5 ml. of carbon tetrachloride. Light was applied from an infrared lamp and hydrogen bromide was copiously evolved. The solvent was removed *in vacuo* to yield a yellow oil which solidified on trituration with petroleum ether. Two recrystallizations from petroleum ether–benzene yielded 135 mg. (67.5%) of yellow needles, m.p. 162–163°. A test for bromine was negative.

Anal. Calcd. for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.35; H, 4.89.

The ultraviolet spectra exhibited absorption peaks at 250 mμ (ϵ_{max} = 30,550) and 357 mμ (ϵ_{max} = 16,500).

Acknowledgement. The authors wish to thank Mr. Robert French for the microanalyses and Dr. J. M. Vandenbelt, Parke, Davis and Company, for ultraviolet spectra.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

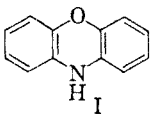
Preparation and Some Reactions of Phenoxazine and Phenoselenazine

PAULETTE MÜLLER, N. P. BUU-HOÏ, AND R. RIPS

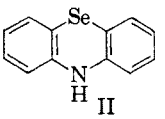
Received July 25, 1958

Improved methods for the preparation of phenoxazine and phenoselenazines have been elaborated, and some reactions of these heterocycles have been investigated. Phenoselenazine and 2-chlorophenoselenazine readily underwent β-cyanoethylation; β-(10-phenoselenazyl)- and β-(2-chloro-10-phenoselenazyl)propionic acid, obtained on hydrolysis of the corresponding nitriles, were successfully cyclized to ketones derived from a new four-ringed nitrogen heterocycle.

Phenoxazine (I) and phenoselenazine (II) are two rarely investigated heterocycles, although they are isologs of phenothiazine, the nucleus of numerous dye-stuffs and pharmaceutical molecules. Recently, however, several phenoxazine derivatives have recaptured interest for their antitubercular activity,[1] and phenoselenazine itself is not devoid of pharmacological interest, since the selenium analogs of promethazine and chlorpromazine have shown antihistamine activity similar to that of their sulfur-containing analogs.[2] These observations prompted an investigation of the methods of



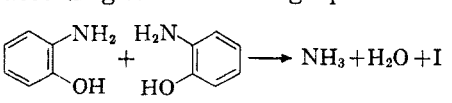
I



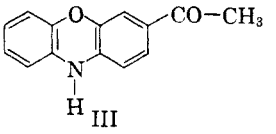
II

preparation of phenoxazine and phenoselenazine, and also of certain aspects of their chemical reactivity.

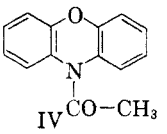
The classic method for preparing phenoxazine, involving the condensation of catechol with *o*-aminophenol,[3] necessitated the use of sealed tubes, and yields were very erratic. A far more convenient method has now been found to consist of the autocondensation of *o*-aminophenol in the presence of iodine according to the following equation:



This preparation of phenoxazine, which can be performed in open vessels and gives reliable yields, recalls the Knoevenagel method for synthesizing secondary diarylamines by iodine-catalyzed condensation of naphthols with primary arylamines.[4] Friedel-Crafts condensation of phenoxazine with acetyl chloride in the presence of aluminum chloride was found to give a monoketone, possibly 3-acetylphenoxazine (III), along with larger quantities of 10-acetylphenoxazine (IV). Position 3 is more probable than position 2, in view of the



III



IV

stronger orienting influence of the imino group.

The procedure described in the literature by Cornelius,[5] and later by Karrer,[6] for the preparation of phenoselenazine, which consisted of the condensation of diphenylamine with selenious chloride in benzene, has now been considerably improved by performing the reaction in chloroform, the use of this solvent allowing a better control of the reaction and enhancing the yield. The same method was also applied for preparing 2-chlorophenoselenazine; in both cases, the purity of the reaction products is greatly enhanced by vacuum-distillation prior to recrystallization.

Both phenoselenazine and 2-chlorophenoselenazine readily underwent β-cyanoethylation with acrylonitrile in the presence of benzyltrimethylammonium methoxide to give β-(10-phenoselenazyl)propionitrile (V) and β-(2-chloro-10-phenoselenazyl)propionitrile (VI). Thus, phenoselenazine

(1) *Cf.* B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499, 1504 (1953); these papers also give earlier relevant references.

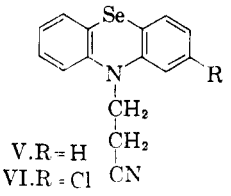
(2) P. Müller, N. P. Buu-Hoï, and R. Rips, unpublished results.

(3) A. Bernthsen, *Ber.*, **20**, 943 (1887); F. Kehrmann, *Ann.*, **322**, 9 (1902); phenoxazine was also prepared by heating *o*-aminophenol with its hydrochloride, by F. Kehrmann and A. A. Neil, *Ber.*, **47**, 3102 (1914).

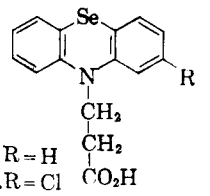
(4) E. Knoevenagel, *J. prakt. Chem.*, [2] **89**, 17 (1914).

(5) W. Cornelius, *J. prakt. Chem.*, [2] **88**, 398 (1913).

(6) P. Karrer, *Ber.*, **49**, 603 (1916).

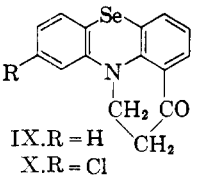


V.R = H
VI.R = Cl

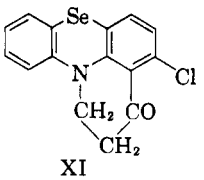


VII.R = H
VIII.R = Cl

and its nuclear substituted derivatives react in a similar manner to phenothiazine, which Smith[7] had already successfully β-cyanoethylated. These new propionitriles could be readily hydrolyzed with alcoholic sodium hydroxide, to give β-(10-phenoselenazyl)propionic acid (VII) and its 2-chloro derivative (VIII), although acid hydrolysis resulted in decomposition to the phenoselenazines. Like β-(10-phenothiazyl)propionic acid, which had been successfully converted into the corresponding cyclic ketone by means of phosphoric anhydride[7] or polyphosphoric acid,[8] β-(10-phenoselenazyl)propionic acid yielded, on similar treatment, 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*] phenoselenazine (IX); in contrast with the acid, which is colorless,



IX.R = H
X.R = Cl



XI

this ketone and its phenylhydrazone both showed a characteristic yellow color, similar to that of their analogs in the phenothiazine series. Cyclization of β-(2-chloro-10-phenoselenazyl) propionic acid similarly gave a yellow ketone, which could perhaps be assigned the structure X in preference to the isomeric structure XI, in view of the known deactivating influence and steric hindrance exerted by the chlorine atom in *ortho* position. In the case of β-(2-chloro-10-phenothiazinyl)propionic acid, Fujii[8] came to a similar conclusion as to the structure of the cyclization product.

10-Methylphenoselenazine, which Cornelius prepared by heating phenoselenazine with methyl iodide and methanol in a sealed tube,[5] was now more conveniently prepared, and in good yield, by methylating phenoselenazine by means of dimethyl sulfate in the presence of sodium hydroxide and in acetone medium; this method could also be applied to the *N*-methylation of phenoxazine.

EXPERIMENTAL

Preparation of phenoxazine. A mixture of 109 g. of *o*-aminophenol and 1 g. of pulverized iodine in a 500-ml. Claisen flask was heated slowly on a sand bath to 270–275° with removal of water, and heating was continued at that temperature for 4 hr. The hot reaction product was poured into a mortar, and the solid obtained on cooling was ground and extracted with toluene in a Soxhlet extraction apparatus; the toluene solution was washed with an aqueous solution of sodium hydrogen sulfite, then several times with aqueous sodium hydroxide to remove the unreacted *o*-aminophenol, and finally with water. After drying over sodium sulfate, the solvent was removed, and the residue distilled in a vacuum. Yield: 30–35% (27–32 g.) of *phenoxazine*, b.p. 215°/4 mm., crystallizing from ethanol in colorless needles.

Friedel-Crafts acetylation of phenoxazine. To a solution of 18 g. of phenoxazine and 13 g. of acetyl chloride in 250 ml. of carbon disulfide, 25 g. of powdered aluminum chloride was added in small portions with stirring. The mixture was kept for 4 hr. at room temperature, then refluxed on a water bath for 3 hr. After cooling, the reaction product was treated with ice and hydrochloric acid, and the organic material taken up in chloroform; the chloroform solution was washed with water and dried over sodium sulfate, the solvent was distilled off, and the residue vacuum-fractionated. A portion boiling at 215°/17 mm. consisted of 10 g. of *10-acetylphenoxazine*, crystallizing from ethanol in colorless prisms, m.p. 146°; the literature[9] gives m.p. 142°.

A higher-boiling portion consisted of 4.5 g. of a monoketone, probably *3-acetylphenoxazine*, b.p. 265–267°/17 mm., crystallizing from ethanol in bright yellow needles, m.p. 221°, giving a violet halochromy in sulfuric acid.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.7; H, 4.9; N, 6.2. Found: C, 74.4; H, 5.0; N, 6.2.

Preparation of 2-chlorophenoselenazine. To a well-stirred solution of 49 g. of 2-chlorodiphenylamine (b.p. 185°/14 mm.) in 200 ml. of anhydrous chloroform, 77 g. of selenious chloride (prepared from selenious anhydride, powdered selenium, and hydrochloric acid in the presence of concentrated sulfuric acid, according to the method of Lenher and Kao[10]), dissolved in 100 ml. of chloroform, was added in small portions, and the mixture refluxed for 6 hr. After cooling, 100 ml. of chloroform was added, and the liquid obtained was filtered rapidly; the filtrate was then poured into water. The selenium formed was again filtered off, the chloroform solution was washed with aqueous sodium carbonate, then with water, and filtered, the organic layer dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. Yield: 37 g. (52%) of *2-chlorophenoselenazine*, b.p. 225°/1 mm., crystallizing from ethanol in colorless needles, m.p. 200°.

Anal. Calcd. for $C_{12}H_8ClNSe$: Cl, 12.7; N, 5.0. Found: Cl, 12.4; N, 4.9.

Preparation of phenoselenazine and 10-methylphenoselenazine. Phenoselenazine, crystallizing from ethanol in shiny colorless needles, m.p. 195°, was prepared as above from diphenylamine, in 60–65% yield. To a solution of 22 g. of phenoselenazine and 7.1 g. of sodium hydroxide (dissolved in the minimum of water) in 170 ml. of acetone, 22 g. of dimethyl sulfate was added portionwise, with stirring. Stirring was continued for 1 hr., a further portion of sodium hydroxide was added, followed by the equivalent amount of dimethyl sulfate, and the mixture then left overnight. After evaporation of the acetone, water was added, the reaction product taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled (b.p. 195–200°/0.2 mm.), giving a 50% yield of *10-methylphenoselenazine*, colorless prisms, m.p. 139° (literature[6] m.p. 138–139°), from ethanol. The same procedure, applied to phenoxazine, afforded 10-methylphenoxazine, in similar yields.

β-(10-Phenoselenazyl)propionitrile (V). To a mixture of 22 g. of phenoselenazine and 27 ml. of acrylonitrile, 1 ml. of 40% benzyltrimethylammonium methoxide was added drop-

(7) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(8) K. Fujii, *Yakugaku Zasshi*, **77**, 1065 (1957); *Chem. Abstr.*, **52**, 5417 (1958).

(9) F. Kehrmann and A. Saager, *Ber.*, **36**, 477 (1903).

(10) V. Lenher and C. H. Kao, *J. Am. Chem. Soc.*, **47**, 772 (1925); N. P. Buu-Hoï and J. Lecocq, *Rev. sci.*, **82**, 39 (1944).

wise with stirring, whereupon a vigorous exothermic reaction set up. The red mixture was then refluxed for 1 hr. on a water bath; after cooling, the acrylonitrile in excess was distilled off in a vacuum, and the residue was recrystallized twice from acetone, giving a 75% yield of fine colorless needles, m.p. 163°. Like its sulfur analog, this nitrile was readily soluble in benzene and acetone, sparingly soluble in ethanol.

Anal. Calcd. for $C_{15}H_{12}N_2Se$: C, 60.2; H, 4.1; N, 9.4. Found: C, 60.2; H, 4.1; N, 9.4.

β-(2-Chloro-10-phenoselenazyl)propionitrile (VI). This nitrile was obtained in 75% yield from 15 g. of 2-chlorophenoselenazine and 19 ml. of acrylonitrile, as for the above. It crystallized from acetone in colorless prisms, m.p. 168°.

Anal. Calcd. for $C_{15}H_{11}ClN_2Se$: Cl, 10.6; N, 8.4. Found: Cl, 10.8; N, 8.5.

β-(10-Phenoselenazyl)propionic acid (VII). A solution of 22 g. of β-(10-phenoselenazyl)propionitrile and 18.5 g. of sodium hydroxide in 350 ml. of ethanol was gently refluxed for 15 hr.; after cooling, 500 ml. of water was added, a small amount of solid was filtered off, and the filtrate was acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol, giving 16.5 g. of lustrous colorless leaflets, m.p. 193°.

Anal. Calcd. for $C_{15}H_{13}NO_2Se$: C, 56.7; H, 4.1; N, 4.4. Found: C, 56.7; H, 4.3; N, 4.4.

β-(2-Chloro-10-phenoselenazyl)propionic acid (VIII). Similarly prepared by hydrolysis of nitrile VI, this acid crystallized from ethanol in shiny colorless needles, m.p. 188°, giving a cherry red coloration in sulfuric acid.

Anal. Calcd. for $C_{15}H_{12}ClNO_2Se$: C, 51.1; H, 3.4; N, 4.0. Found: C, 51.1; H, 3.5; N, 4.1.

2,3-Dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (IX). To a solution of 5 g. of acid VII in 100 ml. of anhydrous benzene, 20 g. of phosphorus pentoxide was added and the mixture was refluxed for 1 hr. on a water bath. After cooling, the benzene was decanted from a dark solid mass, which was cautiously treated with ice, and the reaction product was taken up in benzene. The benzene solution was washed with aqueous sodium carbonate, then with water, dried over sodium sulfate, the solvent was distilled off, and the residue recrystallized several times from ethanol. Yield: 3 g. of shiny yellow needles, m.p. 115°, giving in sulfuric acid a blue halochromy rapidly turning pinkish orange.

Anal. Calcd. for $C_{15}H_{11}NOSe$: C, 60.1; H, 3.7; N, 4.7. Found: C, 60.0; H, 3.9; N, 4.6.

This ketone gave a *phenylhydrazone*, which crystallized from ethanol in shiny dark yellow leaflets, m.p. 180°.

10-Chloro-2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (X). This ketone, prepared in 70% yield by cyclization of acid VIII with phosphorus pentoxide, crystallized from ethanol in microscopic yellow needles, m.p. 146°, giving a brownish red halochromy in sulfuric acid. No isomeric ketone could be isolated, although in the preparation of the corresponding sulfur analog, Fujii[8] detected some of the isomer in the form of its oxime.

Anal. Calcd. for $C_{15}H_{10}ClNOSe$: C, 53.8; H, 3.0; N, 4.2 Found: C, 54.1; H, 3.2; N, 4.3.

Acknowledgment. Our thanks are due to Dr. Nathan L. Smith (University of Florida, Gainesville) for the gift of benzyltrimethylammonium methoxide used in this work. We are also indebted to Professors H. Maureu and P. Chovino and Dr. Lévy, of the Laboratoire Municipal (Paris), for several microanalyses.

PARIS Ve, FRANCE

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Orientation in Friedel-Crafts Acylations of 3-Chloro-2-methoxybiphenyl

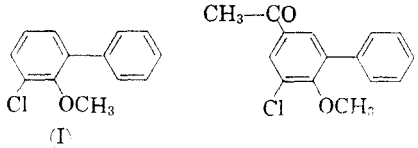
N. P. BUU-HOÏ AND LOUIS PETIT

Received August 20, 1958

Friedel-Crafts acetylation of 3-chloro-2-methoxybiphenyl is shown to occur in position 5 when the catalyst is stannic chloride, and in both positions 5 and 4′ when aluminum chloride is used. In the course of this investigation, a number of new derivatives of 3-chloro-2-methoxybiphenyl have been prepared.

As a part of a general study of biphenyl derivatives,[1] both theoretical (orientation problems) and practical (search for potential pharmaceuticals and germicides), the reactivity of 3-chloro-2-methoxybiphenyl (I) has been investigated.

It is known that Friedel-Crafts acylation of 2-methoxybiphenyl with acetyl chloride in the presence of aluminum chloride[2] occurs at position 5, and that other acid chlorides behave in the same way.[3] Hence it was of interest to investigate the orientation in similar reactions with 3-chloro-2-methoxybiphenyl. In this molecule, the presence of a chlorine atom in position 3 suggests that it would have a deactivating influence on position 5, the prospective site of



(I)

substitution, and, this being the case, then heteronuclear substitution, *e.g.* at position 4′, should also

(1) *Cf.* N. P. Buu-Hoï and R. Royer, *Bull. soc. chim. France*, **17**, 489 (1950); *Rec. trav. chim.*, **70**, 825 (1951); N. P. Buu-Hoï, M. Sy, and J. Riché, *J. Org. Chem.*, **22**, 668 (1957); G. Viel, M. Sy, and N. P. Buu-Hoï, *Bull. soc. chim. biol.*, in press.

(2) K. von Auwers and G. Wittig, *J. prakt. Chem.*, **108**, 106 (1925).

(3) *Cf.* N. P. Buu-Hoï and M. Sy, *J. Org. Chem.*, **21**, 136 (1956).