. Kunckell, *Ber.*, **34**, 637 (1901).

(5) It is realized that this compound could be alternately formulated as 1-phenacyl-2-benzylthio-5-phenylimidazole. Structure IV is preferred by the author because Pyman and co-workers have found that 4(5)-phenylimidazole, on treatment with methyl sulfate, yields 1-methyl-4-phenylimidazole and 1-methyl-5-phenylimidazole in the proportions of 4.8 to 1.

(6) C. E. Hazeldine, F. L. Pyman and J. Winchester, *J. Chem. Soc.*, **125**, 1431 (1924).

phenacyl-2-benzylthio-4-phenylimidazole (IV) was best prepared (73%) by heating an alcoholic solution of one mole of S-benzylisothiourea hydrochloride and two moles of phenacyl bromide under reflux with sodium bicarbonate. The concurrent formation of benzyl phenacyl sulfide (III) and the further reaction of the imidazole with phenacyl bromide satisfactorily explain the moderate yield of 2-benzylthio-4(5)-phenylimidazole obtained.

The formation of 2-amino-4-phenylthiazole on fusion of S-benzylisothiourea hydrochloride with phenacyl bromide introduced the possibility that compound II was 2-benzylamino-4-phenylthiazole, formed by the migration of the benzyl group. This necessitated a proof of structure of the compound. On treatment with acetyl iodide[7] the 2-benzylthio-4(5)-phenylimidazole (II) was cleaved to 2-thiol-4(5)-phenylimidazole, identical with the compound previously prepared by Clemo and coworkers.[8]

Experimental[9]

2-Amino-4-phenylthiazole (I).—A dry mixture of 5.10 g. (0.025 mole) of S-benzylisothiourea hydrochloride, m. p. 172–175°, and 5.00 g. (0.025 mole) of phenacyl bromide was cautiously heated over a free flame until molten. The reaction was stopped when the solution started to boil. The resulting melt was cooled and extracted with 100 ml. of dilute (1:10) hydrochloric acid. The acid extract was decanted through a filter, and the excess acid was neutralized with sodium bicarbonate. The precipitate was separated by filtration and crystallized from benzene. From this reaction 1.57 g. (36%) of 2-amino-4-phenylthiazole, m. p. 149.5–150°, was obtained.

Anal. Calcd. for $C_9H_8N_2S$: C, 61.34; H, 4.58. Found: C, 61.55; H, 4.67.

The acetyl derivative, prepared by the action of acetic anhydride, melted at 212.5°. 2-Amino-4-phenylthiazole and its acetyl derivative are reported to melt at 151–152° and 214–214.5°, respectively.[10]

2-Amino-4-phenylthiazole was also formed in the same yield when the mixture of S-benzylisothiourea hydrochloride and phenacyl bromide were heated under vacuum in an oil-bath at 150–160° until distillation of volatile material ceased.

2-Benzylthio-4(5)-phenylimidazole (II).—A solution of phenacyl bromide in 100 ml. of chloroform, prepared by the bromination of 30.0 g. (0.25 mole) of acetophenone, was added to a solution of 51.0 g. (0.25 mole) of S-benzylisothiourea hydrochloride in 300 ml. of 84% ethyl alcohol. To this combined solution 84.0 g. (1.0 mole) of sodium bicarbonate was added slowly and the suspension heated under reflux for three hours. The solvent was then distilled from the reaction mixture. The residue was treated with 300 ml. of warm water and heated on the steam-bath until all of the inorganic salts had dissolved. The suspension was cooled and decanted through a filter. The product was washed a second time with warm water and dried. It was next treated with 100 ml. of boiling benzene; all lumps were broken; the resulting suspension was cooled in ice, and the product was separated by filtration. The process was repeated with 50 ml. of benzene and the product finally washed on the filter with two 25-ml. portions of cold benzene. From this reaction 25.1 g. (37.7%) of 2-benzylthio-4(5)-phenylimidazole, m. p. 173–177°, was obtained. One crystallization of the compound from alcohol raised its melting point to 176.5–177.5°.

Anal. Calcd. for $C_{16}H_{14}N_2S$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.01; H, 5.38; N, 10.23.

The picrate was prepared in boiling alcohol, m. p. 145–145.5°.

Anal. Calcd. for $C_{22}H_{17}N_5O_7S$: C, 53.33; H, 3.46. Found: C, 53.59; H, 3.52.

The benzene mother liquors from the above preparation were thoroughly shaken with 150 ml. of dilute (1:6) hydrochloric acid. The hydrochloride was separated by filtration and washed on the filter with 100 ml. of water, 100 ml. of ether, and finally 30 ml. of water, then crystallized from alcohol. A solution of this salt in alcohol was made basic with ammonium hydroxide, heated to boiling, diluted with water until slightly cloudy, then cooled. The product was separated by filtration and washed on the filter with 20 ml. of 70% ethyl alcohol. In this way 7.2 g. (15% based on the phenacyl bromide consumed) of 1-phenacyl-2-benzylthio-4-phenylimidazole, m. p. 141.5–143°, was obtained. Crystallization of the compound from alcohol raised its melting point to 143–143.5°.

Anal. Calcd. for $C_{24}H_{20}N_2OS$: C, 74.95; H, 5.24. Found: C, 74.96; H, 5.36.

The organic mother liquors from the filtration of the above hydrochloride were distilled and the residue was crystallized from 95% alcohol. Very crude benzyl phenacyl sulfide (18.2 g.), m. p. 64–76°, was obtained. Repeated crystallizations from alcohol failed to give a pure product. Crystallization from a mixture of benzene and petroleum ether (b. p. 60–70°) gave 11.2 g. (18.5%) of benzyl phenacyl sulfide, m. p. 87.5–88°. A mixture with an authentic sample of benzyl phenacyl sulfide showed no depression of melting point.

From the above benzene and petroleum ether mother liquors a small quantity (1.6 g.) of dibenzyl disulfide, m. p. 69.5–70° was isolated. For purposes of identification this was oxidized to benzyl benzylthiolsulfonate ("dibenzyl disulfoxide"), m. p. 106.5–107°. The reported melting points of these compounds are 72 and 108°, respectively.[11]

Benzyl Phenacyl Sulfide (III).—To a boiling solution of 5.10 g. (0.025 mole) of S-benzylisothiourea hydrochloride and 5.00 g. (0.025 mole) of phenacyl bromide in 50 ml. of ethyl alcohol was added a solution of 3.50 g. (0.0625 mole) of potassium hydroxide in 20 ml. of ethyl alcohol. The resulting suspension was heated under reflux for two hours. It was then cooled to 5°, and the product separated by filtration. The product was washed on the filter with 10 ml. of cold alcohol, then suspended in warm water and stirred thoroughly to free it from potassium bromide and potassium chloride, then again separated from the solution by filtration. From this reaction 4.90 g. (81%) of benzyl phenacyl sulfide, m. p. 86–87°, was obtained. Crystallization of the compound from alcohol raised its melting point to 87.5–88.5°. Oxidation with potassium permanganate gave benzyl phenacyl sulfone, m. p. 112°. The reported melting points of benzyl phenacyl sulfide and benzyl phenacyl sulfone are 89° and 113°, respectively.[12]

1-Phenacyl-2-benzylthio-4-phenylimidazole (IV).—To a solution of 5.10 g. (0.025 mole) of S-benzylisothiourea hydrochloride and 10.00 g. (0.050 mole) of phenacyl bromide in 50 ml. of absolute alcohol was added 8.4 g. (0.10 mole) of sodium bicarbonate. The resulting suspension was heated under reflux for two and one-half hours with periodic shaking, then diluted with water. The product was separated by filtration, powdered, and treated with 200 ml. of ether. The resulting suspension on filtration yielded 5.33 g. of 1-phenacyl-2-benzylthio-4-phenylimidazole, m. p. 139–143°. The ether mother liquors were next extracted with 75 ml. of dilute (1:2)

(7) E. L. Gustus and P. G. Stevens, THIS JOURNAL, **55**, 378 (1933).

(8) G. R. Clemo, T. Holmes and G. C. Leitch, *J. Chem. Soc.*, 753 (1938).

(9) Microanalyses by Messrs. Roger Amidon, Jay Buckley, and William Hunter. All melting points were taken on a Fisher–Johns melting-point apparatus.

(10) R. M. Dodson and L. C. King, THIS JOURNAL, **67**, 2242 (1945).

(11) E. Fromm and J. de Seixas Palma, *Ber.*, **39**, 3308, 3317 (1906).

(12) C. Wahl, *ibid.*, **55**, 1449 (1922).

hydrochloric acid, and the insoluble hydrochloride treated according to the directions given above. An additional 1.68 g. of 1-phenacyl-2-benzylthio-4-phenylimidazole, m. p. 136–139°, was obtained. The total yield of crude product was 7.01 g. or 73%. One crystallization from dilute alcohol gave 6.37 g. of material, m. p. 141.5–142.5°. A mixture with the previously prepared sample showed no depression of melting point. This same product can be made in 78% yield by alkylating 2-benzylthio-4(5)-phenylimidazole with phenacyl bromide in alcohol in the presence of sodium bicarbonate.

The picrate of 1-phenacyl-2-benzylthio-4-phenylimidazole was prepared by mixing the base and picric acid in hot alcohol, m. p. 169–171°.

Anal. Calcd. for $C_{30}H_{23}N_5O_9S$: C, 58.72; H, 3.78. Found: C, 58.90; H, 3.74.

2-Thiol-4(5)-phenylimidazole.—Red phosphorus (3.7 g.) was added to 15 g. of iodine in 25 ml. of glacial acetic acid, and the resulting suspension was heated under reflux for twenty minutes. Then 3.00 g. of 2-benzylthio-4(5)-phenylimidazole was added and the solution was heated under reflux for three and one-half hours. The solution was filtered to free it from phosphorus, decolorized with sodium bisulfite, diluted with two volumes of water, and neutralized with ammonium hydroxide. The resulting suspension was cooled in ice, and the product was separated from the solution by filtration. To free the 2-thiol-4(5)-phenylimidazole from starting material, it was dissolved in 50 ml. of 10% sodium hydroxide solution. After separating the insoluble 2-benzylthio-4(5)-phenylimidazole (0.34 g., m. p. 172–175°), the filtrate was neutralized with 8 ml. of glacial acetic acid, and cooled. On filtration 1.13 g. (64% on the basis of the starting material consumed) of 2-thiol-4(5)-phenylimidazole, m. p. 249–255°, was obtained. Crystallization of the compound from a mixture of acetone and benzene raised its melting point to 261–262°. The picrate, formed in absolute alcohol, crystallized as garnet-red prisms, m. p. 178–179° (dec.). For further identification of 2-thiol-4(5)-phenylimidazole was oxidized with dilute nitric acid to 4(5)-phenylimidazole, m. p. 130–131°; 4(5)-phenylimidazole nitrate, m. p. 167–167.5° (dec.). These physical constants agree well with those previously recorded for these compounds.[8,13]

Summary

1. It has been shown that the reaction of S-benzylisothiourea with phenacyl bromide can form any one of four products, 2-amino-4-phenylthiazole, benzyl phenacyl sulfide, 2-benzylthio-4-(5)-phenylimidazole and 1-phenacyl-2-benzylthio-4-phenylimidazole, depending upon the conditions of the reaction.

2. The 2-benzylthio-4(5)-phenylimidazole was cleaved to the known 2-thiol-4(5)-phenylimidazole by the action of acetyl iodide.

(13) R. L. Grant and F. L. Pyman, *J. Chem. Soc.*, **119**, 1893 (1921).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Synthesis of Some Substituted 2-Thiouracils

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Considerable interest has developed within the last few years in the treatment of hyperthyroid disturbances by chemical means.[1] Among the most effective substances employed have been 2-thiouracil and some of its derivatives. In the course of a study of the chemotherapeutic properties of several types of nitrogen and sulfur containing compounds, it was decided, therefore, to synthesize several derivatives of 2-thiouracil for examination.

The 6-substituted-2-thiouracils were prepared by the usual method of condensing β-oxo esters with thiourea in the presence of sodium ethoxide.

Three different methods were employed in the preparation of the necessary β-oxo esters. They were the alkylation of ethyl acetoacetate, the Claisen condensation of esters, and the carbethoxylation of ketones with ethyl carbonate.

By alkylating sodio ethyl acetoacetate with γ-diethylaminopropyl chloride and with γ-diethylaminopropyl β-chloroethyl sulfide, the respective β-oxo esters, 1-diethylamino-4-carbethoxyhexanone-5 and 1-(γ-diethylaminopropylmercapto)-3-carbethoxypentanone-4, were prepared, isolated, and some of their important physical constants determined as well as those of some of their precursor compounds.

We were unable to condense successfully these two complex β-oxo esters with thiourea to form 2-thiouracils by the usual procedures. Only polymeric, gummy residues, quite unlike the probable properties of the expected compounds, were obtained. Anderson, *et al.*,[2] report the formation of unidentified by-products in considerable amount in preparing some of the longer chain (butyl, *n*-amyl, *n*-hexyl) 6-substituted-2-thiouracils. The yields in these condensations are not high at best.

The α-,β-, and γ-pyridoylacetates were prepared by the Claisen condensation of the pyridinecarboxylic acid esters and ethyl acetate. Although these β-oxo esters have been reported heretofore,[3,4,5,6] it was found possible to prepare the first two of them in greatly improved yields by a suitable modification of the Claisen condensation procedure using benzene as a diluent. The preparation of the necessary sodium ethoxide *in situ* in benzene suspension also obviates the necessity of preparing fresh, anhydrous, solid sodium ethoxide for the condensation as is usually done. The isolation of pure liquid ethyl picolinoylacetate does not appear to have been done. Pinner[3] isolated it as its sodium salt; Burrus and Powell[4] obtained it as

(1) Roblin, *Chem. Rev.*, **38**, 255 (1946).

(2) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

(3) Pinner, *Ber.*, **34**, 4237 (1901).

(4) Burrus and Powell, THIS JOURNAL, **67**, 1468 (1945).

(5) Bloom, Breslow and Hauser, *ibid.*, **67**, 2207 (1945).

(6) Miller, Dessert and Anderson, *ibid.*, **70**, 500 (1948).