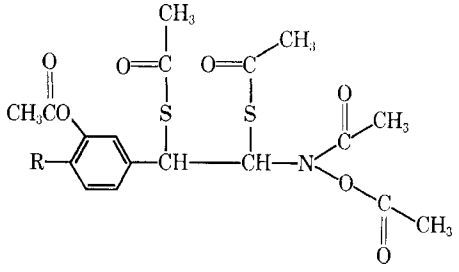
Potential Radiation Protective Agents V. Synthetic Approaches to 2-Aryl-2-mercaptoethylamines

By BENG-THONG HO and WALTER C. McCARTHY

β-Acetthiohydrocinnamoyl azide, through the Curtius degradation, gave 2-mercapto-2-phenylethylamine hydrochloride in low yield. Following the nitro-thiolacetate route to 2-aryl-2-mercaptoethylamines, two acetoxy-substituted β-nitrostyrenes were found to undergo an anomalous reaction with thiolacetic acid involving reduction of the nitro group, formation of elemental sulfur, and the isolation of products containing four more acetyl groups than the starting material.

THE CURTIUS degradation (1) route to 2-aryl-2-mercaptoethylamines was investigated. Cinnamic acid was converted through β-acetthiohydrocinnamic acid to the corresponding azide, which was rearranged and hydrolyzed to 2-mercapto-2-phenylethylamine hydrochloride. In view of the low yield, no attempt was made to extend this route to substituted members of the series.

The nitro-thiolacetate route (2, 3) to 2-aryl-2-mercaptoethylamines was studied to delineate further limitations of this synthetic sequence. Although several alkoxy-substituted β-nitrostyrenes had been shown to add thiolacetic acid to give the expected 1-aryl-1-acetthio-2-nitroethanes in good yield (3), two acetoxy-substituted β-nitrostyrenes were found to undergo a much more complex reaction under these conditions. The nitro group was reduced, elemental sulfur was formed, and the isolated products contained four more acetyl groups than the starting acetoxy-β-nitrostyrenes, as in structures I*a* and I*b*.



I

a, R = CH_3-CO_2-
b, R = H—

EXPERIMENTAL

β-Acetthiohydrocinnamoyl Chloride—β-Acetthiohydrocinnamic acid (4) was converted to its acid chloride by heating with thionyl chloride, followed by removal of the excess reagent under reduced pressure, and recrystallization from ligroin, in 99% yield, m.p. 81–82.8°.

2-Mercapto-2-phenylethylamine Hydrochloride—Activated sodium azide (5) (1.43 Gm., 0.022 mole) was added to a solution of 4.85 Gm. (0.02 mole) of β-acetthiohydrocinnamoyl chloride in 20 ml. of dry benzene, and the mixture was refluxed under nitrogen for 21 hr. After cooling, the solid matter was filtered, and the clear benzene filtrate was hydrolyzed by refluxing under nitrogen with 25 ml. of concentrated hydrochloric acid for 6 hr. Evaporation of the aqueous layer to dryness, followed by three recrystallizations from isopropyl alcohol gave 0.25 Gm. (7%) of 2-mercapto-2-phenylethylamine hydrochloride, m.p. 161–162.5°. The infrared spectrum was identical with that from the compound prepared *via* lithium aluminum hydride reduction of 1-phenyl-1-acetthio-2-nitroethane (2).

Upon cooling the separated benzene phase from the hydrolysis, a white solid crystallized, and subsequent recrystallization from a mixture of benzene and petroleum ether gave 0.56 Gm. of white crystals, m.p. 111.5–112.5°. The infrared spectrum of this product showed absorption peaks at 2565 cm.$^{-1}$ and 699 cm.$^{-1}$ characteristic of the mercapto group and at 1710 cm.$^{-1}$ characteristic of the carbonyl stretching vibration of the carboxyl group. The melting point is in agreement with that previously reported for β-mercaptohydrocinnamic acid (4, 6).

Evaporation of the benzene filtrate left 1.91 Gm. of gummy residue not further investigated.

N,O-Diacetyl-N-[β-(3,4-diacetoxyphenyl-)α,β-bis(acetthio)ethyl]hydroxylamine (Ia)—3,4-Diacetoxy-β-nitrostyrene (0.265 Gm., 0.001 mole) (7) was dissolved in 0.6 ml. (0.64 Gm., 0.008 mole) of thiolacetic acid by warming. After cooling, 5 drops of tri-*n*-butylamine was added. An exothermic reaction took place, and the mixture was allowed to stand overnight at room temperature. Filtration gave 0.295 Gm. of white solid, m.p. 166–167.5°, with a trace of yellow sulfur. (Addition of 10 ml. of 95% ethanol to the filtrate precipitated 26 mg. of yellow sulfur, m.p. 113–114.5°.) Successive recrystallization of the white solid from xylene, dioxane, and 95% ethanol raised the m.p. to 172–172.5°.

Anal.—Calcd. for $C_8H_5NO_3S_2Ac_6$: C, 49.48; H, 4.77; N, 2.88; O, 29.66; S, 13.21; acetyl, 53.2. Found: C, 49.40; H, 4.91; N, 3.01; O, 29.49; S, 13.07; acetyl, 54.0.

The infrared spectrum showed a carbonyl absorption peak at 1750 cm.$^{-1}$ and a thiolacetate peak at 1680 cm.$^{-1}$; the absorption peak of the nitro group at 1545 cm.$^{-1}$ was absent.

The NMR spectrum, in deuterochloroform at 60 Mc. with tetramethylsilane as internal reference, showed a 3-proton aromatic singlet at τ 2.84, two methine doublets centered at τ 3.67 and 4.86, J = 9.5 c.p.s., and six methyl singlets at τ 7.70, 7.74, 7.75, 7.79, 7.86, and 7.94.

3-Acetoxy-β-nitrostyrene—To a stirred solution of 10 Gm. (0.0608 mole) of *m*-acetoxybenzaldehyde, 8.2 ml. (0.152 mole) of nitromethane, and 60 ml. of 95% ethyl alcohol cooled to 5°, there was added 26 ml. of 10% (0.0604 mole) aqueous sodium hydroxide. The reaction time was limited to 30 sec. (8), after which the reaction was arrested by the addition of 200 ml. of 2% (0.067 mole) of aqueous acetic acid.

Received October 12, 1966, from the College of Pharmacy, University of Washington, Seattle, WA 98105
Accepted for publication February 28, 1967.
Part of this work was done under contract DA-49-193-MD-2048 with the U. S. Army Medical Research and Development Command, Office of the Surgeon General, Washington, D. C.

A yellow oil (10.7 Gm.) separated. (Increasing the reaction time to 1 min. gave only half this yield of yellow oil.) The infrared spectrum of this material was consistent with that expected for the nitro-alcohol condensation product, but this material was sufficiently labile that it was not convenient to purify a sample for analysis. This oil was dehydrated by mixing with 10.7 Gm. of powdered fused sodium acetate and 53.4 Gm. (0.523 mole) of acetic anhydride and boiling under reflux for 10 min. After cooling, the mixture was poured into 120 ml. of water. A yellowish brown solid was obtained, 8.25 Gm., m.p. 76–79°. Recrystallization from 95% ethanol gave 6.35 Gm. (51%) of yellow crystals, m.p. 83.5–84.5°.

Anal.—Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76; O, 30.89. Found: C, 58.12; H, 4.50; N, 6.82; O, 30.93.

N,O-Diacetyl-N-[β-(3-acetoxyphenyl-)α,β-bis(acetthio)ethyl]hydroxylamine (Ib)—3-Acetoxy-β-nitrostyrene (0.193 Gm.) was dissolved in 0.5 ml. of thiolacetic acid. Addition of 5 drops of tri-*n*-butylamine caused an exothermic reaction. The resulting solution was allowed to stand at room temperature for 20 hr. Upon addition of 1 ml. of 95% ethanol followed by cooling and scratching, there was precipitated 75 mg. of white solid, m.p. 110–111°. Recrystallization from ethanol did not raise the m.p.

Anal.—Calcd. for $C_8H_6NO_2S_2Ac_5$: C, 50.57; H, 4.95; N, 3.28; S, 15.00; acetyl, 50.3. Found: C, 49.76; H, 5.03; N, 3.39; S, 14.89; acetyl, 49.9.

REFERENCES

(1) Smith, P. A. S., *Organic Reactions*, **3**, 337(1946).
(2) McCarthy, W. C., and Ho, B.-T., *J. Org. Chem.*, **26**, 4110(1961).
(3) Bhat, K. V., and McCarthy, W. C., *J. Pharm. Sci.*, **53**, 1545(1964).
(4) Holmberg, B., and Schjamberg, E., *Arkiv Kemi*, **14A**, No. 7, 22(1940).
(5) Newman, M. S., *J. Am. Chem. Soc.*, **57**, 732(1935).
(6) Fischer, E., and Brieger, W., *Ber.*, **47**, 2469(1914).
(7) Kanao, S., *J. Pharm. Soc. Japan*, **49**, 238(1929).
(8) Heacock, R. A., Hutzinger, O., and Nerenberg, C., *Can. J. Chem.*, **39**, 1143(1961).

Oxidative Effect of Perbenzoic Acid on *N*-Methylated Pyrrole, Indole, and Carbazole

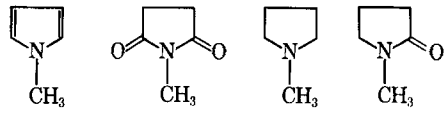
By I. NABIH and E. HELMY*

Perbenzoic has been shown to oxidize *N*-methylpyrrole to *N*-methylsuccinimide, *N*-methylpyrroline to *N*-methylpyrrolidone, and 2,3-dihydro-*N*-methylindole to *o*-dimethylaminobenzaldehyde. Under similar conditions *N*-methylcarbazole and 1,4-dihydro-*N*-methylcarbazole are not oxidized.

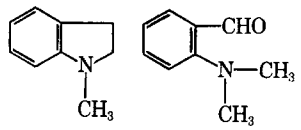
EXTENSIVE STUDIES have been carried out on the oxidation of pyrrole, indole, and carbazole using a variety of oxidizing agents (1–5).

In this work, the oxidative effect of perbenzoic acid on the *N*-methylated forms of pyrrole, indole, and carbazole is studied. Generally, peracids have been mostly used for the selective oxidation of the carbon-carbon double bond. As an electrophilic reaction, the rate is enhanced through the presence of an electron-donating group in the substrate (6). In systems where double bond is conjugated with other multiple bonds, this rate decreases since the delocalization of the π electrons reduces the electron density at all the double bonds.

Usually, the oxidation with peracids leads to the epoxide; however, the products may undergo subsequent rearrangements, as in the case of chloroolefins, where the over-all products are the chloroketones (7). Also, epoxidation of aliphatic enol-acetate leads after intermolecular rearrangements to α-acetoxy-ketones (8). By this route, the olefins *via* the epoxidation products can be converted after undergoing rearrangement to carbonyl compounds (9). In the present work, when *N*-methylpyrrole (I) was subjected to the oxidizing effect of perbenzoic acid in chloroform solution, the analytical measurements showed that two atoms of oxygen had been involved in the reaction. Preparative experiments showed that the reaction product was *N*-methyl succinimide (II) in 92% yield. It appears in this reaction that the initially formed epoxides at both double bonds, favored through the presence of the electron rich *N*-methyl group, undergo internal rearrangement to give the imide.



I II III IV



V VI

When *N*-methyl-3-pyrroline (III) was similarly treated, the product was *N*-methyl-α-pyrrolidone (IV) in 79% yield. The analytical data showed that only one oxygen atom had been consumed.

Under the same condition, 2,3-dihydro-*N*-methylindole (V) is oxidized with the fission of the pyrrole nucleus and *o*-dimethylaminobenzaldehyde (VI) is obtained in 81% yield. The analytical measurement indicated the consumption of one oxygen atom during the reaction.

N-Methylcarbazole and 1,4-dihydro-*N*-methyl carbazole could not be oxidized with the same oxidizing agent.

Received October 31, 1966, from the National Research Centre, Cairo, Egypt.
Accepted for publication January 20, 1967.