and may be separated from each other as well as from the nucleotides during the procedure. The three isomers of adenylic and of inosinic acids may be separated.

The applications of this technique to analysis, isolation, investigation and manufacture are indicated.

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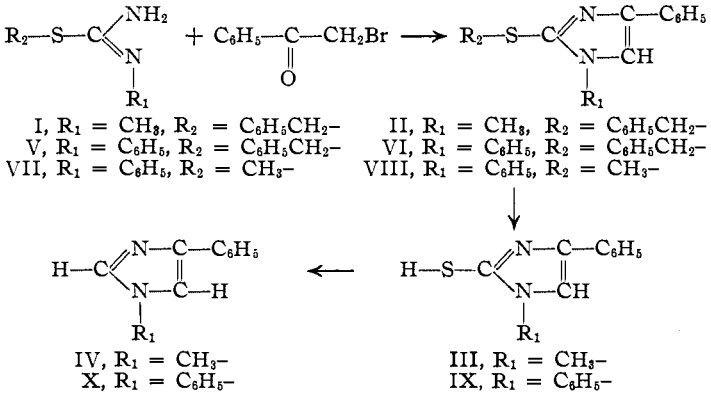
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

The Preparation of 2-Alkylthioimidazoles

BY R. M. DODSON AND FRANK ROSS[1]

It has recently been shown that 2-benzylthio-4(5)-phenylimidazole could be prepared by the reaction of S-benzylisothiourea with phenacyl bromide.[2] This reaction has now been extended to the preparation of 1-substituted-2-alkylthio-4-phenylimidazoles by the condensation of N-substituted-S-alkylisothioureas with phenacyl bromide. Thus, 1-methyl-2-benzylthio-4-phenylimidazole (II) was prepared in low yield from N-methyl-S-benzylisothiourea (I). Although two isomeric compounds, 1-methyl-2-benzylthio-4-phenylimidazole (II) and 1-methyl-2-benzylthio-5-phenylimidazole, could be expected from the reaction, only compound II was found. The structure of compound II was established by its cleavage to 1-methyl-2-thiol-4-phenylimidazole (III) with phosphorus and iodine in glacial acetic acid, followed by oxidation of III to the known 1-methyl-4-phenylimidazole (IV).[3]



1-Methyl-2-benzylthio-4-phenylimidazole (II) was independently synthesized by the direct methylation of 2-benzylthio-4(5)-phenylimidazole[2] with methyl sulfate and alkali. The odor of mercaptan indicated that some cleavage of the sulfide was taking place. Orientation in the methylation of 2-benzylthio-4(5)-phenylimidazole was similar to that in the methylation of 4(5)-phenylimidazole. Pyman and co-workers[3] found that 4(5)-phenylimidazole, on treatment with methyl sulfate yields 1-methyl-4-phenylimidazole and 1-methyl-5-phenylimidazole in the ratio of 4.8 to 1. We did not succeed in isolating any 1-methyl-2-benzylthio-5-phenylimidazole from our methylation.

By analogous reactions, N-phenyl-S-benzylisothiourea (V) and N-phenyl-S-methylisothiourea (VII) were condensed with phenacyl bromide to give 1,4-diphenyl-2-benzylthioimidazole (VI) and 1,4-diphenyl-2-methylthioimidazole (VIII), respectively, in yields of 51 and 40%. None of the 1,5-diphenyl-2-alkylthioimidazole was found in either of these preparations. Compounds VI and VIII were cleaved to the same 1,4-diphenyl-2-thiolimidazole (IX) with phosphorus and iodine in glacial acetic acid,[4] and the 2-thiolimidazole (IX) was then oxidized to 1,4-diphenylimidazole (X).

In order to establish the structures of compounds VI and VIII, 1,4-diphenyl-2-thiolimidazole (IX) was independently synthesized from N-phenacylaniline and potassium thiocyanate. This 1,4-diphenyl-2-thiolimidazole was then alkylated with benzyl chloride and with methyl iodide to produce 1,4-diphenyl-2-benzylthioimidazole (VI) and 1,4-diphenyl-2-methylthioimidazole (VIII), respectively.

A comparison of the above reactions of S-alkylisothioureas with the alkylation of N-substituted benzamidines indicates that the reactions are similar. Pyman[5] has shown that N-phenylbenzamidine monomethylated in good yield on the nitrogen holding the phenyl group. The isomeric product, N-phenyl-N^1-methylbenzamidine was formed in only 0.6% yield. Analogously, N-phenyl-S-benzylisothiourea reacted with phenacyl bromide to form the imidazole VI in good yield; the isomer obtained corresponds to primary alkylation of the nitrogen holding the phenyl group with phenacyl bromide. On the other hand, N-methylbenzamidine monomethylated in poor yield and gave a mixture of the two expected isomers.[5] Similarly, S-benzyl-N-methylisothiourea reacted poorly with phenacyl bromide

(1) Abstracted from a thesis by Frank Ross presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the M.S. degree, June, 1949.

(2) R. M. Dodson, THIS JOURNAL, **70**, 2753 (1948).

(3) Hazeldine, Pyman and Winchester, *J. Chem. Soc.*, **125**, 1431 (1924).

(4) The cleavage of sulfides with phosphorus and iodine in glacial acetic acid may prove to be a general reaction. This possibility is being investigated.

(5) F. L. Pyman, *J. Chem. Soc.*, **123**, 3359 (1923).

to form an imidazole. However, only one isomer II was isolated. It is possible that N-alkyl-N¹-phenacylamidines will not cyclize under these conditions to form imidazoles.

Experimental[6]

1,4-Diphenyl-2-benzylthioimidazole (VI).—A solution of phenacyl bromide in 75 ml. of carbon tetrachloride, prepared by the bromination of 12.0 g. (0.1 mole) of acetophenone, was added to a solution of 24.2 g. (0.1 mole) of N-phenyl-S-benzylisothiourea (V)[7] in 50 ml. of 95% ethanol and 5 ml. of water. Twenty grams of solid sodium bicarbonate was then added, and the resulting suspension was heated under reflux for three hours. The suspension was filtered; the solvent was removed from the filtrate by evaporation; and the residue was extracted with 50 ml. of warm water and 50 ml. of benzene. When the benzene solution was extracted with 50 ml. of dilute (1:5) hydrochloric acid, a light yellow solid, insoluble in water and benzene, separated. This solid was dissolved in ethanol and the solution was neutralized with excess dilute ammonium hydroxide. The product, which separated as a light cream-colored oil, was extracted with ether, and the ether was removed on the steam-bath. Crystallization of the residue from dilute ethanol yielded 17.4 g. (51%) of 1,4-diphenyl-2-benzylthioimidazole, m. p. 65–68°. Further crystallization of the compound from ethanol raised the melting point to 70–71°.

Anal. Calcd. for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.01; H, 5.52; N, 8.01.

1-Methyl-2-benzylthio-4-phenylimidazole (II).—A solution of N-methyl-S-benzylisothiourea hydrochloride, prepared by heating 35.0 g. (0.4 mole) of methylthiourea and 50.64 g. (0.4 mole) of benzyl chloride in 40 ml. of absolute ethanol for one hour, was treated with 79.60 g. (0.4 mole) of phenacyl bromide, 200 ml. of absolute ethanol and 100 g. of solid sodium bicarbonate. The condensation was effected, and the product was isolated as described above. The color was removed from the product by treatment of its benzene solution with activated alumina. The residue from the evaporation of the benzene solution, on crystallization from dilute ethanol, yielded 14.55 g. (10%) of 1-methyl-2-benzylthio-4-phenylimidazole, m. p. 83–85°. Vacuum distillation of this product and repeated crystallizations from dilute ethanol failed to raise the melting point.

Anal. Calcd. for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.47; H, 5.68; N, 9.87.

Attempts to isolate the isomeric 1-methyl-2-benzylthio-5-phenylimidazole from the crude basic products of this reaction, both by crystallization of the hydrochlorides and the picrates, were unsuccessful.

1,4-Diphenyl-2-methylthioimidazole (VIII).—This compound was prepared by the condensation of N-phenyl-S-methylisothiourea hydroiodide[8] with phenacyl bromide in the presence of sodium bicarbonate as described above. Crystallization of the basic product from dilute ethanol gave a 40% yield of 1,4-diphenyl-2-methylthioimidazole, m. p. 63–66°. One additional crystallization from dilute ethanol raised the melting point to 65–66°.

Anal. Calcd. for $C_{16}H_{14}N_2S$: C, 72.18; H, 5.26; N, 10.52. Found: C, 72.35; H, 5.34; N, 10.58.

1-Methyl-2-thiol-4-phenylimidazole (III).—1-Methyl-2-benzylthio-4-phenylimidazole (3.9 g.) was cleaved by the use of red phosphorus, iodine and glacial acetic acid as previously described.[2] The yield of crude, alkali-soluble material was 2.43 g. (91%). By crystallization from dilute ethanol, pure 1-methyl-2-thiol-4-phenylimidazole, m. p. 220–221°, was obtained.

Anal. Calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.29; N, 14.72. Found: C, 63.40; H, 5.49; N, 14.04, 14.77.

1,4-Diphenyl-2-thiolimidazole (IX).—Both 2-methylthio-1,4-diphenylimidazole (VIII) and 2-benzylthio-1,4-diphenylimidazole (VI) were cleaved to the same thiol in yields of 76 and 60%, respectively, by the use of red phosphorus, iodine and glacial acetic acid.[2] Crystallization of the thiol from dilute ethanol yielded a pure product, m. p. 216–217°. A mixture of the thiols from compounds VI and VIII showed no melting-point depression.

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.57; H, 4.64; N, 10.58, 11.41.

1-Methyl-4-phenylimidazole (IV).—A solution of 1.0 g. of 1-methyl-2-thiol-4-phenylimidazole (III) in 50 ml. of glacial acetic acid was treated with 10 ml. of concentrated nitric acid in 90 ml. of hot water. The resulting solution was heated under reflux for thirty minutes, cooled, neutralized with concentrated ammonium hydroxide and saturated with sodium chloride. The suspension was extracted with two 50-ml. portions of benzene. The benzene solution was dried and filtered, and the product was precipitated with gaseous hydrogen chloride. The yellow liquid which separated crystallized on cooling to give 0.60 g. of the hydrochloride. A solution of 0.45 g. of this hydrochloride in 10 ml. of warm water was neutralized with ammonium hydroxide, the solution was saturated with ammonium chloride and cooled. By filtration, 0.30 g. of 1-methyl-4-phenylimidazole, m. p. 105–110°, was obtained. Crystallization of the compound from petroleum ether, b. p. 60–68°, raised the melting point to 109–111°. The picrate, m. p. 243–245°, was prepared in boiling ethanol and recrystallized from very dilute ethanol. 1-Methyl-4-phenylimidazole and its picrate are reported to melt at 110–111° and 245°, respectively. 1-Methyl-5-phenylimidazole and its picrate are reported to melt at 96–97° and 139°, respectively.[3]

1,4-Diphenylimidazole.—A solution of 1.0 g. of 1,4-diphenyl-2-thiolimidazole in 50 ml. of glacial acetic acid was cooled in an ice-bath and a solution of 0.1 g. of sodium nitrite[9] in 4 ml. of dilute (1:3) nitric acid was added with stirring at such a rate that the temperature did not rise above 35°. The solution was stirred for fifteen minutes after the addition was complete, then neutralized with concentrated ammonium hydroxide. The resulting precipitate (0.80 g., m. p. 90–94°) was purified by precipitation from ether with gaseous hydrogen chloride, by crystallization of the hydrochloride from methanol and ether, and finally by crystallization of the free base from dilute methanol. The analytical sample melted at 96–98°.

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.78; H, 5.49; N, 12.72. Found: C, 82.09; H, 5.57; N, 12.59.

1-Methyl-2-benzylthio-4-phenylimidazole (II) from 2-Benzylthio-4(5)-phenylimidazole.—A solution of 2.66 g. (0.01 mole) of 2-benzylthio-4(5)-phenylimidazole, 1.52 g. (0.012 mole) of methyl sulfate and 1.0 g. of potassium hydroxide in 50 ml. of methanol was heated under reflux for two hours. The solution was diluted with 200 ml. of water, cooled and the resulting precipitate was separated by filtration and dried. Extraction of the precipitate with 30 ml. of cold benzene left a residue of 1.0 g. of 2-benzylthio-4(5)-phenylimidazole (m. p. 175–177°). Evaporation of the benzene solution gave 1.56 g. of crude product. This was combined with 1.40 g. of the benzene-soluble material from a second identical reaction. Crystallization of this material from dilute alcohol yielded 1.74 g. of 1-methyl-2-benzylthio-4-phenylimidazole, m. p. 79–83°. Further crystallization from dilute ethanol raised the melting point to 83–85°. A mixture with the 1-methyl-2-benzylthio-4-phenylimidazole prepared from N-methyl-S-benzylisothiourea showed no depression of melting point. An attempt to isolate the isomeric 1-methyl-2-benzylthio-5-phenylimidazole from the mother liquors by crystallization of the picrates was not successful.

1,4-Diphenyl-2-thiolimidazole (IX) from N-Phenacylaniline.—A solution of 40 g. (0.19 moles) of N-phenacyl-

(6) Microanalyses by Messrs. Jay Buckley, Ralph Kelly and William Cummings. All melting points, except those of the thiols, were taken on a Fisher–Johns melting point apparatus. The melting points of the thiols were taken in sealed tubes.

(7) E. A. Werner, *J. Chem. Soc.*, **57**, 283 (1890).

(8) A. Bertram, *Ber.*, **25**, 49 (1892).

(9) R. G. Jones, THIS JOURNAL, **71**, 644 (1949).

aniline[10] in 1250 ml. of 95% ethanol was treated with 18.51 g. (0.19 mole) of concentrated hydrochloric acid and 18.25 g. of potassium thiocyanate in 50 ml. of water. The resulting solution was heated under reflux for two hours, cooled, then poured into two liters of water containing 20 ml. of concentrated ammonium hydroxide. Separation of the product by filtration yielded 45.5 g. of crude 1,4-diphenyl-2-thiolimidazole. Crystallization of the product from ethanol gave 31.0 g. (65%) of the desired thiol, m. p. 214–216°. A mixture with the thiol obtained from the cleavage of 1,4-diphenyl-2-benzylthioimidazole (VI) melted at 215–217°.

1,4-Diphenyl-2-methylthioimidazole (VIII) from 1,4-Diphenyl-2-thiolimidazole (IX).—A solution of 5.04 g. (0.02 mole) of 1,4-diphenyl-2-thiolimidazole, prepared from N-phenacylaniline, 2.84 g. (0.02 mole) of methyl iodide and 0.80 g. of sodium hydroxide in 160 ml. of 90% ethanol was heated under reflux for one hour. The yellow oil remaining after the removal of the solvent was extracted with 25 ml. of water and 25 ml. of benzene. On extraction of the benzene solution with dilute (1:5) hydrochloric acid, a green oil, insoluble in benzene and hydrochloric acid, separated. This was dissolved in the minimum amount of ethanol and the solution was poured into 100 ml. of water containing 10 ml. of concentrated ammonium hydroxide. The oil which separated solidified when stirred. In this way 3.23 g. (61%) of 1,4-diphenyl-2-methylthioimidazole, m. p. 63–66.5°, was obtained. Crystallization from dilute ethanol raised the melting point to 64–66°. This material was identical with that obtained by the condensation of phenacyl bromide with N-phenyl-S-methylisothiourea.

1,4-Diphenyl-2-benzylthioimidazole (VI) from 1,4-Diphenyl-2-thiolimidazole (IX).—1,4-Diphenyl-2-thiolimidazole (5.04 g.), prepared from N-phenacylaniline, was alkylated with benzyl chloride and the product isolated as described in the preceding experiment. Crystallization of the product from dilute alcohol yielded 2.75 g. (40%) of the desired 1,4-diphenyl-2-benzylthioimidazole, m. p. 69–70°. A mixed melting point determination proved that this compound was identical with the product from the condensation of N-phenyl-S-benzylisothiourea with phenacyl bromide.

(10) A. Bischler, *Ber.*, **25**, 2860 (1892).

Summary

1. The condensation of N-substituted-S-alkylisothioureas with phenacyl bromide produced 1-substituted-2-alkylthio-4-phenylimidazoles. No 1-substituted-2-alkylthio-5-phenylimidazoles were isolated from these reactions.

2. The structures of the imidazoles were established either by degradation to a known imidazole or by independent synthesis.

3. Red phosphorus and iodine in glacial acetic acid cleaved the 2-alkylthioimidazoles to 2-thiolimidazoles. Both benzyl and methyl groups were removed in this way.

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[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

The Reaction of Styrene Oxide with Methanol

BY WILKINS REEVE AND IVAN CHRISTOFFEL

The reactions of styrene oxide with various nucleophilic reagents have recently been studied by a number of investigators, but there appears to be no agreement as to whether a nucleophilic reagent can be expected to attack the α carbon or the terminal β carbon. The α position is reported to be the more reactive toward pyridine hydrochloride,[1] sodium phenoxide[2] and allyl alcohol in the presence of sodium alloxide.[3] An ether solution of magnesium iodide, and also hydrogen iodide dissolved in petroleum ether, add to styrene oxide with the iodine going to the α-position.[4,5] On the other hand, the β-position is reported to be the more reactive toward lithium aluminum hydride,[6] sodium malonic ester,[7] sodium methyl mercaptide,[8] most Grignard reagents[4,9] and various amines.[10] The acid catalyzed reaction of styrene oxide with alcohols is reported to give the secondary alcohol–primary ether isomer in the case of ethanol and butanol-1,[10] and to give a mixture of both isomers consisting predominantly of the secondary alcohol in the case of allyl alcohol.[3]

The reaction of styrene oxide with aliphatic alcohols was first studied by Emerson[10]; however, it was previously observed by Späth[11] that an alcoholic solution of sodium ethoxide reacted with 1-phenyl-2-chloroethanol to produce styrene oxide and a monoethyl ether of styrene glycol. The latter could have resulted from the reaction of the excess alcohol with the styrene oxide. This observation rendered invalid the structural proof advanced by Tiffeneau[12] and later by Emerson[10] in support of the alcohol ethers they synthesized from 1-phenyl-2-haloethanol. Kaelin[13] demonstrated the presence of 1-phenyl-2-methoxyethanol in the material obtained by the sodium methoxide catalyzed reaction of styrene oxide and methanol. He believed this material contained both isomers.

The object of this work was to reinvestigate the reaction of styrene oxide with a typical aliphatic alcohol such as methanol, and to determine the ratio of the isomers produced in the base and acid catalyzed reactions. The experimental approach

(1) King, Berst and Hayes, THIS JOURNAL, **71**, 3498 (1949).
(2) Guss, *ibid.*, **71**, 3460 (1949).
(3) Swern, Billen and Knight, *ibid.*, **71**, 1152 (1949).
(4) Golumbic and Cottle, *ibid.*, **61**, 996 (1939).
(5) Tiffeneau, *Ann. chim. phys.*, [8] **10**, 348 (1907).
(6) Trevoy and Brown, THIS JOURNAL, **71**, 1675 (1949).
(7) Russell and VanderWerf, *ibid.*, **69**, 11 (1947).
(8) Gilman and Fullhart, *ibid.*, **71**, 1478 (1949).
(9) Kharasch and Clapp, *J. Org. Chem.*, **3**, 355 (1938). These investigators found the site of reaction of phenylmagnesium bromide to depend on the order of addition of the reagents.
(10) Emerson, THIS JOURNAL, **67**, 516 (1945).
(11) Späth, *Monatsh.*, **36**, 7 (1915).
(12) Tiffeneau, *Compt. rend.*, **145**, 811 (1907).
(13) Kaelin, *Helv. Chim. Acta*, **30**, 2132 (1947).