Measurements and Results.—The heat content measurements were made with previously described[3] apparatus and techniques. The substances were enclosed during the measurements in platinum–rhodium capsules. Corrections for the heat contents of these capsules were determined by separate experiments. The results are expressed in defined calories (1 cal. = 4.1833 int. joules), and molecular weights accord with the 1949 International Atomic Weights.

The measured heat content data are listed in Table I. The precision uncertainty, considering all the measurements for each substance, is less than 0.1%, although an occasional determination may deviate from a smooth curve by as much as 0.5%. Both substances show regular behavior, there being no evidence of any transformation or region of anomalous heat capacity. The heat content of the orthotitanate, the heat content of the dititanate is less than the sum for the metatitanate and rutile by 6.4% at 400°K., and greater than this sum by 1.7% at 1800°K. No previous high temperature heat content data for either the orthotitanate or dititanate were found in the literature.

TABLE I

HEAT CONTENTS ABOVE 298.16°K. (CAL./MOLE)

T, °K.	$H_T - H_{298.16}$	T, °K.	$H_T - H_{298.16}$	T, °K.	$H_T - H_{298.16}$
Mg_2TiO_4 (mol. wt. 160.54)					
392.4	3,080	1086.6	31,260	1197.9	36,420
493.9	6,780	1092.1	31,590	1286.8	40,490
592.6	10,560	1092.7	31,410	1286.8	40,550
695.3	14,640	1097.9	31,910	1295.4	41,000
789.2	18,500	1106.5	32,260	1392.1	45,650
894.8	22,910	1109.8	32,420	1490.4	50,290
999.3	27,370	1113.1	32,420	1597.2	55,400
1004.7	27,530	1113.6	32,610	1705.9	60,750
1006.0	27,550	1114.0	32,530	1792.4	64,860
1027.8	28,670	1124.6	33,050	1817.8	66.510
1074.2	30,700				
$MgTi_2O_5$ (mol. wt. 200.12)					
396.8	3,650	901.9	26,330	1389.5	50,910
492.7	7,590	998.8	30,950	1500.5	56,920
587.8	11,750	1084.4	35,120	1601.9	62,440
695.5	16,660	1182.4	40,050	1696.2	67,790
795.0	21,190	1287.9	45,440	1812.1	74,160

TABLE II

HEAT CONTENTS (CAL./MOLE) AND ENTROPIES (CAL./DEG. MOLE) ABOVE 298.16°K.

	Mg_2TiO_4		$MgTi_2O_5$	
T, °K.	$H_T - H_{298.16}$	$S_T - S_{298.16}$	$H_T - H_{298.16}$	$S_T - S_{298.16}$
400	3,340	9.61	3,780	10.87
500	6,990	17.74	7,910	20.08
600	10,850	24.77	12,290	28.06
700	14,840	30.92	16,830	35.06
800	18,930	36.38	21,470	41.25
900	23,120	41.31	26,200	46.82
1000	27,430	45.86	31,010	51.89
1100	31,910	50.13	35,910	56.56
1200	36,510	54.13	40,930	60.92
1300	41,200	57.88	46,090	65.05
1400	45,960	61.41	51,410	69.00
1500	50,760	64.72	56,850	72.75
1600	55,600	67.84	62,370	76.31
1700	60,470	70.79	67,940	79.68
1800	65,370	73.59	73,530	82.88

(3) K. K. Kelley, B. F. Naylor and C. H. Shomate, U. S. Bur. Mines Tech. Paper, 686 (1946).

Table II contains heat content and entropy increments above 298.16°K. at even 100° intervals, for use by those who prefer the tabular method of thermodynamic calculations. The entropy increments have been calculated to match the heat contents by the method of Kelley.[4]

The heat contents are represented, to within the average deviation indicated in parentheses, by the equations

Mg_2TiO_4: $H_T - H_{298.16} = 35.96T + 4.27 \times 10^{-3}T^2 + 6.89 \times 10^5T^{-1} - 13{,}412$; (298 – 1800°K.; 0.3%)

$MgTi_2O_5$: $H_T - H_{298.16} = 40.68T + 4.60 \times 10^{-3}T^2 + 7.35 \times 10^5T^{-1} - 15{,}003$; (298 – 1800°K.; 0.3%)

(4) K. K. Kelley, *U. S. Bur. Mines Bull.*, 476 (1949).

MINERALS THERMODYNAMIC BRANCH
REGION III, BUREAU OF MINES
UNITED STATES DEPARTMENT OF THE INTERIOR
BERKELEY 4, CALIFORNIA

The Identity of Neamine and Neomycin A

BY BYRON E. LEACH AND CHARLOTTE M. TEETERS

RECEIVED FEBRUARY 11, 1952

The hydrolysis of the antibiotic neomycin with mineral acid yields a crystalline biologically active base which has been named neamine.[1] Peck and co-workers[2] had previously reported the isolation of neomycin A hydrochloride from the fermentation broths of *Streptomyces fradiae*. An exchange of samples with Dr. R. L. Peck[3] has revealed that neamine is identical with neomycin A.

Neomycin A hydrochloride was converted to the free base and crystallized from ammoniacal methanol. The melting point was 256° (dec.), and showed no depression in melting point when mixed with neamine. The infrared absorption spectra, measured in liquid petrolatum (Nujol) suspension, of the hydrochloride and the crystalline free base of neomycin A were identical with neamine hydrochloride and its crystalline free base, respectively. Paper chromatograms using wet *n*-butanol containing 2% *p*-toluenesulfonic acid monohydrate[4] and also *n*-butanol–acetic acid–water (2:1:1) systems showed no differences in R_f values for these two substances; the slopes of the *B. subtilis* bioassay curves were also identical.

Hydrolysis of neamine with boiling 48% hydrobromic acid yielded the hydrobromide of an optically inactive base. The analytical data obtained for this compound are in good agreement with those calculated for the dihydrobromide of 1,3-diamino-4,5,6-trihydroxycyclohexane which Kuehl, *et al.*,[5]

(1) B. E. Leach and C. M. Teeters, THIS JOURNAL, **73**, 2794 (1951).

(2) R. L. Peck, C. E. Hoffhine, Jr., P. Gale and K. Folkers, *ibid.*, **71**, 2590 (1949).

(3) We are grateful to Dr. R. L. Peck, Research Laboratories, Merck and Co., Rahway, N. J., for the sample of neomycin A hydrochloride.

(4) D. H. Peterson and L. M. Reineke, THIS JOURNAL, **72**, 3598 (1950).

(5) F. A. Kuehl, Jr., M. N. Bishop and K. Folkers, *ibid.*, **73**, 881 (1951).

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.

RESEARCH LABORATORIES
THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

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).