reported as a degradation product of neomycin A. Our previously proposed empirical formula[1] of $C_6H_{12-14}N_2O_3$ for neamine appeared, from the molecular weight data, to represent the molecular formula. Unless the cyclohexane degradation product arises merely from racemization or rearrangement, the molecular weight data are anomalous and the molecular formula of neamine would now appear to be a multiple of C_6.

Experimental

Crystalline Neomycin A.—A 15.9-mg. sample of neomycin A hydrochloride[3] was suspended in 1 ml. of commercial methanol and the mixture was saturated with ammonia gas. The neomycin A hydrochloride dissolved completely in the ammoniacal methanol and after standing at room temperature for thirty minutes, neomycin A free base crystallized. The crystals were collected on a filter stick and washed twice with 0.5-ml. portions of methanol. The dried crystals weighed 8.0 mg. The compound decomposed in a capillary tube at 256° and showed no depression in the decomposition point when mixed with neamine.

Neamine Hydrochloride.—A 100-mg. sample of crystalline neamine prepared as described previously[1] was dissolved in 10 ml. of water and titrated to *p*H 4.5 with *N* hydrochloric acid. The solution was freeze-dried to give a quantitative yield of neamine hydrochloride.

Hydrolysis of Neamine with 48% Hydrobromic Acid.—A 5.0-g. sample of neamine was dissolved in 150 ml. of 48% hydrobromic acid and heated under reflux for 18 hours. The reaction mixture became colored rather quickly. The solution was evaporated *in vacuo* to dryness, 50 ml. of water was added and again evaporated to dryness. This process was repeated twice to insure complete removal of the excess hydrobromic acid. The residue was treated with 50 ml. of boiling methanol and filtered. The methanol insoluble fraction weighed 4.59 g. It was dissolved in 50 ml. of water, treated with 10 g. of Darco G-60, filtered and the solution concentrated *in vacuo* until crystals appeared. After refrigerating overnight, the crystals were collected, washed with 0.5 ml. of ice water and dried to yield approximately 2.5 g. of crystals. These crystals decompose at 280° (micro-block) and show no optical activity.

Anal. Calcd. for $C_6H_{14}N_2O_3 \cdot 2HBr$: C, 22.24; H, 4.98; N, 8.65; Br, 49.33, eq. wt., 162. Found: C, 22.58; H, 4.95; N, 8.64; Br, 48.58, eq. wt., 156.

The analytical data for this product are in good agreement with those calculated for the dihydrobromide of 1,3-diamino-4,5,6-trihydroxycyclohexane which has been reported by Kuehl, *et al.*,[5] to be a degradation product of neomycin A.

The methanolic extract of the hydrolysate above yielded a small amount of ammonium bromide and other unidentified degradation products.

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Preparation of Anhydrous Alcohol

BY HAKON LUND

RECEIVED MARCH 5, 1952

The method of Lund and Bjerrum[1] for the preparation of absolute alcohol by means of magnesium seems now to be in general use and is described in several books on organic syntheses[2] in the original form using iodine as a catalyst for the initiation of the reaction. It might be useful to point out that small amounts of aliphatic halogen compounds are better catalysts than iodine.[3] If traces of the halogen compound are harmless in the alcohol obtained, chloroform or carbon tetrachloride may serve, but when halogen compounds have to be strictly excluded ethyl bromide can be used. In that case the catalyst is removed with the first few cc. of the distillate.

AARHUS, DENMARK

(1) Lund and Bjerrum *Ber.*, **64**, 210 (1931).

(2) For instance L. F. Fieser, "Experiments in Organic Chemistry," and David A. Shirley, "Preparation of Organic Intermediates."

(3) *Ber.*, **37**, 936 (1934).

Reaction of Vanillin and Its Derived Compounds. XV.[1] 3-Ethoxy-4-hydroxybenzoic Acid and Some of Its Esters.[2]

BY IRWIN A. PEARL AND DONALD L. BEYER

RECEIVED JANUARY 16, 1952

The treatment of disseminated histoplasmosis with ethyl vanillate has been reported recently by Christie, Middleton, Peterson, and McVicker.[3] These investigators found that ethyl vanillate is the only known effective therapeutic agent for disseminated and progressive histoplasmosis, but that the margin between effective therapeutic levels and those which produce toxic manifestations is only about 25 to 30%, a margin of safety too small for a desirable therapeutic agent. These results led to the investigation of the effect of changes in the ethyl vanillate molecule on the therapeutic activity of the compound. The present paper reports the preparation of the related 3-ethoxy-4-hydroxybenzoic acid and representative esters prepared therefrom.

Larsson[4] has recently prepared 3-ethoxy-4-hydroxybenzoic acid from the corresponding aldehyde by a number of different procedures. We have now prepared it by the oxidation of 3-ethoxy-4-hydroxybenzaldehyde with silver oxide in aqueous alkaline solution. The low temperature caustic fusion procedure used so successfully for the preparation of vanillic acid from vanillin[5] when applied to ethylvanillin yielded only protocatechuic acid and unchanged ethylvanillin indicating that, under the conditions of caustic fusion, the ethoxyl group of ethylvanillin is more susceptible to dealkylation than is the aldehyde group to oxidation.

The desire to derive 3-ethoxy-4-hydroxybenzoic acid from our basic raw material, vanillin, led to a study of its preparation from protocatechuic acid, a compound easily prepared by caustic fusion of vanillin at temperatures above 240°.[5] Following the procedure employed by Bertram[6] for the preparation of vanillin from protocatechualdehyde, ethyl protocatechuate was treated with one mole of ethyl bromide and two moles of potassium carbonate in boiling ethanol. In addition to the desired ethyl 3-ethoxy-4-hydroxybenzoate, chromatographic separation of the reaction product yielded the ethyl

(1) For paper XIV of this series, see THIS JOURNAL, **74**, 1357 (1952).

(2) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(3) A. Christie, J. G. Middleton, J. C. Peterson and D. L. McVicker, *Pediatrics*, **7**, 7 (1951).

(4) E. Larsson, *Trans. Chalmers Univ. Technol. Gothenberg*, No. **59**, 21 (1947).

(5) I. A. Pearl, THIS JOURNAL, **68**, 2180 (1946).

(6) J. Bertram, German Patent 63,007 (Aug. 19, 1890); *Ber.*, **25**, R823 (1892).