obtained, b.p. 106–107°/1.0–1.8 mm., $n^{23}D$ 1.5558, 21.6 g. (55%); this was redistilled to provide an analytical sample, b.p. 90°/0.25 mm., $n^{23}D$ 1.5550.

Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16. Found: C, 60.88; H, 6.14.

o-Methylmercaptobenzoic Acid, Isopropyl Ester.—To 19.62 g. (0.1 mole) of *o*-mercaptobenzoic acid isopropyl ester was added 40 ml. of 10% solution of sodium hydroxide (0.1 mole); the oil dissolved and the resulting solution solidified on cooling. To this cold solid was added 13.8 g. (0.11 mole) of methyl sulfate. The reaction was exothermic and a water-insoluble oil was obtained. The reaction mixture was heated in a steam bath for approximately 15 min.; the oil was extracted with ether and the ether solution was dried and then concentrated under reduced pressure to give a crude product, $n^{24}D$ 1.5569; 20.95 g. (99%); a sample of this was distilled to provide an analytical sample, b.p. 136°/1.2 mm., $n^{23}D$ 1.5598.

2-Methanesulfonylbenzoic Acid, Isopropyl Ester.—To the solution of 10.5 g. (0.05 mole) of 2-methylmercaptobenzoic acid isopropyl ester in 25 ml. of glacial acetic acid was added 6.25 g. of 30% hydrogen peroxide, keeping the temperature at 10°. The mixture warmed up to 40–50° and was kept at this temperature during the addition of another 6.25 g. of 30% hydrogen peroxide. The mixture was heated at 70–100° for 1 hr. and then concentrated under reduced pressure. A yellow oil was obtained which crystallized on cooling and was recrystallized from ethanol–water, m.p. 86–88°, 8 g. (69%). After drying, the melting point of the analytical sample was 98–100°.

Anal. Calcd. for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82. Found: C, 54.83; H, 5.97.

Syntheses of 1-Aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazines Involving Addition of Alkyl Halides to Substituted Epoxides

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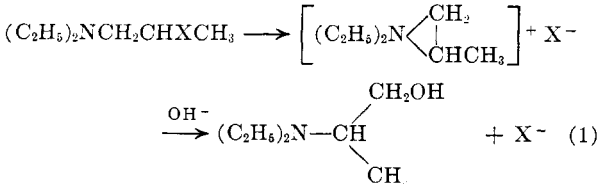
Received September 7, 1961

The syntheses of 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazines by the reaction of benzhydryl chloride (or bromide) with 1,2-epoxy-3-methoxypropane followed by aminolysis of the resulting 1-halo-2-benzhydryloxy-3-methoxypropane with the appropriate 1-arylpiperazine have been accomplished. These are the first reported examples of this series and are the first instances of the addition of an alkyl halide to a substituted epoxide under mild experimental conditions.

The pharmacological activities of the piperazines, amino ethers, and benzhydryloxy compounds are well recognized. The amino ethers, particularly those of the ethanolamine series, have been used successfully as antihistamines. Their usefulness seems to be enhanced by the introduction of a benzhydryloxy group.[1] In recent years there has been a widespread interest in disubstituted piperazines with respect to their effect on the central nervous system. Among other examples of especially effective compounds to combat hypertension and hypertensive encephalopathy are the 1-aryl-4-(2-methoxyethyl)piperazines and 1-aryl-4-(3-methoxypropyl)piperazines.[2] The interest in the synthesis of 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl) piperazines is, therefore, readily apparent.

Attempts to prepare these ethers from the sodium salt of 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine were unsuccessful. Alternatively, benzhydryl ethers may be prepared by the reaction of benzhydrol or its sodium salt with the appropriate halogen derivative.[3] However, it has been shown that, in the preparation and reaction of β-haloamines of this type, rearrangement through an intermediate ethylenimmonium ion occurs as indicated in equation 1.[4]



(1) (a) Robert F. Doerge, *Am. Profess. Pharmacist*, **18**, 1103 (1952). (b) George Rieveschl, Jr., U. S. Patent 2,421,714 (1947).

(2) G. m. b. H. Nordmarke-Werke, British Patent 813,473 (1958).

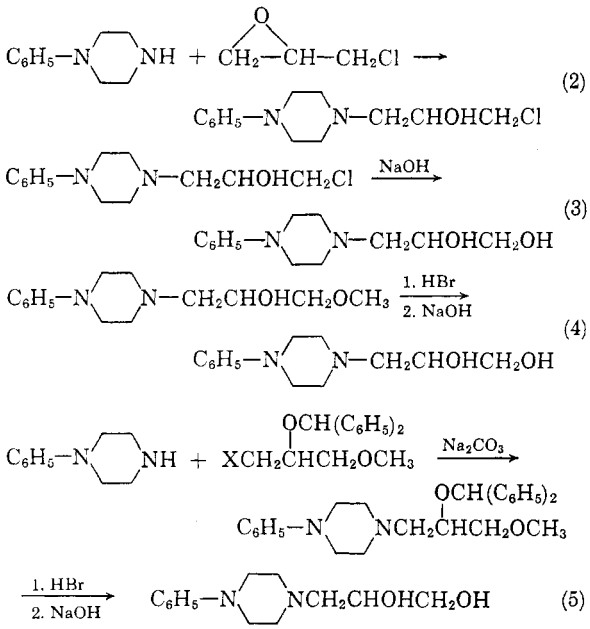
(3) Yoshi Uyeno *et al.*, Japanese Patent 1529 (1959).

Therefore, another synthetic route was required. Investigation of various possibilities resulted in the discovery that the reaction of the benzhydryl halide with 1,2-epoxy-3-methoxypropane yields 1-halo-2-benzhydryloxy-3-methoxypropane. Further, it was found that this intermediate reacts with the appropriate piperazine to give the desired benzhydryl ether derivative of the substituted piperazine.

Proof that this benzhydryl ether derivative of the substituted piperazine was indeed 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazine could be obtained by showing it to be the same product as that obtained from the reaction of benzhydryl halide with the sodium salt of 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine. However, an attempt to effect the latter reaction resulted in a product whose infrared spectrum showed that it was not the desired benzhydryl ether.

Consequently, the following series of reactions was carried out to give substantial proof of the structures proposed for the halo-intermediates and for the products of their reactions with 1-aryl-piperazines:

(4) (a) S. D. Doss, *J. Am. Chem. Soc.*, **69**, 2982 (1947); (b) R. H. Reitsems, *J. Am. Chem. Soc.*, **71**, 2041 (1949).



Reaction 2 was established by carrying out the reaction to obtain the indicated product and by taking into consideration the established fact that the reaction of such epoxides as epichlorohydrin with secondary amines yield the corresponding secondary alcohol.[5-8]

The same solid product (m.p. 106.5–107.5°) was obtained from reactions 3, 4, and 5. The glycol indicated as the product in the above reactions is the only product which would be expected from reaction 3. Since the products from 3 and 4 were the same, it must be concluded that reaction 4 occurs as indicated. We may therefore conclude that the formation of a secondary bromide intermediate and subsequently an ethylenimmonium ion as described in reaction 1 does not occur. Since no such rearrangement occurs in reaction 4, it appears improbable that it would occur in reaction 5. Therefore, the indicated structure for the benzhydryl ether derivative of 1-phenylpiperazine produced in reaction 5 is probably correct. Pollard has shown that no rearrangement occurs in the displacement of halogen from similar halo-compounds by 1-phenylpiperazine.[8] We may reasonably assume then that the identification of the halo intermediates as 1-halo-2-benzhydryloxy-3-methoxypropane is also correct.

It is recognized that allyl halides do not generally react with epoxides. The only reports of reactions of this type have referred to the addition of methyl iodide, ethyl iodide, ethyl bromide, and propyl bromide to cyclohexene epoxide[9] and of the addition of benzhydryl bromide to ethylene oxide.[10] These reactions were carried out under forcing conditions in sealed tubes. There has been no report of the addition of any alkyl chloride to an epoxide. In contrast, we are able to report the addition of both benzhydryl chloride and bromide to 1,2-epoxy-3-methoxypropane under the relatively mild conditions of moderate temperature and atmospheric pressure. Furthermore, the less reactive and relatively inexpensive benzhydryl chloride can be made to undergo the reaction with excellent yields of the desired ether. In the preparation of derivatives from compounds having a reactive hydrogen, the production of hydrogen chloride instead of hydrogen bromide as a by-product potentially has less tendency to enter into side reactions with the product molecule. Therefore, benzhydryl chloride is in some respects a more desirable halogen intermediate than is benzhydryl bromide.

Changes were observed in the infrared spectrum of 1-halo-2-benzhydryloxy-3-methoxypropane upon long standing of this material in air in a screw-cap bottle. Unless stored under an inert atmosphere, the reagent became contaminated with products showing infrared absorption at 2.8, 5.8, and 6.0 μ which is the region usually attributed to hydroxyl and carbonyl groups.

The mixture gave a positive ferric hydroxamate test for an ester and partial separation gave a fraction whose infrared spectrum was very similar to that of benzophenone. The presence of both these products could be accounted for by the formation and decomposition of an intermediate hydroperoxide.

Experimental[11]

The synthesis of the benzhydryl ethers of the 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazines was accomplished by the preparation of 1-halo-2-benzhydryloxy-3-methoxypropane and reaction of this intermediate with the appropriate *N*-substituted piperazine. Two such ethers have been prepared. The 1-halo-2-benzhydryloxy-3-methoxypropane was prepared by the reaction of benzhydryl halide with 1,2-epoxy-3-methoxypropane.

The preparation of 1-bromo-2-benzhydryloxy-3-methoxypropane in heptane solution is described below. It was also prepared in 60% yield in the same manner (except that the reaction time was cut to 3.5 hr.) as that described for the preparation of 1-chloro-2-benzhydryloxy-3-methoxypropane.

1-Bromo-2-benzhydryloxy-3-methoxypropane.—A stirred solution of benzhydryl bromide (0.1 mole) in heptane (100 ml.) was warmed to 75–80° and 1,2-epoxy-3-methoxypropane (0.11 mole) was added dropwise through an addition funnel. After complete addition, the solution was refluxed for 1.5 hr. The solvent and lower boiling components were removed by distillation at atmospheric pressure and the residue distilled to give 48% yield of product, b.p. 147–150° at 0.1–0.2 mm.

(5) D. R. Boyd and A. S. Knowlton, *J. Chem. Soc.*, 1803 (1909).
(6) D. R. Boyd, *J. Chem. Soc.*, 1791 (1910).
(7) S. J. Castro and C. R. Noller, *J. Am. Chem. Soc.*, **68**, 203 (1946).
(8) C. B. Pollard and T. H. Wicker, U. S. Patent 2,575,122 (1950).
(9) Pierre Bedos, *Compt. rend.*, **183**, 562 (1926).
(10) Yoshiyuki Yonemoto, Japanese Patent 1711 (1951).

(11) All melting points and boiling points are uncorrected. Benzhydryl bromide and benzhydryl chloride were obtained commercially from the Aldrich Chemical Co., Inc., and the Eastman Kodak Co., respectively. *N*-Phenylpiperazine was purchased from the Chemapuro Manufacturing Corp. and 1,2-epoxy-3-methoxypropane from Peninsular ChemResearch, Inc. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Anal. Calcd. for $C_{17}H_{19}BrO_2$: C, 60.90; H, 5.71; Br, 23.84. Found: C, 60.88; H, 5.92; Br, 23.82.

1-Chloro-2-benzhydryloxy-3-methoxypropane.—1,2-Epoxy-3-methoxypropane (0.68 mole) and redistilled benzhydryl chloride (0.33 mole, b.p. 97° at 0.2 mm.) were put in a 300 ml., three-neck, round bottom flask equipped with an inlet tube, thermometer, condenser, and outlet tube. The system was flushed with nitrogen, a bubble-counter attached to the outlet tube, and the flow rate adjusted to maintain a slight positive pressure. When the temperature had been raised to approximately 90°, and 0.5 ml. of water was added. The mixture was stirred under nitrogen at a temperature of 115° to 125° for 4 days. The product was cooled under nitrogen at a slightly increased flow rate. The excess epoxide was partially removed by distillation at atmospheric pressure. The residue was distilled bulb-to-bulb to give 78% yield of crude 1-chloro-2-benzhydryloxy-3-methoxypropane, b.p. 138–144° at 0.2 mm. On cooling to room temperature, the distillation residue (14%) partially solidified. The addition of methanol facilitated crystallization and subsequent filtration. The melting point and NMR spectrum indicated that the product thus obtained was dibenzhydryl ether. The crude 1-chloro-2-benzhydryloxy-3-methoxypropane was redistilled at 125–126° at 0.1 mm., through a 6-in. Vigreux column.

Anal. Calcd. for $C_{17}H_{19}ClO_2$: C, 70.21; H, 6.59; Cl, 12.19. Found: C, 70.47; H, 6.77; Cl, 12.06.

Preparation of 1-Aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazines.—*N*-Phenylpiperazine (0.1 mole) and sodium carbonate (0.1 mole) were heated with stirring for about 0.5 hr. at 100° to 135°. The mixture was cooled to approximately room temperature and 1-chloro-2-benzhydryloxy-3-methoxypropane (0.1 mole) was added dropwise. The mixture was then heated at 115–125° with stirring for several hours. The solids were removed by filtration, dissolved in aqueous alkali, and extracted with ether. The dried ether layer was combined with the filtrate and evaporated on the steam bath. The residue failed to crystallize on cooling. Additional *N*-phenylpiperazine (0.1 mole) was added and the mixture was heated on the steam bath. Needles began to form almost immediately. The heating was continued with occasional shaking for about 12 hr. The product was then thoroughly mixed with ether, filtered, and the ether evaporated on the steam bath. The excess phenylpiperazine was removed by distillation under vacuum and the residue was poured into methanol. Ether was added until the product precipitated as crystals rather than an oil when cooled. The yield was 34% and upon recrystallization from a methanol–ether solution, the product melted at 63.5–65°.

Anal. Calcd. for $C_{27}H_{32}N_2O_2$: C, 77.84; H, 7.74; N, 6.73. Found: C, 77.77; H, 7.73; N, 6.53. The monohydrochloride melted at 141°. Neut. equiv.: calcd., 453; found, 458.

1-*p*-Chlorophenyl-4-(2-benzhydryloxy-3-methoxypropyl)-piperazine was similarly prepared from *N*-*p*-chlorophenylpiperazine and 1-bromo-2-benzhydryloxy-3-methoxypropane. The yield was 70% and when recrystallized from a methanol–ether solution the product melted at 89–89.5°.

Anal. Calcd. for $C_{27}H_{31}ClN_2O_2$: C, 71.90; H, 6.93; N, 6.21. Found: C, 72.94; H, 7.00; N, 6.04.

Ether Cleavage of 1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine with Hydrobromic Acid.—1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine (0.008 mole) was dissolved in 40% aqueous hydrobromic acid (50 ml.) and heated to boiling. Solid sodium hydroxide was added until the solution was basic. The solution was extracted with ether and the extract was dried and evaporated on the steam bath. A solid product was obtained and recrystallized from benzene–heptene solution, m.p. 106.5–107.5°. If the product is assumed to be 1-phenyl-4-(2,3-dihydroxypropyl)piperazine, the yield was 53%.

Ether Cleavage of 1-Phenyl-4-(2-benzhydryloxy-3-methoxypropyl)piperazine with Hydrobromic Acid.—1-Phenyl-4-(2-benzhydryloxy-3-methoxypropyl)piperazine (0.005 mole) was treated with 40% aqueous hydrobromic acid (50 ml.) using the same procedure described immediately above. Assuming the product also to be the same, the yield was 27%, m.p. 106.5–107.5°.

Reaction of 1-Phenyl-4-(2-hydroxy-3-chloropropyl)piperazine with Aqueous Sodium Hydroxide.—An unweighed amount of 1-phenyl-4-(2-hydroxy-3-chloropropyl)piperazine was refluxed several hours in 25% aqueous sodium hydroxide. The oil layer was removed, dissolved in benzene, and extracted several times with water. The water extracts were combined and extracted once with benzene. The benzene solution was dried and the benzene removed by evaporation on the steam bath. The residue crystallized upon cooling. The crude product melted 103–105°.

A mixture of the products obtained from the above three reactions failed to show a depression in melting point. The infrared spectrum of the product was consistent with its identification as 1-phenyl-4-(2,3-dihydroxypropyl)piperazine.

Preparation of 1-Phenyl-4-(2-hydroxy-3-chloropropyl)-piperazine.—Epichlorohydrin (0.25 mole) was added slowly to an ethereal solution of *N*-phenylpiperazine (0.25 mole) at room temperature. The mixture was stirred for about 24 hr. and the solid reaction product removed by filtration; yield 77%, recrystallized from ether, m.p. 63.5–64.5°.

Anal. Calcd. for $C_{13}H_{19}ClN_2O$: C, 61.28; H, 7.51; N, 10.89. Found: C, 61.46; H, 7.40; N, 11.24.

Amino Acid Derivatives of Kojic Acid

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Received November 20, 1961

An extension of our study on physiologically active derivatives from kojic acid, 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one, has led to the preparation of several new derivatives of the latter from amino acids with the substituents entering position 6 of kojic acid. Some amino acids were found to be unreactive.

The present work represents a continuation of our interest in preparing and investigating kojic acid derivatives which might have some potential physiological activity. A group of amino derivatives of kojic acid was discussed in a previous article[1] from this laboratory.

(1) G. O'Brien, J. M. Patterson, and J. R. Meadow, *J. Org. Chem.*, **25**, 86 (1960).