Anal. Calcd. for $C_{17}H_{18}O_4S$: C, 64.15; H, 5.66; neut. equiv., 318. Found: C, 64.08, 64.35; H, 5.63, 5.54; neut. equiv., 316.

KNOXVILLE, TENNESSEE

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Preparation of Some 10-Substituted Phenoxazines[1]

BY HENRY GILMAN AND LEONARD O. MOORE[2]

RECEIVED FEBRUARY 13, 1957

An improved procedure for the synthesis and purification of phenoxazine has been developed which is applicable to the preparation of larger amounts than previously reported. Several 10-alkyl- and 10-arylphenoxazines have been prepared. Iodine has been shown to have little, if any, catalytic activity in the preparation of 10-arylphenoxazines from aryl bromides.

In the study of the chemistry of phenoxazine it was desired to use variously 10-substituted compounds for comparison of substitution reactions and also to use the aryl derivatives for testing as solutes in liquid scintillators.[3]

Phenoxazine was made first by Bernthsen[4] in 1887, and, though known for many years, has not had a systematic study made of its chemistry. Oxazine dyes, which are derivatives of phenoxazine, are widely used at present as biological stains.[5] They have been studied for staining brain tumors,[6] and as tuberculostatic agents.[7] In general the reactions of phenoxazine which have been studied have related directly to these dyes. The majority of reactions studied have been cyclization, oxidation–reduction to oxazonium salts, and some substitution of the oxazonium compounds.

Related heterocycles containing an N–H bond have been used quite extensively in reactions to prepare N-substituted compounds. Carbazole[8] and phenothiazine[9] both have had various alkyl and aryl groups substituted for the hydrogen on the nitrogen. Relatively few N-substituted derivatives of phenoxazine have been prepared. Morris and Snyder[10] prepared several 10-sulfolanyl- and 10-sulfolenylphenoxazines from phenoxazine and various sulfolene compounds in a basic solution. All other 10-substituted phenoxazines have been prepared by cyclization. Some 10-benzyl derivatives[11] were prepared for testing as tuberculostatic agents; some 10-(nitrophenyl)-phenoxazines[12] and one 10-methyl derivative[13] were prepared in studies of a cyclization mechanism.

We have studied the preparation of phenoxazine, varying the methods reported in the literature.[14] The best method for large amounts is to heat an equimolar mixture of *o*-aminophenol and *o*-aminophenol hydrochloride, allowing the water produced to distil. The completion of the reaction can be determined by measuring the amount of water produced. The addition of sea sand to facilitate extraction of the mass decreased the yield as also did heating the reaction for an extended length of time. The purification by chromatography was much less tedious than the methods reported in the literature. This procedure consistently gave 26 to 30% of a relatively pure product in runs of 0.5 to 2.5 moles.

In light of the patent by Waterman and Vivian[15] as well as their articles[16] on the preparation of phenothiazines and carbazoles from aromatic nitro compounds, attempts were made to produce phenoxazine from *o*-nitrophenyl phenyl ether. Heating this ether with powdered iron or ferrous oxalate yielded no phenoxazine.

The alkyl phenoxazines were prepared in liquid ammonia using 10-phenoxazylsodium, prepared from sodium amide and phenoxazine, with an alkyl iodide or a benzyl chloride.[17] Phenoxazine, similar to carbazole, is not acidic enough to condense with ethyl iodide in a refluxing acetone solution of potassium hydroxide, as do nitrocarbazoles.[18]

---

(1) This work was supported in part by the United States Atomic Energy Commission under Contract No. AT(11-1)-59.

(2) Du Pont Teaching Fellow, 1956–1957.

(3) F. Newton Hayes, *Intern. J. Applied Radiation Isotopes*, **1**, 46 (1956). Evaluation of these compounds for scintillator activity is being made by Wright N. Langham, F. N. Hayes and D. G. Ott of the Los Alamos Scientific Laboratory who will report the results later.

(4) A. Bernthsen, *Ber.*, **20**, 942 (1887).

(5) For a discussion of oxazine dyes see H. A. Lubs, ed., "The Chemistry of Synthetic Dyes and Pigments," Reinhold Publ. Corp., New York, N. Y., 1955, p. 259; and K. Venkataraman, "The Chemistry of Synthetic Dyes," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 780.

(6) M. L. Crossley, P. F. Dreisbach, C. M. Hofmann and R. P. Parker, THIS JOURNAL, **74**, 573 (1952); M. L. Crossley, R. J. Turner, C. M. Hofmann, P. F. Dreisbach and R. P. Parker, *ibid.*, **74**, 578 (1952); M. L. Crossley, C. M. Hofmann and P. F. Dreisbach, *ibid.*, **74**, 584 (1952).

(7) R. A. Clapp, J. H. Clark, J. P. English, C. E. Fellows, R. E. Grotz and R. G. Shepherd, *ibid.*, **74**, 1989 (1952).

(8) See (a) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 70; (b) W. Freudenberg in R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 291; and (c) N. Campbell and B. M. Barclay, *Chem. Revs.*, **40**, 359 (1947), for reviews on carbazole. Also more recently (d) H. Gilman and J. B. Honeycutt, Jr., *J. Org. Chem.*, **21**, 226 (1957).

(9) S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).

(10) R. C. Morris and A. V. Snyder (to Shell Development Co.), U. S. Patent 2,530,070, Nov. 14, 1950; *C.A.*, **45**, 2983 (1951).

(11) B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499, 1504 (1953).

(12) K. C. Roberts and C. G. M. de Worms, *ibid.*, 1309 (1935).

(13) K. C. Roberts and H. B. Clark, *ibid.*, 1312 (1935).

(14) S. Granick, L. Michaelis and M. P. Schubert, THIS JOURNAL, **62**, 7802 (1940); see also F. Kehrmann and A. A. Niel, *Ber.*, **47**, 3102, 3107 (1914).

(15) H. C. Waterman and D. L. Vivian, U. S. Patent 2,292,808, Aug. 11, 1942; *C.A.*, **37**, 892 (1943).

(16) H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, **14**, 289 (1949); see also D. L. Vivian, J. L. Hartwell and H. C. Waterman, *ibid.*, **20**, 797 (1955), for other leading references.

(17) See refs. 9 and 10 for methods used for carbazole and phenothiazine.

(18) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

In the preparation of 10-ethylphenoxazine it was thought that perhaps 2,2′-dilithiodiphenyl ether[19] might react with ethyl dichloramide in the same way that other organometallic reagents do with haloamines[20] to give 10-ethylphenoxazine, but none of the desired product was obtained even though multiple fractional distillations were made in an attempt to isolate even a small amount.

The 10-aryl derivatives were prepared by heating phenoxazine and an aryl iodide or bromide with anhydrous potassium carbonate and a small amount of copper bronze powder as a catalyst. The aryl bromides required higher temperatures for reaction than did the aryl iodides, and even so did not usually give as good yields. Since iodine had been added in preparing some N-arylcarbazoles from aryl bromides, it was thought that perhaps iodine might act as a catalyst for the aryl bromides. But when 4,4′-dibromobiphenyl was heated with phenoxazine as described above with and without added iodine, it was found that the iodine had no observable effect on the yield. The effect of temperature, however, is very marked, since heating *p*-bromoiodobenzene with phenoxazine to 200° for 24 hr. gave a good yield of 10-(*p*-bromophenyl)-phenoxazine and no 1,4-bis-(10-phenoxazyl)-benzene; heating in the same manner except for a period of 30 min. at 300° gave 7% of the disubstituted compound.

Attempts to use nitrobenzene as a solvent were not successful. When used in the preparation of 10-phenylphenoxazine none of the expected product was found; in the preparation of 4,4′-bis-(10-phenoxazyl)-biphenyl only a 4% yield was obtained; and in the attempted preparation of 10-*p*-biphenylylphenoxazine an amino compound with a high nitrogen content was the only product isolated.

A comparison of the melting points of the derivatives prepared with the corresponding ones of carbazole and phenothiazine show no definite relationship but some trends. The methyl and ethyl derivatives melt much lower than those of the other heterocycles, but the benzyl and phenyl melt higher (see Table I).

TABLE I

MELTING POINTS OF N-SUBSTITUTED DERIVATIVES OF RELATED HETEROCYCLES, °C.

Substituted group	Phenothiazine[a]	Phenoxazine	Carbazole
H–	185	153–154	246–248
CH_3–	101–103	35–37	87[b]
CH_3CH_2–	103–104.5	46–47	70–72[b]
$C_6H_5CH_2$–	90–92	127.5–128	
C_6H_5–	94.5	138–139	91.5[b]
p-$C_6H_5C_6H_4$–		191–194	224–226[c]
Disub. *p*-C_6H_4–		249–250.5	320–322[c]
4,4′-$C_6H_4C_6H_4$–		339–342	282.5–284[c]

[a] See ref. 6 for references to these derivatives. [b] See ref. 8a for references to these derivatives. [c] See ref. 8d.

Experimental[21]

Phenoxazine.—In a 2-l. round-bottom flask with a three-hole cork, through which was inserted a nitrogen inlet tube, a thermometer, and a short tube leading to a distilling condenser, were mixed 500 g. (4.59 moles) of *o*-aminophenol and 185 ml. (2.23 mole) of concentrated hydrochloric acid. This mixture was heated in a slow stream of nitrogen and water distilled off, first at a mass temperature of 115° for 4.33 hours; then, as a fine white solid began to subline, the temperature rose slowly to 265° and was maintained at 265–290° for 4 hours or until the expected 180 ml. of water had distilled over. The mass was extracted with 1.5 l. of refluxing benzene for 48 hours and then with 1 l. more for 48 hours. The combined solution was chromatographed on a 50 × 450 mm. column of alumina with benzene as the eluent. There was collected 3 l. of solution which was distilled to 150 ml. and chilled. Filtration yielded 103 g. of light tan solid, m.p. 149–153°. From a fourth liter eluted there was obtained 7.1 g., m.p. 140–146°. The total represents a 26% yield. In several other runs, yields of 26 to 30% were obtained consistently. Sublimed white platelets had a m.p. 158–159°.

This compound formed a very dark green picrate, m.p. 141.5–142.0°.

Reaction of *o*-Nitrophenyl Phenyl Ether with Ferrous Oxalate.—In a 2-l. flask with air condenser 21.5 g. (0.1 mole) of *o*-nitrophenyl phenyl ether, 120 g. (0.40 mole) of ferrous oxalate dihydrate[22] and 250 g. of lead shot were heated to 370–400° for two hours.[23] Extraction by benzene and chromatography of the resulting solution on an alumina column with benzene as the eluent produced a red-brown oil, which was shown to be mainly *o*-nitrophenyl phenyl ether by the infrared spectrum.

Chromatography of a known mixture of phenoxazine and *o*-nitrophenyl phenyl ether with benzene showed that the *o*-nitrophenyl phenyl ether was the first eluted, but that the phenoxazine was washed off the column immediately after with only a relatively small amount of eluent.

Reaction of *o*-Nitrophenyl Phenyl Ether with Iron Powder.—In a thick wall flask with air condenser and solids trap at the top, were placed 200 g. of 20 mesh iron filings, 250 g. of hydrogen-reduced iron powder and 100 g. (0.47 mole) of *o*-nitrophenyl phenyl ether. These were heated slowly to 360° at which temperature fumes came off, first white then brown, with refluxing in the air condenser. Extraction with benzene and chromatography on an alumina column with benzene as eluent gave only red tars which could not be made to crystallize. The infrared spectrum indicated the presence of some N–H but had no other spectral bands indicative of phenoxazine. The major substance was the starting ether.

10-Ethylphenoxazine.—To 0.33 mole of sodium amide[24] in a 1-l. flask was added 54.96 g. (0.3 mole) of phenoxazine in small portions and this mixture stirred for 1 hour. Ethyl iodide (88.3 g., 0.57 mole) was added dropwise and the mixture allowed to stir while the ammonia evaporated. The residue was extracted with benzene, filtered and chromatographed on an alumina column. This gave a violet solution, from which the benzene was distilled and the residue distilled under reduced pressure, b.p. 138–143° (0.6 mm.). This gave 56.7 g. (89.4%) of a yellow liquid which solidified on chilling to give a yellow solid, m.p. 46–47°. If the liquid is not cooled below 20° nor seeded, then physical constants can be measured on the supercooled liquid, n^{25}_{D} 1.6445, d^{25}_{25} 1.1584; *MR* calcd. 63.6, found 66.0.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.65; N, 6.63. Found: C, 79.77, 79.79; H, 6.85, 6.96; N, 7.22, 7.15.

This compound formed a very dark green picrate, m.p. 93.5–94.0°.

The reaction of phenoxazine (9.16 g., 0.05 mole), ethyl iodide (14.7 g., 0.095 mole) and potassium hydroxide (5.7 g., 0.1 mole) in 250 ml. of refluxing acetone for 6 hours gave only phenoxazine (mixed melting point).

Reaction of 2,2′-Dilithiodiphenyl Ether with Ethyl Dichloramide.—To 0.17 mole of 2,2′-dilithiodiphenyl ether[19] in 1500 ml. of anhydrous ether was added with vigorous

---

[19] K. Oita and H. Gilman, THIS JOURNAL, **79**, 339 (1957).

[20] G. H. Coleman, *ibid.*, **55**, 3001 (1933); see also M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N.Y., 1954, pp. 1243–1248, for leading references.

[21] All melting points are uncorrected.

[22] W. Franke, *Ann.*, **491**, 30 (1931).

[23] Ferrous oxalate dehydrates at *ca.* 160° and decomposes above 300°; see P. L. Günther and H. Rehaag, *Z. anorg. allgem. Chem.*, **243**, 60 (1939).

[24] C. R. Hauser, F. W. Swamer and J. T. Adams, in R. Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc , New York, N.Y., 1954, p. 122.

stirring an ether solution of ethyl dichloramide.[25] After stirring for 72 hours, Color Test I[26] was negative and the mixture was hydrolyzed, the layers separated, and the ether layer washed with water and 10% sulfuric acid until a sample on neutralization failed to become turbid. The ether was distilled and the residue distilled three times under reduced pressure using the fraction boiling nearest to that expected for 10-ethylphenoxazine. Physical constants on the liquid obtained from the last distillation did not indicate any 10-ethylphenoxazine. Infrared spectra of the various fractions indicated the product of the reaction to be mainly diphenyl ether, with some ethylaminodiphenyl ether, since there were some bands for the N–H bond and for the ethyl group, though these were weak. Neutralization of the sulfuric acid solution gave only a small amount of brown tarry material.

10-Methylphenoxazine.—Using the method described for 10-ethylphenoxazine for a 0.05-mole run, there was obtained 7.0 g. (71%) of a yellow liquid, b.p. 151–154° (3.0 mm.), which solidified on chilling to give a yellow solid, m.p. 35–37°.

Anal. Calcd. for $C_{13}H_{11}NO$: N, 13.14. Found: N, 13.20, 13.21.

This compound formed a dark green picrate, m.p. 101–102°.

10-Benzylphenoxazine.—Using the same method described for 10-ethylphenoxazine for a 0.05-mole run, there was obtained on distillation of the eluted solution 5.5 g. (40%) of white crystals, m.p. 126.5–128.0°. Recrystallization from 95% ethanol gave an analytical sample, m.p. 127.5–128.0°.

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.54; N, 5.13. Found: C, 83.59, 83.30; H, 5.60, 5.72; N, 4.97, 5.02.

10-(*p*-Bromobenzyl)-phenoxazine.—Using the method described for 10-ethylphenoxazine for a 0.1-mole run, there was obtained on distillation of the eluted solution 8.0 g. (45.5%) of brown solid, melting range 73–111°. Recrystallization from petroleum ether (b.p. 60–70°) gave 3.49 g. of white needles, m.p. 113–114°.

Anal. Calcd. for $C_{19}H_{14}BrNO$: N, 3.98. Found: N, 4.25, 4.24.

10-Phenylphenoxazine.—In a 500-ml. flask were mixed 45.8 g. (0.25 mole) of phenoxazine, 68.3 g. (0.33 mole) of iodobenzene, 35 g. of potassium carbonate and 2.0 g. of copper bronze powder and this mixture heated to 200° for 48 hr. The mixture was extracted with 200 ml. of benzene, filtered and chilled to give 59.6 g. of white solid, m.p. 134.5–137.5°. Concentration of the filtrate gave 9.49 g. more of pale tan solid, m.p. 130–135°. This represents a crude yield of 81.5%. Recrystallization from benzene gave an analytical sample, m.p. 138–139°.

Anal. Calcd. for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.45; H, 5.13; N, 5.39.

10-(*o*-Bromophenyl)-phenoxazine.—*o*-Bromoiodobenzene was used in the procedure described for 10-phenylphenoxazine for a 0.05-mole run except that the reaction time was cut to 24 hr. The product was purified by chromatography on a column of alumina using benzene as the eluent. Concentration of the eluted solution gave 6.60 g. (39%) of light brown solid, melting range 159–187°, which was recrystallized from ethyl acetate to give 2.35 g. of white solid, m.p. 213–214°. Multiple recrystallizations gave an analytical sample, m.p. 214.5–215.5°.

Anal. Calcd. for $C_{18}H_{12}BrNO$: N, 4.14. Found: N, 4.21, 4.24.

10-(*p*-Bromophenyl)-phenoxazine.—Using the same method as described for the *o*-isomer, there was obtained 5.18 g. (61%) of a brown solid, m.p. 190–200°, which was recrystallized from benzene to give 2.63 g. of pale pink prisms, m.p. 200–202°.

Anal. Calcd. for $C_{18}H_{12}BrNO$: C, 63.92; H, 3.66; N, 4.14. Found: C, 63.96, 64.02; H, 3.53, 3.37; N, 3.83, 3.86.

The use of a higher temperature (same as above except for 30 min. at 300°) and addition of iodine gave 7% of *p*-bis-(10-phenoxazyl)-benzene.

10-(*p*-Biphenylyl)-phenoxazine. Method A.—This compound was prepared in the same manner as 10-phenylphenoxazine in a 0.03-mole run using 4-iodobiphenyl. The mass was extracted with benzene, concentrated to 75 ml. and chilled to give a tarry solid, m.p. 180–186°, which was recrystallized from toluene to give 4.38 g. (43.5%) of yellow needles, m.p. 191.5–193.0°. Further recrystallization raised the melting point to 191.5–194.0°.

Anal. Calcd. for $C_{24}H_{17}NO$: N, 4.18. Found: N, 4.23, 4.24.

Method B. (Attempted).—The use of 4-bromobiphenyl in the reaction as described for 9-(*p*-biphenylyl)-carbazole[8d] gave 0.38 g. (5%) of a white solid, m.p. 217–236°, which was recrystallized from benzene to give 0.16 g., m.p. 255.5–256.2°, of a product containing 8.14% nitrogen. This corresponds very nearly to an aniline-10-(*p*-biphenylyl)-phenoxazine. The infrared spectrum of this compound has bands for an N–H bond, and bands very similar to those of 10-(*p*-biphenylyl)-phenoxazine.

***p*-Bis-(10-phenoxazyl)-benzene.**—Using the procedure as for 10-(*o*-bromophenyl)-phenoxazine but substituting *p*-diiodobenzene for *p*-bromoiodobenzene, for a 0.02-mole run, there was obtained 10.05 g. (100%) of a tan solid, m.p. 215–240°, which was recrystallized several times from benzene to give only 17% of white needles, m.p. 249.0–250.5°.

Anal. Calcd. for $C_{30}H_{20}N_2O_2$: N, 6.36. Found: N, 6.38, 6.51.

4,4′-Bis-(10-phenoxazyl)-biphenyl.—In a 200-ml. flask 5.04 g. (0.0275 mole) of phenoxazine, 3.90 g. (0.0125 mole) of 4,4′-dibromobiphenyl, 7.6 g. of anhydrous potassium carbonate and 0.5 g. of copper bronze powder were heated to 300° for 23 hours. The mass was extracted with hot benzene, then with hot water and the water solution and solid were washed with benzene. The total of 175 ml. of benzene solution was chromatographed on a 35 × 350 mm. column of alumina using benzene as the eluent. There was collected 150 ml. of a forerun then 1000 ml. of yellow solution. Distillation of solvent and chilling gave 2.13 g. (33%) of pale yellow crystals, m.p. 332.0–335.5°.

In a second run, identical with the above except that 0.75 g. of iodine was added as a possible catalyst, there was obtained 2.09 g. (32.4%) of pale yellow crystals, m.p. 332.5–336.0°. The iodine appears to have no catalytic activity in this reaction.

Recrystallization of an analytical sample from benzene gave a solid, m.p. 339–342°.

Anal. Calcd. for $C_{36}H_{24}N_2O_2$: N, 5.42. Found: N, 5.30, 5.29.

Acknowledgment.—We are indebted to R. McCord and E. Miller Layton of the Ames Laboratory of the Atomic Energy Commission for assistance in the infrared spectra determinations.

AMES, IOWA

---

(25) Prepared by the method of G. H. Coleman, THIS JOURNAL, **55**, 3001 (1933). Attempts to use the method of J. Tscherniak, *Ber.*, **9**, 146 (1876), resulted in a vigorous, nearly explosive reaction.

(26) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).