The Aminomethylation of Selenophenol

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Selenophenol was condensed with formaldehyde and the following amines: benzylamine, dibenzylamine, aniline, methylaniline, as well as ammonia, to form N,N-bis(phenylselenomethyl)benzylamine [$(C_6H_5SeCH_2)_2NCH_2C_6H_5$], phenylselenomethyldibenzylamine [$C_6H_5SeCH_2N(CH_2C_6H_5)_2$], N,N-bis(phenylselenomethyl)aniline [$(C_6H_5SeCH_2)_2NC_6H_5$], N-methyl-N-phenylselenomethylaniline [$C_6H_5SeCH_2N(CH_3)C_6H_5$], and tris(phenylselenomethyl)amine [$(C_6H_5SeCH_2)_3N$], respectively. If this condensation is carried out in a strong acid solution and employing an aromatic amine unsubstituted in the *para* position, *p*-aminobenzyl phenyl selenides, rather than the isomeric phenylselenomethylamines, are obtained. The infrared and nmr spectra of the new compounds prepared are described and are in agreement with the structures assigned to them.

In 1921, McLeod and Robinson prepared dialkylaminomethyl alkyl sulfides by condensing formaldehyde and mercaptans with secondary aliphatic amines.[1] Recently Grillot and his students[2] have described the aminomethylation of thiophenols by condensing them with formaldehyde and either primary or secondary aliphatic and aromatic amines. Thus, the claim made by Weatherbee, Sleeter, and Han[3] that they were the first to condense thiophenols, formaldehyde, and primary amines is unjustified.

Further, Grillot and Schaffrath[2] previously found no evidence for the formation of a 3,4-dihydro-1,3,2H-benzo[*m*]thiazine when the condensation of the thiophenol, aniline, and formaldehyde in a mole ratio of 1:1:2 was attempted. Also, Grillot and Schaffrath[2] previously described 1,3,5-triaryl-1,5-dithia-3-azapentanes formed by condensing thiophenols, formaldehyde, and primary aromatic amines in the ratio of 2:2:1 and, thus, this does not represent a new class of compounds, as claimed by Weatherbee, *et al.*[3]

The condensation of thiophenols and formaldehyde with aromatic amines unsubstituted in the *para* position in the presence of acids in which *p*-aminobenzyl aryl sulfides are usually obtained has also been reported.[4]

No studies of the analogous reactions of the selenophenols have, as yet, appeared in the literature.

When a secondary amine was condensed with formaldehyde and selenophenol in a 1:1:1 ratio, the product was an N-phenylselenomethyl-N,N-dialkylamine or an N-alkyl-N-phenylselenomethyl-N-arylamine. When utilizing the primary amines, aniline, and benzylamine in a ratio of 1:2:2 in this condensation, the products were N,N-bis(phenylselenomethyl)aniline (1,3,5-triphenyl-1,5-diselena-3-azapentane), mp 58–60°, yield 42% and N,N-bis(phenylselenomethyl)benzylamine (3-benzyl-1,5-diselena-3-azapentane) mp 65–66.5°, yield 96%, respectively. When ammonia was employed in place of the amine utilizing a ratio of 1:3:3 the product was tris(phenylselenomethyl)amine (mp 30.5–31.5°, crude yield 72%). The attempted condensation of selenophenol and formaldehyde with aniline in a 1:1:1 ratio gave a mixture of products which was not completely separated, but was assumed to be $C_6H_5SeCH_2NHC_6H_5$ contaminated by $(C_6H_5SeCH_2)_2NC_6H_5$.

p-Aminobenzyl phenyl selenides, rather than the isomeric phenylselenomethylamines, are obtained when this condensation is carried out in a strong acid solution with aromatic amines that are unsubstituted in the *para* position. Thus, the condensation of selenophenol and formaldehyde with aniline, methylaniline, and dimethylaniline in the presence of HCl produces *p*-aminobenzyl phenyl selenide (p-$H_2NC_6H_4CH_2SeC_6H_5$), mp 53–55°, crude yield >95%, *p*-N-methylaminobenzyl phenyl selenide (p-$CH_3NHC_6H_4CH_2SeC_6H_5$), mp 77.5–79.5°, yield 76%, and *p*-(N,N-dimethylamino)benzyl phenyl selenide [p-$(CH_3)_2NC_6H_4CH_2SeC_6H_5$], mp 99–101°, yield 7%, respectively.

p-(N,N-Dimethylamino)benzyl phenyl selenide was also prepared in a yield (crude) exceeding 95% when selenophenol was refluxed for 10 min with an acid solution of N-(*p*-N′,N′-dimethylaminobenzyl)-N-methylaniline, whereas as noted above, direct condensation of selenophenol with an acidified solution of formaldehyde and dimethylaniline produced this selenide in a 7% yield.

N-(*p*-N′,N′-Dimethylaminobenzyl)-N-methylaniline, p-$(CH_3)_2NC_6H_4CH_2N(CH_3)C_6H_5$, mp 68–70°, has been prepared in a yield of 86% by the action of the Grignard reagent of *p*-bromodimethylaniline on N-phenylthiomethyl-N-methylaniline, $C_6H_5SCH_2N(CH_3)C_6H_5$.[2] The action of Grignard reagents on arylaminomethyl sulfides appears to have potentialities as an excellent method for the N-monoalkylation and N,N-dialkylation or aromatic amines.

The investigation of these reactions of selenophenol has been undertaken as a result of some doubt regarding the mechanism recently proposed by Grillot and Lau[5] for the acid-catalyzed condensation. Grillot and Lau postulated that the reaction proceeds through the "normal Mannich base" which then cleaves into the amine and a resonance-stabilized carbonium–sulfonium ion, [$ArSCH_2^+ \leftrightarrow ArS^+{=}CH_2$], and subsequently this ion couples with the *para* position of the aromatic amine, in analogy to the diazonium coupling reaction. It was felt that the analogous carbonium–selenonium ion, if we may coin the word [$C_6H_5SeCH_2^+ \leftrightarrow C_6H_5Se^+{=}CH_2$], would not be stabilized to any appreciable extent[6] and hence should not lead to the so-called "rearranged product."

The observations made in this study suggest that the proposed mechanism postulated by Grillot and Lau[5] does not represent the true course of this rearrangement. It is suggested that an N-(*p*-aminobenzyl)aniline, rather than a Mannich base, is an intermediate in these

(1) C. M. McLeod and G. M. Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

(2) G. F. Grillot, *et al.*, *J. Am. Chem. Soc.*, **76**, 3969 (1954); G. F. Grillot and R. E. Schaffrath, *J. Org. Chem.*, **24**, 1035 (1959).

(3) C. Weatherbee, R. T. Sleeter, and P. Z. Han, *Tetrahedron Letters*, 4069 (1965).

(4) P. T. S. Lau and G. F. Grillot, *J. Org. Chem.*, **28**, 2763 (1963).

(5) G. F. Grillot and P. T. S. Lau, *ibid.*, **30**, 28 (1965).

(6) John W. Baker, G. F. C. Barrett, and W. T. Tweed, *J. Chem. Soc.*, 2831 (1952).

acid-catalyzed reactions. The authors are preparing a communication in which other objections to the Grillot–Lau mechanism will be cited and in which a new mechanism will be proposed.

Experimental Section

Instruments.—The nmr specta were obtained on a Varian A-60 nmr spectrometer. The infrared spectra were obtained on a Perkin-Elmer Infracord.

Materials.—Selenophenol was prepared by the method of Duncan G. Foster.[7] The amines were commercial grade and were used without further purification.

N-(*p*-N′,N′-Dimethylaminobenzyl)-N-methylaniline.—To the Grignard reagent obtained from 220 g (1.1 moles) of *p*-bromo-N,N-dimethylaniline and 36 g (1.5 moles) of magnesium turnings in 250 ml of tetrahydrofuran (THF) freshly redistilled over $LiAlH_4$, was added slowly a solution of 229 g (1 mole) of N-phenylthiomethyl-N-methylaniline, $PhSCH_2N(CH_3)Ph$, prepared by the method of Grillot and Schaffrath,[2] in 200 ml of THF. At the end of the addition the reaction mixture was refluxed for an additional 1 hr, and hydrolyzed in 500 g of crushed ice and a saturated solution of ammonium chloride. After extraction with ether, washing the extract with 10% NaOH, and drying with KOH pellets, the volatile solvents were removed. The residual oil (235 g, 96% of theory) solidified on standing and was recrystallized from 300 ml of ethanol, mp 68–70°, yield 206 g, or 86% of the theory. The infrared spectrum showed no NH stretching bands, but showed bands characteristic of both a *para*-disubstituted and a monosubstituted benzene rings. The nmr spectrum showed three sharp singlets at 168, 170, and 268 cps, in addition to aromatic protons in the region between 385 and 430 cps. The area ratio was 6:3:2:9, respectively, in agreement with the structure of N-(*p*-dimethylaminobenzyl)-N-methylaniline. *Anal.* Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.08; H, 8.58; N, 11.21.

Aminomethylation of Selenophenol in Absence of Acid N-Phenylselenomethyl-N-methylaniline.—To a cooled solution of 15.7 g (0.10 mole) of selenophenol in 50 ml of 95% ethanol, was added 11 ml (0.1 mole) of N-methylaniline, and 7.6 ml (0.1 mole) of 37% formaldehyde. After 30 min of refluxing with stirring, and cooling, the two liquid phases that appeared were separated. The bottom, oily layer was washed with 10% NaOH, followed with water and cold ethanol. The weight of oily residue after removal of volatile materials under vacuum was 23.4 g (85% theory). Chilling in the refrigerator overnight caused the oil to crystallize and melt at 10°. The compound boils at 160–165° (2 mm) with slight decomposition. The infrared spectrum showed no NH stretching bands. The nmr spectrum in deuterated chloroform showed two types of protons, singlets at 157 and 295 cps, in addition to the aromatic protons in the region between 390 and 460 cps. These were in the area ratio of 3:2:10, respectively, in agreement with the structure of N-methyl-N-phenylselenomethylaniline. *Anal.* Calcd for $C_{14}H_{15}NSe$: C, 60.87; H, 5.48; N, 5.08. Found: C, 60.73; H, 5.48; N, 4.95.

N,N-Bis(phenylselenomethyl)aniline.—To a cooled solution of 7.85 g (0.05 mole) or selenophenol in 25 ml of alcohol was added 2.5 ml of aniline (0.025 mole) and 3.8 ml (0.05 mole) of 37% formaldehyde. After 30 min of refluxing, the phases were separated. The bottom oily layer was washed with 10% NaOH and chilled in acetone–Dry Ice when the material crystallized. Recrystallization from 400 ml of alcohol gave 4.5 g (42% of theory) of an amorphous solid that melted at 58–60°. Its infrared spectrum showed no NH stretching bands. Its nmr spectrum had only one sharp singlet at 293 cps, in addition to the aromatic protons in the region between 395 and 460 cps. The area ratio was 4:15, respectively, in agreement with the formula of N,N-bis(phenylselenomethyl)aniline. *Anal.* Calcd for $C_{20}H_{19}NSe_2$: C, 55.69; H, 4.48; N, 3.25. Found: C, 55.81; H, 4.30; N, 3.48.

N,N-Bis(phenylselenomethyl)benzylamine.—To a cold solution of 7.85 g (0.05 mole) of selenophenol in 25 ml of alcohol was added 2.675 g (0.025 mole) of benzylamine and 3.85 ml (0.05 mole) of 37% formaldehyde. After refluxing for 30 min, the phases were separated and the oily layer was washed with base. On chilling the oil solidified. After washing with water and drying, the crude material weighed 10.5 g (96% of theory). Recrystallization from 200 ml of alcohol gave colorless, small needles, melting at 65–66.5°. Its infrared spectrum showed no NH stretching bands. Its nmr spectrum showed two sharp singlets at 225 and 275 cps, in addition to the aromatic protons in the region between 410 and 460 cps. These were in the area ratio of 2:4:15, respectively, in agreement with the formula of N,N-bis(phenylselenomethyl)benzylamine. *Anal.* Calcd for $C_{21}H_{21}NSe_2$: C, 56.64; H, 4.76; N, 3.15. Found: C, 56.56; H, 4.61; N, 2.92.

N,N,N-Tris(phenylselenomethyl)amine.—To a cold solution of 11.78 g (0.075 mole) of selenophenol in alcohol was added 1.57 ml (0.025 mole) of concentrated aqueous ammonia (sp gr 0.9) and 5.7 ml (0.075 mole) of 37% formaldehyde. After 30 min of refluxing 200 ml of water was added. The bottom, oily layer was separated and washed with base. The oil which did not crystallize on cooling was dissolved in 100 ml of ether and dried with KOH pellets. After removal of the ether there was left 9.3 g of residue (72% of theory) that crystallized on cooling. The melting point of the crude crystals was 20–25°. Recrystallization from 15 ml of benzene and 75 ml of absolute alcohol gave 6 g of colorless flakes that after drying in air melted at 30.5–31.5°.

This compound's infrared spectrum showed no NH stretching bands. Its nmr spectrum showed one sharp singlet at 273 cps, in addition to the aromatic protons in the region between 420 and 460 cps. These were in the ratio of 6:15, respectively, in agreement with the formula of tris(phenylselenomethyl)amine. *Anal.* Calcd for $C_{21}H_{21}NSe_3$: C, 48.10; H, 4.06; N, 2.67. Found: C, 48.11; H, 3.98; N, 2.70.

N,N-Dibenzyl-N-(phenylselenomethyl)amine.—To a cooled solution of 3.93 g (0.025 mole) of selenophenol in 25 ml of alchol was added 4.975 g (0.025 mole) of dibenzylamine and 1.9 ml (0.025 mole) of 37% formaldehyde. After refluxing for 30 min, 200 ml of water was added. The oily layer was separated and washed with 10% NaOH. The oil which would not crystallize on chilling was dissolved in 100 ml of ether and dried over KOH pellets. The ether was removed leaving behind a liquid residue that weighed 8.6 g (94% of theory). After washing with alcohol, discarding the alcohol layer, and removing the residual alcohol under vacuum, the oil was submitted for analyses. Its infrared spectrum showed no NH stretching bands. Its nmr spectrum showed two singlets at 216 and 274 cps, in addition to aromatic protons in the region of 410 and 460 cps. These were in the area ratio of 4:2:15, respectively, in agreement with the formula of N,N-dibenzyl-N-phenylselenomethylamine. *Anal.* Calcd for $C_{21}H_{21}NSe$: C, 68.83; H, 5.78; N, 3.83. Found: C, 67.71; H, 6.12; N, 4.39.

Attempt to Prepare N-(Phenylselenomethyl)aniline.—To a cooled solution of 7.85 g (0.05 mole) of selenophenol in 25 ml of alcohol was added 5.5 ml (0.06 mole) of aniline and 3.8 ml of 37% formaldehyde (0.05 mole). After refluxing for 30 min the reaction mixture was cooled and the lower, oily layer was separated and washed with 50 ml of 10% NaOH. The oil was dissolved in 50 ml of ether and dried over KOH pellets, and the ether was removed. The residual oil (which weighed 6.9 g) was washed with cold petroleum ether (bp 30–60°) followed by a washing with cold alcohol. Chilling would not induce crystallization. After removal of the residual alcohol under vacuum, the infrared spectrum indicated that the material was not homogeneous; it did however show a single NH stretching band at 2.9 μ, indicating the presence of a secondary amine. The nmr spectrum, too, indicated that the material was not a single product. However, no further purification was attempted. *Anal.* Calcd for $C_{13}H_{13}NSe$: C, 59.55; H, 5.00; N, 5.35. Found: C, 66.26; H, 5.41; N, 5.50.

Condensations in the Presence of Acid. *p*-(N-Methylamino)-benzyl Phenyl Selenide.—To a cooled solution of 15.7 g (0.10 mole) of selenophenol in 50 ml of 95% ethanol was added, in sequence, 11.0 ml (0.10 mole) of N-methylaniline, 7.6 ml (0.1 mole) of 37% formaldehyde, and 9.0 ml (0.1 mole) of concentrated hydrochloric acid (sp gr 1.19). After refluxing for 30 min with stirring, the reaction mixture was made strongly basic with 10% NaOH. The crystalline solid was collected, filtered, washed with water, and recrystallized from 70 ml of alcohol mp 77.5–79.5°, yield 21 g (76% of theory). A second recrystallization from alcohol did not raise the melting point. The infrared spectrum showed absorption at 2.9 μ, owing to an NH stretching band of a secondary amine. Furthermore, it possessed a strong band at 12.1-μ characteristic of a *para*-disubstituted benzene ring and two strong bands at 13.65 and 14.5 μ for a

(7) E. C. Horning Ed., "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 771.

monosubstituted benzene ring. The nmr spectrum showed three singlets at 159, 207, and 241 cps, in addition to aromatic protons in the region between 375 and 453 cps. These were in the area ratio of 3:1:2:9, respectively. The aromatic protons were further resolved into three sets of multiplets, which enable the elucidation of the structure unequivocally, a doublet with suggestions of secondary splittings centered at 483 cps, J = 9 cps, for the *ortho* (to the amino group) protons of the *para*-disubstituted aniline ring; a complex multiplet between 412 and 435 cps for the *meta* protons of the same ring and the *meta* and *para* protons of the selenobenzene ring; and, finally, a multiplet centered at 444 cps for the *ortho* protons of the selenobenzene ring. These aromatic protons were in the ratio of 2:5:2, respectively, in agreement with the formula of *p*-(N-methylamino)-benzyl phenyl selenide. *Anal.* Calcd for $C_{14}H_{15}NSe$: C, 60.87; H, 5.48; N, 5.08. Found: C, 60.68; H, 5.41; N, 5.18.

p-Aminobenzyl Phenyl Selenide.—To a cooled solution of 7.85 g (0.05 mole) of selenophenol in 25 ml of alcohol was added 4.65 ml (0.05 mole) of aniline, 3.82 ml (0.05 mole) of 37% formaldehyde, and 4.50 ml (0.05 mole) of concentrated hydrochloric acid (sp gr 1.19). After refluxing for 30 min, the reaction mixture was made strongly basic with 10% NaOH. The crystalline solid was filtered and washed with water. The yield of crude crystals exceeded 95% of the theory. Recrystallization from 150 ml of alcohol gave 5 g of crystals that melted at 53–55°. The infrared spectrum showed two NH stretching bands for a primary amine, and strong bands indicating a *para* disubstituted, as well as a monosubstituted benzene ring. The nmr spectrum showed two types of protons, a broad band, centered at *ca.* 200 cps and a sharp singlet at 242 cps, in addition to the aromatic protons in the region between 385 and 355 cps. The area ratio of these protons were 2:2:9, repectively. The aromatic protons had the characteristic pattern described above for its N-methyl derivative. Thus, the nmr and the infrared spectra are in agreement with the structure of *p*-aminobenzyl phenyl selenide. *Anal.* Calcd for $C_{13}H_{13}NSe$: C, 59.55; H, 5.00; N, 5.35. Found: C, 59.43; H, 4.93; N, 5.17.

p-(N,N-Dimethylamino)benzyl Phenyl Selenide. Method A. *Via* **"Model Intermediate."**—To a chilled suspension of 12 g (0.05 mole) of N-*p*-(N′,N′-dimethylamino)benzyl-N-methylaniline in 25 ml of 95% alcohol was added 7.85 g (0.05 mole) of selenophenol, followed by 4.5 ml (0.05 mole) of concentrated hydrochloric acid (sp gr 1.19). After refluxing for 10 min the reaction mixture was made strongly basic with 10% sodium hydroxide. The crystalline solid was collected and washed with water (yield of crude product exceeded 95% of theory, mp 93–97°). Recrystallization from 200 ml of 95% alcohol gave 11 g (76% of theory) of colorless, columnar crystals, mp 99–101°. Its infrared spectrum showed no NH stretching bands but showed strong bands at 12.1 μ for a *para*-disubstituted benzene ring and strong bands at 13.5 and 14.5 μ for a monosubstituted benzene ring. The nmr spectra showed two sharp singlets at 169 and 242 cps, in addition to the characteristic aromatic bands indicated for the two previously described compounds. The area ratios were 6:2:9 in agreement with the formula for *p*-(N,N-dimethylamino)benzyl phenyl selenide. *Anal.* Calcd for $C_{15}H_{17}NSe$: C, 62.08; H, 5.91; N, 4.83. Found: C, 62.36; H, 5.83; N, 5.09.

Method B. Direct Condensation.—To a chilled solution of 7.85 g (0.05 mole) of selenophenol in 25 ml of 95% alcohol, was added in sequence 6.1 g (0.05 mole) of dimethylaniline, 3.85 ml (0.05 mole) of 37% formaldehyde, and 4.5 ml (0.05 mole) of concentrated hydrochloric acid (sp g 1.19). After refluxing for 60 min this reaction mixture was made basic. The oily layer was separated and when it did not crystallize on chilling the oil was washed with 95% alcohol to remove any unreacted dimethylaniline. The residue was acidified with hydrochloric acid and extracted with ether to remove any diphenyl diselenide and diphenyl selenide. The remaining residue was then made basic with 10% NaOH, extracted with ether, and the ether extract was dried over KOH pellets. Removal of the solvent gave about 1 g (7% of thoery) of a crystalline solid of mp 99–100°. Its infrared and nmr spectra were identical with those of the compound obtained by method A above.

Products from the Base-Catalyzed Chlorination of Phenol. A New Synthesis of (±)-Caldariomycin[1]

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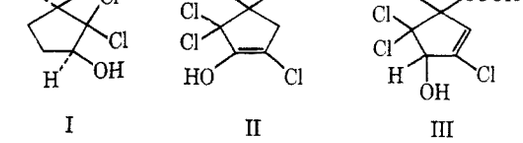
Chlorination of phenol or 2,4,6-trichlorophenol in cold, alkaline solution—a reaction first described by Hantzsch in 1887—is shown to yield 1,4-dihydroxy-3,5,5-trichloro-2-cyclopentene-1-carboxylic acid (III). Catalytic hydrogenation of this product, followed by treatment with lead tetraacetate and then with lithium borohydride, afforded a 5:1 mixture of the *cis* and *trans* isomers of 2,2-dichloro-1,3-cyclopentanediol, the latter being the racemic form of the mold metabolite caldariomycin (I). Structures of other transformation products of the acid III were also determined or confirmed.

Caldariomycin, one of the simplest known chlorine-containing mold metabolites, was first isolated in 1940 from *Caldariomyces fumago.*[3] Its properties and chemical behavior indicated it to be (+)-2,2-dichloro-*trans*-1,3-cyclopentanediol (I, or its mirror image). More recently, studies on its biosynthesis with labeled chlorine and carbon have been described,[4] along with a confirmatory total synthesis of racemic caldariomycin[5] based on the dichlorination of 1,3-cyclopentanedione and subsequent reduction to a mixture of the corresponding 2,2-dichloro-*cis*- and -*trans*-1,3-diols.



I II III

In our approach[1] to the synthesis of caldariomycin, introduction of the geminal chlorine atoms was planned for an earlier stage than in the route just cited. A search of the literature for an intermediate suitable for this purpose led to consideration of a compound formed by the base-catalyzed chlorination of phenol in a reac-

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