from ethanol yielded colorless prisms (0.21 g., 72.4%) which after several recrystallizations, melted at 99–100°, reported m.p. 84°.[5]

*Anal.* Calcd. for $C_{20}H_{17}Cl$: C, 82.04; H, 5.85; Cl, 12.11. Found: C, 81.79; H, 5.95; Cl, 12.17.

A mixture of III (0.1 g.) and 10% ethanolic potassium hydroxide (2 ml.) was refluxed on a water-bath for 2 hours. Then the reaction mixture was poured into water (20 ml.) and kept overnight in a refrigerator. The precipitate recrystallized from methanol as colorless prisms which were identified as triphenylethylene, m.p. 69–71°, reported m.p. 69–70°.[6]

Although 1,1,2-triphenyl-1-chloroethane is converted to triphenylethylene by heating for 5 hours with pyridine,[7] III was recovered unchanged after this treatment.

A mixture of II (0.27 g.), phosphorus trichloride (0.1 g.) and benzene (1 ml.) was heated under reflux for 3 hours. After cooling, the benzene layer was washed with water, dried over calcium chloride and evaporated to dryness. The resinous residue was treated with methanol to give a halogen-free, crystalline product (m.p. 65–66.5°) which showed no depression of the melting point on admixture with authentic triphenylethylene

**1-*p*-Anisyl-2,2-diphenylethanol (IV).**—IV was prepared from the corresponding *p*-methoxy ketone[8] as described for II; a satisfactory yield (83.3%) was obtained when twice the amount of sodium borohydride was used. The crude product was recrystallized from hot benzene to give colorless prisms (m.p. 160–161°) which were sparingly soluble in benzene, alcohol and glacial acetic acid.

*Anal.* Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62; mol. wt., 304.4. Found: C, 83.06; H, 6.48; mol. wt. (Rast), 308.6.

The acetate of IV separated as colorless platelets from glacial acetic acid; m.p. 121–123°.

*Anal.* Calcd. for $C_{23}H_{22}O_3$: C, 79.75; H, 6.36. Found: C, 80.03; H, 6.32.

The treatment of IV in glacial acetic acid with bromine (1 molar equivalent) yielded a bromine-containing compound which crystallized from methanol as almost colorless prisms, m.p. 128–129°; Carter, *et al.*,[9] reported that 1-*p*-anisyl-2,2-diphenylbromoethylene melted at 130°.

**4-Methoxybenzil.**—4-Methoxydesoxybenzoin (11.3 g., 0.05 mole) and selenium dioxide (7.5 g., 0.067 mole) in pyridine (15 ml.) were heated at 100° for 1 hour, and at 120° for another 2 hours with occasional stirring. After cooling, the selenium (4 g.) was filtered and washed with ethanol (10 ml.). The filtrate and washings were poured into water (300 ml.), and the yellowish precipitate collected and washed with water; yield 11.6 g. (96.7%). After crystallization from benzene–petroleum ether, it melted at 64–65°, reported m.p. 62–63°.[10,11]

*p*-Methoxybenzilic acid[12] was obtained by the benzilic acid rearrangement of 4-methoxybenzil; yield 90%.

***p*-Anisylphenylacetic Acid (V).**—A mixture of *p*-methoxybenzilic acid (5.2 g., 0.02 mole), stannous chloride hydrate (15 g., 0.066 mole), concentrated hydrochloric acid (30 ml.) and glacial acetic acid (40 ml.) was stirred for 2 hours at 30°, and then for 10 minutes at 70°. The mixture, when cool, was poured into water (400 ml.) and kept overnight in a refrigerator. The resulting crystals, yield 4.6 g. (94.7%), were recrystallized from benzene–petroleum ether; m.p. 104–105°, reported m.p. 100°.[13] V is very soluble in glacial acetic acid, benzene and ethanol, sparingly in hot water and insoluble in ligroin.

*Anal.* Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.16; H, 5.42.

**Diphenylacetic acid** was prepared from benzilic acid as described above; yield 90%.

**Action of Phosphorus Trichloride on *p*-Anisylphenylacetic Acid (V).**—A mixture of V (1.45 g., 0.0060 mole), phosphorus trichloride (0.5 g., 0.0036 mole) and benzene (3 ml.) was refluxed over a water-bath for 3 hours and then cooled. The benzene solution was decanted and the benzene and excess phosphorus chloride distilled, leaving a brown oily residue which was thought to be the acid chloride. A solution of this residue in benzene–petroleum ether, on standing in a refrigerator for 2 months, gradually deposited crystals (0.5 g.); this was accompanied by the faint evolution of hydrogen chloride. The colorless platelets (m.p. 120–121°) obtained by several recrystallizations from benzene–petroleum ether gave a negative Beilstein test for chlorine and analytical data corresponding to those of the acid anhydride. Upon hydrolysis with ethanolic potassium hydroxide, the starting acid was recovered quantitatively.

*Anal.* Calcd. for $C_{30}H_{26}O_5$: C, 75.10; H, 5.58; mol. wt., 466.5. Found: C, 75.18; H, 5.18; mol. wt. (Rast), 477.5.

After standing for a few days at room temperature, a mixture of the oily acid chloride and concentrated aqueous ammonia solidified. Crystallization from hot benzene gave the colorless amide as prisms, m.p. 136–137°.

*Anal.* Calcd. for $C_{15}H_{15}O_2N$: N, 5.81. Found: N, 5.86.

Our attempts to prepare α-phenyldesoxyanisoin by the condensation of the oily acid chloride with anisole in the presence of aluminum chloride or stannic chloride yielded a glassy resin from which no compound could be isolated chromatographically.

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## Synthesis of 2,3-Bis-(β-Hydroxyethoxyethoxy)-dioxane

BY C. O. OBENLAND AND B. B. SCHAEFFER

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The synthesis and physical properties of a series of chlorophenoxyethoxyethanols from polychlorobenzenes has been reported recently from this Laboratory.[1] An analogous reaction has been applied now to the preparation of β-hydroxyethoxy derivatives of dioxane by the reaction of 2,3-dichlorodioxane with the sodium salts of glycols.

The reaction of 2,3-dichlorodioxane and ethylene glycol in equimolar quantities has been reported by Boeseken.[2,3] Hexahydro-*p*-dioxino[b]-*p*-dioxin was the main product.

In the present study using an excess of diethylene glycol at 60°, 2,3-bis-(β-hydroxyethoxyethoxy)-dioxane was obtained in 39% yield. This was confirmed in a second experiment at 70° from which a 35% yield of this compound was obtained. Although ethylene, triethylene and thiodiethylene glycols reacted with 2,3-dichlorodioxane under similar conditions, products of definite composition were not isolated from these respective reaction mixtures by distillation.

### Experimental

**2,3-Bis-(β-hydroxyethoxyethoxy)-dioxane.**—Ten moles (1061 g.) of diethylene glycol was placed in a three-liter 3-necked flask and heated to 80° and 46 g. of sodium metal

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then was added in small portions. During addition, the temperature rose to 130° and the mixture turned dark brown. When all the sodium had reacted, the mixture was cooled to 55° and one mole (157.1 g.) of 2,3-dichlorodioxane was added dropwise. After this addition, the mixture was heated to 55–60° for five hours and then filtered. Distillation of the dark filtrate at 20 mm. yielded 787 g. of unreacted diethylene glycol and 269 g. of residue as a black oil. This residue was filtered to remove suspended solids and the filtrate distilled, yielding 115.5 g. (39%) of amber oil, b.p. 214–224° (2 mm.), $n^{25}D$ 1.4730.

*Anal.* Calcd. for $C_{12}H_{24}O_8$: OH, 11.5; mol. wt., 296. Found: OH, 11.1; mol. wt., 277.

Hydroxyl value was determined by acetylation of a sample with acetic anhydride, and titration of the liberated acid with a standard base.

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## The Synthesis of 4-Hydroxy-6-quinaldine Carbohydrazide[1,2]

BY CHIN-TZU PENG AND T. C. DANIELS

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The antituberculous activity of isonicotinic acid hydrazide and its related compounds[3] coupled with the knowledge that 4-hydroxyquinoline and 4-hydroxy-3-quinolinecarboxylic acid shows mild tuberculostatic activity[4] prompted a study of the influence of an acid hydrazino group in the 6-position of the quinaldine nucleus. For this purpose, 4-hydroxy-6-quinaldine carbohydrazide was prepared.

6-Cyano-4-methoxyquinaldine was obtained using a modification of the Sandmeyer synthesis[5] by treating the neutralized diazonium salt solution of 6-amino-4-methoxyquinaldine with cuprous cyanide. The cyano compound, like many other aromatic nitriles, was resistant to hydrolysis. The ordinary procedures, such as refluxing with concentrated sulfuric acid and absolute ethanol or reaction with methanol and dry hydrogen chloride, failed to effect the conversion of the nitrile into the corresponding acid ester. Refluxing with 90% sulfuric acid for 2 hours and subsequent treatment with sodium nitrite[6] yielded a mixture from which the desired product could not be isolated. The hydrolysis was accomplished by heating with 15% potassium hydroxide in glycerol at 150–170° for 9 hours. A concomitant demethylation occurred. Comparison of the ultraviolet absorption spectra revealed a closer structural resemblance of the acid to 4-hydroxyquinoline than to 4-methylquinoline.[7] The spectrum of 6-cyano-4-methoxyquinaldine shows a marked similarity to that of 4-methoxyquinoline but differs from the spectrum of the acid or its ester. The observed demethylation may be explained on the basis of an electron deficiency at $C_4$ of the quinoline ring which facilitates the nucleophilic substitution by the OH group.

The reactivity of the $C_4$-position toward nucleophilic reagents is evident from the amination reactions of 4,7-dichloroquinoline[8] and 4,6-dichloroquinaldine[9] in which it is reported that only the chlorine in the 4-position was replaced by the amino group.

The unusually high melting point (above 300°) of 4-hydroxy-6-quinaldinecarboxylic acid together with its insolubility in non-polar solvents suggested the probable existence of the acid in the form of a zwitterion. Unfortunately, the insolubility of the compound in dioxane precluded the measurement of its dipole moment. The acid reacted with ferric chloride to give a very faintly brownish-yellow color in aqueous solution, behaving much like carbostyril in this respect.

4-Hydroxy-6-quinaldine carbohydrazide was tested against *Mycobacterium tuberculosis* H37Rv according to the method of Fisher[10] and was found to be inactive.[11] The intermediates, when screened for their antibacterial activity, failed to inhibit the visible growth of *Escherichia coli*, *Micrococcus pyogenes* var. *aureus*, *Bacillus megatherium* and *Pseudomonas aeruginosa* at the concentration of 0.2 mg. per ml.

### Experimental[12]

**6-Cyano-4-methoxyquinaldine.**—The nitrile was prepared from the corresponding amino derivative[13] by the procedure of Clarke and Read.[5] After the reaction was complete the solution was extracted successively with 100-ml. portions of chloroform. A small amount of alcohol was effective in overcoming the persistent emulsion which formed during the extraction. The combined chloroform extract was washed, dried over anhydrous sodium sulfate and concentrated to a volume of 30 to 50 ml. by distillation. Addition of petroleum ether precipitated the nitrile as buff-colored solid. The crude compound was decolorized with Darco and recrystallized from 50% ethanol to give 12 g. (60%) of product melting at 162–165° (uncor.).

6-Cyano-4-methoxyquinaldine was found to be very soluble in chloroform, ethanol and methanol, soluble in ether, sparingly soluble in benzene, and insoluble in cold water. The analytically pure compound, obtained by recrystallization from 75% methanol, appeared as colorless thin hairs which melted at 172–173°; $\lambda\lambda_{max}^{EtOH}$: 321.5 mμ (log ε 3.30), 294 (3.92), 287.5 (3.92), 238 (4.89); $\lambda\lambda_{min}^{EtOH}$: 319 (3.25), 256 (3.54).

*Anal.* Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09. Found: C, 72.92; H, 5.54.

**Hydrolysis of 6-Cyano-4-methoxyquinaldine.**—Fifteen grams (0.076 mole) of 6-cyano-4-methoxyquinaldine was

(1) Abstracted from a thesis submitted by C. T. Peng in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Chemistry, June, 1953.

(2) Presented in summary under the heading, "The Synthesis of Some 6-Substituted Amido Derivatives of 4-Aminoquinaldine and a Study of Their *in Vitro* Antibacterial Activity" before the Division of Medicinal Chemistry at the 123rd National Meeting of the American Chemical Society at Los Angeles, Calif., March, 1953.

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