To 470 g. (5.0 moles) of phenol heated with stirring on the steam-bath was added 15.3 g. (0.10 mole) of 4(5)-chloromethylimidazole hydrochloride in five equal portions over a period of five hours. The solution was then heated on the steam-bath for sixty-five hours with stirring, cooled and extracted four times by vigorously stirring for two hours with 100 ml. of 2 *N* hydrochloric acid and separating. The combined extracts were treated with three 150-ml. portions of benzene and the water removed under reduced pressure giving 6.3 g. of an oil which was then dissolved in 60 ml. of absolute ethyl alcohol. To this was added 6.8 g. of picric acid dissolved in 110 ml. of absolute ethyl alcohol. The solution was evaporated to about one-sixth of its original volume, cooled and filtered giving 4.2 g. of material; m. p. 150–160°.

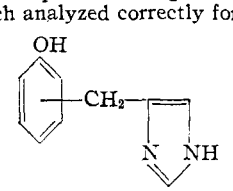
The filtrate was concentrated to one-half its volume, cooled and filtered; 0.6 g., m. p. 110–116°. Further evaporation of the filtrate gave an orange oil which could be crystallized from water; 2.6 g., m. p. 147–150°.

The entire process was repeated three times; that is, the extraction of the original reaction mixture with several portions of 2 *N* hydrochloric acid, the removal of the water, the conversion of the resulting oil to the picrate with an equivalent amount of picric acid (based on the composition of the product as $C_{10}H_{10}ON_2$), and, finally, the fractional crystallization of the picrates.

All fractions which melted below 120° were combined and recrystallized from water. This gave 2.7 g. of material, m. p. 119–121°, which was identified as picric acid by mixed melting point.

All fractions melting above 155° were combined and recrystallized from water giving 5.5 g. (17%) of material; m. p. 189–191° with earlier softening. Several recrystallizations raised the melting point to 203–204°. This product was identified as 4(5)-hydroxymethylimidazole picrate (by melting point and analysis).

The fractions melting between 140 and 155° were recrystallized from water giving 6.1 g. (15%) of material; m. p. 149–151°. Further purification gave a product (m. p. 152–152.5°) which analyzed correctly for $C_{10}H_{13}O_2N_5$ or



Anal. Calcd. for $C_{10}H_{13}O_8N_5$: C, 47.66; H, 3.22. Found: C, 47.80; H, 3.25.

Identification of the latter product as *p*-4(5)-imidazolylmethylphenol picrate was accomplished as follows.

Six-tenths of a gram (0.0015 mole) of the imidazolylmethylphenol picrate was mixed with 10 ml. of water, 3 ml. of 2 *N* hydrochloric acid and extracted with 20 ml. of benzene at 60°. The aqueous layer was separated, extracted five times with 20-ml. portions of warm benzene and treated with charcoal. Removal of the water under reduced pressure gave an oil which was treated with 0.3 g. of potassium hydroxide in 5 ml. of water and placed in an ice-bath. Methylation in the usual fashion gave an oily solid (0.26 g.) (0.0013 mole) which was then dissolved in 10 ml. of water and added to a solution of 0.95 g. (0.006 mole) of potassium permanganate in 50 ml. of water. The solution was heated on the steam-bath for one hour and filtered from manganese salts giving a colorless filtrate which was concentrated to 5 ml. and acidified with 6 *N* hydrochloric acid. The resulting precipitate was recrystallized from water three times giving 0.10 g. (44%) of the product (m. p. 182–183°, cor.) which gave no depression with a known sample of *p*-methoxybenzoic acid, m. p. 183.5–184.5° (cor.) (lit., m. p. 184° cor.).

Pharmacological testing[20] has indicated that for the most part the compounds prepared thus far are relatively inactive as antihistaminic agents.

Acknowledgment is made to Dr. S. B. Binkley and Dr. L. C. Cheney of the Bristol Laboratories, Syracuse, N. Y., for their interest and encouragement.

Summary

A series of alkyl and aryl ethers of 4(5)-hydroxymethylimidazole have been prepared starting with 4(5)-chloromethylimidazole hydrochloride.

An explanation for the failure of the Williamson reaction in the aliphatic series has been offered.

N-Alkylation rather than O-alkylation occurs when 4(5)-hydroxymethylimidazole is treated with methyl iodide in the Williamson reaction.

p-4(5)-Imidazolylmethylphenol is formed when 4(5)-chloromethylimidazole hydrochloride is treated with an excess of phenol.

The ethers prepared in this study have been tested for pharmacological activity.

(20) We are indebted to Dr. H. L. Dickison of the Bristol Laboratories, Syracuse, N. Y., for this report.

SYRACUSE 10, N. Y. RECEIVED APRIL 3, 1950

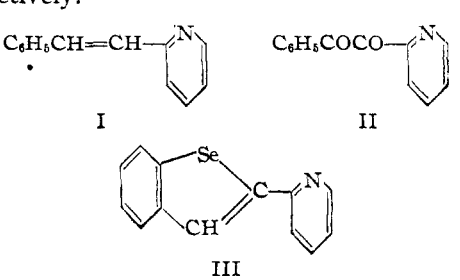
[CONTRIBUTION NO. 79 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Reaction of α- and γ-Stilbazoles with Selenium Dioxide

BY C. A. BUEHLER, JAMES O. HARRIS AND WILLIAM F. ARENDALE

The action of selenium dioxide on alkenes leads, usually, to the formation of oxygenated substances without cleavage of the carbon chain.[1] To cite an example, stilbene gives benzil in 86% yield.[2,3]

In attempting to utilize such an oxidation for the preparation of phenyl α-pyridyl diketone (II) from α stilbazole (I) it was found that the diketone was produced together with 2-α-pyridyl selenonaphthene (III) in yields of 31 and 20%, respectively.

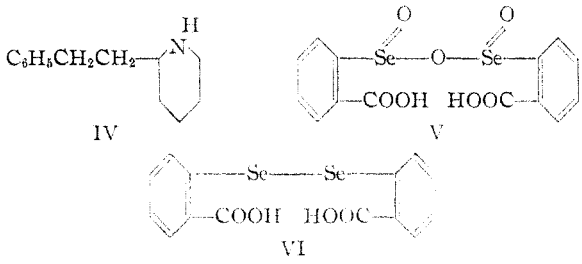


(1) Rabjohn, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 353.

(2) Astin, Moulds and Riley, *J. Chem. Soc.*, 903 (1935).

(3) Rostowsky and Lugorokin, *Ber.*, **68**, 854 (1935).

Structure III has been assigned to this product on the basis of its analysis and a study of its reactions. Similar to selenonaphthene[4] it forms a monobromo derivative, probably the 3-bromo-. When it is reduced with sodium and amyl alcohol, the selenium-containing ring is broken to give selenium and 2-β-phenylethylpiperidine (IV). When it is oxidized with hydrogen peroxide, it is converted into *o*-seleninbenzoic acid (V) which on reduction with sodium metabisulfite yields 2,2′-dicarboxydiphenyldiselenide (VI). These reactions demonstrate that the compound contains the same carbon skeleton as the starting material, and that the cyclic selenium atom is attached to the benzene nucleus at the *o*-position.



IV V

VI

The oxidation of γ-stilbazole with selenium dioxide produced 2-γ-pyridyl selenonaphthene, but none of the expected diketone. The structure of this selenonaphthene was proved by the reactions given above. Although it was not possible to form a bromo derivative from it, reduction as before yields selenium and 4-β-phenylethylpiperidine and the oxidation treatment followed by reduction gives likewise 2,2′-dicarboxydiphenyl diselenide (VI).

Acknowledgment.—The authors are indebted to the Chemical Corps, U. S. Army, for a grant in support of a portion of this work.

Experimental[5]

Products from α-Stilbazole

α-Stilbazole (I).—This alkene was prepared essentially by the method of Chiang and Hartung,[6] yield 75%, m. p. 90–91° (Wagstaff[7] gives 90–91°).

Phenyl-α-pyridylethane-1,2-dione (II).—α-Stilbazole, 100 g., was heated to 200–210° and held at this temperature while 100 g. of Canadian Copper Refiners C. P. selenium dioxide was added in small portions. After the addition, the mixture was held at the same temperature until water ceased to distil off. Upon cooling, the mixture was diluted with 200 cc. of methanol and filtered to remove selenium. Dilution of the alcoholic filtrate with water and neutralization with sodium bicarbonate was followed by extraction with ether. The ethereal solution was treated with Norit A and filtered, and the ether was removed by heating. Distillation of the residue through a short column at 1–2 mm. pressure gave 36 g. of crude diketone (31%), b. p. 168–173°. Several crystallizations from ethanol–ligroin and one from methanol–water gave a m. p. of 72.0–72.5° (Ladenburg and Kroener[8] give 78–79°).

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.64. Found: C, 74.37, 74.28; H, 4.48, 4.49; N, 6.63.

The *p*-nitrophenylhydrazone crystallized from absolute ethanol in bright yellow crystals, m. p. 178°.

Anal. Calcd. for $C_{19}H_{14}O_3N_4$: N, 16.18. Found: N, 16.26, 16.37.

2-α-Pyridylselenonaphthene (III).—The most satisfactory recovery of the selenonaphthene was obtained by modifying the procedure indicated above, immediately after the selenium was removed, as follows: After treatment with Norit A and cooling to about 0°, the filtrate yielded yellow crystals which were removed by filtration. Removal of about one-half of the alcohol gave additional crystals to make a total of from 25 to 30 g. (about 20%), m. p. 137–140°. Crystallization twice from carbon tetrachloride, once from methanol and again from carbon tetrachloride, using Norit A in each case, yielded faintly yellow crystals, m. p. 142°.

Anal. Calcd. for $C_{13}H_9NSe$: C, 60.47; H, 3.51; mol. wt., 258. Found: C, 60.42, 60.65; H, 3.71, 3.52; mol. wt. (Menzies and Wright), 263, 264.

3(?)-Bromo-2-α-pyridylselenonaphthene.—Three grams of the selenonaphthene dissolved in 100 cc. of carbon tetrachloride was treated with a solution of bromine in carbon tetrachloride until the reddish brown color was maintained. The red crystals which separated were filtered off and crystallized from ethanol to give red needles, m. p. 185°. By treatment with boiling 10% aqueous sodium hydroxide followed by crystallization twice from ethanol–water, 2 g. of white needles, m. p. 129°, were obtained.

Anal. Calcd. for $C_{13}H_8NBrSe$: Br, 24.58; mol. wt., 337. Found: Br, 24.37, 24.29; mol. wt. (Menzies and Wright), 347, 344.

2-β-Phenylethylpiperidine Hydrochloride.—The selenonaphthene, 0.5 g., in 75 cc. of amyl alcohol was refluxed while 8 g. of sodium was added in small portions so that the reaction could be controlled. When the sodium had disappeared the solution was poured into an equal volume of water containing a small excess of hydrochloric acid over that required for neutralization. The solution was warmed thirty minutes on the steam-bath and an almost quantitative yield of selenium separated. An equal volume of ether was added to the alcoholic layer and the aqueous layer was extracted with ether both before and after neutralization with sodium hydroxide. The combined ether layers, dried with potassium carbonate and saturated with dry hydrogen chloride, were treated with dry benzene and the ether was distilled from the mixture. On the addition of ligroin followed by cooling, white, hygroscopic crystals which, after drying over phosphorus pentoxide at low pressure, weighed 0.35 g. and melted at 153–153.5° (Baurath[9] gives 155°).

α-Stilbazole reduced under the above conditions gave the hydrochloride, m. p. 154–154.5°. No depression was produced on melting the mixture.

Anal. Calcd. for $C_{13}H_{20}NCl$: Cl, 15.70. Found for sample from selenonaphthene: Cl, 15.27, 15.21; for sample from stilbazole: 14.71, 14.64, 14.57, 14.72.

1-Benzenesulfonyl-2-β-phenylethylpiperidine.—Since the analyses of the hydrochlorides were not satisfactory due to their hygroscopic nature, the benzene sulfonamides were prepared from each sample of amine hydrochloride in the usual manner. Silvery plates melting at 130° in each case were obtained. A mixed melting point gave no depression.

Anal. Calcd. for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04. Found for sample from selenonaphthene: C, 68.91, 69.06; H, 6.75, 6.86; for sample from stilbazole: C, 68.81, 68.94; H, 6.83, 6.94.

Anhydride of *o*-Seleninbenzoic Acid (V).—The selenonaphthene, 1 g., dissolved in 60 cc. of glacial acetic acid was heated on a steam-bath while 90 cc. of 30% hydrogen peroxide was added in small portions over a period of one hour.

(4) Komppa and Nyman, *J. prakt. Chem.*, **139**, 235 (1934).

(5) B. p.'s and m. p.'s are uncorrected; latter were obtained using an aluminum melting point block.

(6) Chiang and Hartung, *J. Org. Chem.*, **10**, 21 (1945).

(7) Wagstaff, *J. Chem. Soc.*, 277 (1934).

(8) Ladenburg and Kroener, *Ber.*, **36**, 124 (1903).

(9) Baurath, *Ber.*, **21**, 822 (1888).

The solution was held at this temperature for an additional fifteen minutes and the acetic acid was removed by distillation with steam. The mixture upon being cooled was extracted with ether to remove unreacted selenonaphthene and a colored impurity. The aqueous layer was evaporated to about 15 cc. and about 15 cc. of concentrated hydrochloric acid was added. Heating at the boiling point was continued until the evolution of chlorine ceased, after which the solution was cooled until precipitation was complete. The solid, 0.1 g. (12%), was filtered and crystallized four times from water to yield pure *o*-seleninbenzoic acid, m. p. 226–227° (Lesser and Weiss[10] give 228–229°). Drying to constant weight under vacuum at room temperature gave the anhydride,[11] m. p. 227.5–228.5°.

Anal. Calcd. for $C_{14}H_{10}O_7Se_2$: C, 37.52; H, 2.25. Found: C, 37.09, 37.26; H, 2.38, 2.53.

Reduction by sodium metabisulfite gives the 2,2′-dicarboxydiphenyl diselenide described below.

2,2′-Dicarboxydiphenyl Diselenide (VI).—The selenonaphthene, 0.9 g., in 60 cc. of glacial acetic acid was heated on a steam-bath and 50 cc. of 30% hydrogen peroxide was added in small portions over a forty-five minute period. After fifteen more minutes of heating, the solution was diluted with about 250 cc. of water and the total was extracted with ether. To the aqueous layer neutralized with sodium hydroxide an excess of sodium metabisulfite was added. Upon acidification with hydrochloric acid, the mixture was digested on a steam-bath for about thirty minutes and filtered. White crystals, 0.2 g. (29%), m. p. 295–296°, were obtained. Purification by crystallization from acetic acid–water elevated the melting point to 296–297°. A mixed melting point with an authentic sample, m. p. 296–297°, prepared by the method of Gaythwaite, Kenyon and Phillips[12] from anthranilic acid showed no depression. When each of the two specimens was warmed with concentrated sulfuric acid, the solution became dark green in color, but the application of more heat produced a blue-violet, a test reported by Lesser and Weiss.[10]

Anal. Calcd. for $C_{14}H_{10}O_4Se_2$: C, 42.02; H, 2.52. Found for sample from selenonaphthene: C, 42.10, 42.05; H, 2.69, 2.53; for synthetic sample: C, 41.72, 41.83; H, 2.55, 2.55.

Products from γ-Stilbazole

γ-Stilbazole.—This compound was prepared in 75% yield (based on γ-picoline) by a method similar to that employed for the α-isomer; m. p. 127° (Wagstaff[7] gives 127°).

2-γ-Pyridylselenonaphthene.—The oxidation of 50 g. of γ-stilbazole with selenium dioxide at 200°, as in the case of the α-isomer, gave a dark red oil. Treatment with 300 cc. of methanol followed by filtration removed the selenium. After evaporation to about one-fourth of the original volume, the precipitate which formed was filtered off and put into solution in boiling water by the addition of concentrated hydrochloric acid. The insoluble tar was removed by filtration and the filtrate was allowed to cool. The hydrochloride of the selenonaphthene often precipitated; however, a better yield was obtained if the solution was neutralized with sodium bicarbonate. The mixture was then filtered and the solid was washed with a solution of sodium bicarbonate. A white compound, m. p. 187°, was usually obtained after three crystallizations from methanol using Norit A. Best results are obtained if the methanol solutions are cooled for several hours in the coldest part of the refrigerator.

Anal. Calcd. for $C_{13}H_9NSe$: C, 60.47; H, 3.51. Found: C, 60.33, 60.38; H, 3.37, 3.38.

Treatment with bromine gave yellow crystals melting at 225°, but it was not possible to convert this product into a pure monobromo derivative.

4-β-Phenylethylpiperidine Hydrochloride.—This hydrochloride was prepared from the γ-selenonaphthene and from γ-stilbazole by procedures already described. In each case white, hygroscopic crystals, m. p. 147–152°, were obtained. A mixed melting point gave no depression.

1-Benzenesulfonyl-4-β-phenylethylpiperidine.—Since the m. p.'s of the hydrochlorides were not sharp, the benzenesulfonamides of each sample of the amine were prepared by the procedures given for the α-isomers. In each case long, white needles, m. p. 118–119°, were obtained. A mixed melting point showed no depression.

Anal. Calcd. for $C_{19}H_{23}NO_2S$: C, 69.26; H, 7.04. Found for sample from selenonaphthene: C, 69.34, 69.26; H, 6.67, 6.66; for sample from stilbazole: C, 69.19, 69.36; H, 6.74, 6.85.

2,2′-Dicarboxydiphenyl Diselenide (VI).—The γ-selenonaphthene, 0.45 g., was oxidized by the procedure employed for the α-isomer and there resulted 0.1 g. (29%) of impure diselenide, m. p. 293–296°. Purification by crystallization from methanol–water three times, using Norit A, gave a product, m. p. 296–297°, which was not depressed on mixing with an authentic sample.

Anal. Calcd. for $C_{14}H_{10}O_4Se_2$: C, 42.02; H, 2.52. Found: C, 42.08, 42.07; H, 2.33, 2.47.

Summary

Oxidation of α-stilbazole with selenium dioxide produced phenyl-α-pyridylethane-1,2-dione and 2-α-pyridylselenonaphthene; a similar oxidation of γ-stilbazole yielded only 2-γ-pyridylselenonaphthene.

The structures of the selenonaphthenes were proved by degradation to 2-β- and 4-β-phenylethylpiperidine and 2,2′-dicarboxydiphenyl diselenide.

KNOXVILLE, TENNESSEE RECEIVED MARCH 9, 1950

(10) Lesser and Weiss, *Ber.*, **46**, 2644 (1913).

(11) Since more severe drying conditions remove another molecule of water, it is possible that the compound melting at 227.5–228.5° is actually the cyclic rather than the linear anhydride of *o*-seleninbenzoic acid.

(12) Gaythwaite, Kenyon and Phillips, *J. Chem. Soc.*, 2286 (1928).