

Thus the 3-ketone has been enol-acetylated as expected, while the dimethylacetal at C-21 has been cleaved and replaced by a diacetate,⁵ under the strongly acidic acetylating conditions.

Experimental⁶

21,21-Dimethoxy-4-pregnen-3,11,20-trione (I) from Cortisone.—One hundred milligrams of cortisone was dissolved in 10 ml. of methanol and treated with 0.25 ml. of acetyl chloride (equiv. to 1% HCl in the solution). The mixture was allowed to stand at room temperature for 18 hours and then was neutralized by the addition of aqueous potassium acetate solution. The mixture was concentrated to give a precipitate which was collected and dried *in vacuo*, weight 0.07 g., m.p. 145–150°. Recrystallization from isopropyl alcohol gave 30 mg. of 21,21-dimethoxy-4-pregnen-3,11,20-trione, m.p. 160–162°, ϵ_{\max} 15,600 at 236 μ (EtOH), $[\alpha]_D^{25} +211.4^\circ$ (acetone). The infrared spectrum (Nujol mull) showed peaks at 5.85 μ (C₁₁ and C₂₀ carbonyl), 5.96 μ (C₃ carbonyl), 6.16 μ (Δ^4) and 9.04 μ (C–O–C), and was identical with that of material obtained by the same procedure from cortisone acetate.

21,21-Dimethoxypregnan-3,11,20-trione (II).—Two grams of pregnan-17 α ,21-diol-3,11,20-trione 21-acetate was suspended in 100 ml. of absolute methanol. To this was cautiously added 2.5 ml. of acetyl chloride. The mixture was warmed to dissolve the solid and allowed to stand 20 hours. Thereupon the clear solution was treated with 4 g. of potassium acetate in water and evaporated to dryness *in vacuo*. Upon crystallization from isopropyl alcohol and heptane, the residue gave 21,21-dimethoxy-pregnan-3,11,20-trione, m.p. 131–132.4°, $[\alpha]_D^{25} +107.8^\circ$ (dioxane). *Anal.* Calcd. for C₂₉H₃₄O₅: C, 70.74; H, 8.78. Found: C, 70.90; H, 8.84. The infrared absorption spectrum (Nujol mull) showed carbonyl peaks at 5.78 and 5.88 μ and a strong C–O–C peak at 9.15 μ .

3,5-Pregnadiene-3,21,21-triol-11,20-dione Triacetate (III).—One gram of 21,21-dimethoxy-4-pregnene-3,11,20-trione (I) was dissolved in 4 ml. of acetic anhydride and treated with 5 mg. of *p*-toluenesulfonic acid. The mixture was refluxed for 30 minutes and chilled to give crystals which were collected and washed with cold methanol, weight 0.28 g., m.p. 170–176°, E_{\max} 385 at 231 μ (EtOH). Crystallization from isopropyl alcohol gave the triacetate, m.p. 176.5–179°, $[\alpha]_D^{25} +3.4^\circ$ (dioxane).

The infrared spectrum (Nujol mull) showed the following bands: 5.67 and 5.75 μ (21-acetate-20-carbonyl interaction), 5.88 (11-carbonyl), 5.98 and 6.09 ($\Delta^{4,5}$ -diene), 8.21 (C–O–C of acetate and enol acetate). *Anal.* Calcd. for C₂₇H₃₄O₈: C, 66.65; H, 7.04. Found: C, 66.89; H, 7.11.

Dilution of the mother liquor with aqueous methanol gave 0.55 g. of crude enol acetate, m.p. 160–172°, showing the same ultraviolet spectrum as above.

(5) Cf. W. Schulz, *Ber.*, **85**, 249 (1952).

(6) All melting points are corrected. $E_{1\text{cm}}^{1\%} = (1/cd) \log I_0/I$; $\epsilon = E \times M.W./10$. Analyses and optical data were obtained by the Microanalytical and Physical Chemical Departments of this Laboratory.

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The Heat of Combustion of Lanthanum¹

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Introduction.—The literature^{2–6} values for the heat of formation of lanthanum oxide, like most

(1) This work was performed under the auspices of the A. E. C.

(2) W. Muthmann and L. Weiss, *Ann.*, **331**, 1 (1904).

(3) W. A. Roth, U. Wolf and O. Fritz, *Z. Elektrochem.*, **46**, 42 (1940).

(4) J. E. Moose and S. W. Parr, *THIS JOURNAL*, **46**, 2656 (1924).

(5) F. R. Bichowsky and F. D. Rossini, "The Thermochemistry of the Chemical Substances," 1936, p. 337.

(6) L. Brewer, "The Thermodynamics of the Rare Earth Oxides," UCRL-1931, September, 1952.

of the rare earths, show wide variations. The discrepancies are probably due to the use of impure lanthanum metal. This paper reports the results of burning very pure lanthanum in oxygen to determine the heat of formation of the oxide.

Method.—The method involves the determination of the heat evolved from burning a weighed sample of the metal in an oxygen bomb calorimeter at 25 atmospheres pressure. The energy equivalent of the calorimeter was determined from the heat of combustion of standard benzoic acid and also was determined electrically. The completeness of combustion was determined by treating the combustion products with 6 *N* hydrochloric acid and measuring the amount of hydrogen evolved from any unburned metal present.

The uncertainties given are twice the corresponding standard deviations.

Results are expressed both in absolute joules and in defined calories; 1 defined calorie = 4.1840 absolute joules.

Apparatus.—Details of the construction and calibration of the calorimeter have been described.⁷ The energy equivalent of the calorimeter was 10,096 \pm 3.1 joules/degree.

Lanthanum Metal.—The lanthanum metal was supplied by Dr. F. H. Spedding of the Ames Laboratory of the A. E. C. This metal was analyzed with the following results: Na, 0.005%; Mg, 0.005%; Ca, 0.005%; C, 0.006%; N, 0.0075%; H, 0.001%; O, 0.061%. Any other metallic impurities were present in amounts too small to be detected by the spectroscopic method used. A Debye X-ray pattern showed lines only of α -lanthanum.

Combustion of Lanthanum.—The lanthanum was burned as chunks on sintered discs of 98% pure La₂O₃ supported on a platinum platform weighing 103.8 g. Two new discs were used for each run. They were formed by pressing the lanthanum oxide with an added 2.5% beeswax in a steel die. Ignition was carried out at 1200° for eight hours in air after which the discs were removed at 100° to a desiccator to prevent absorption of water. No lanthanum carbide is believed to be formed during this process since the discs when treated with 6 *N* HCl, evolve no gas and dissolution is complete. Pure magnesium fuse wire was used. The heat of combustion was taken as 24,667 joules/g.⁷ The amount varied from 0.0053 to 0.0056 g. The formation of a double oxide MgO·La₂O₃ from the two oxides is possible. The heat of formation of such an oxide is probably not great, and since only a small fraction of the total magnesium is close to the lanthanum metal and because the amount of magnesium is not large, a correction would probably be very small. Correction was made for the electrical energy used in igniting the wire. The total energy equivalent of the calorimeter and contents was used, taking into account the discs, the platinum, and the difference between the La₂O₃ formed and the oxygen used. The completeness of combustion of the lanthanum varied from 99.97 to 100.00%. The initial temperature was 24.6° and the average final temperature was 25.9°. The results are summarized in Table I.

TABLE I
COMBUSTION OF LANTHANUM

Mass La, g.	ΔT , °C.	Total energy, abs. joules	Energy from La, abs. joules/g.	Deviation, abs. joules/g.
2.1274	1.3626	13801.0	6414.7	2.5
2.0694	1.3247	13415.2	6413.8	1.6
2.0351	1.3035	13199.8	6413.2	1.0
1.9492 ₅	1.2477	12640.1	6410.0	2.2
2.0533	1.3143	13312.8	6409.5	2.7
			Av. 6412.2	2.0

2 \times standard deviation = 2.1

(7) C. E. Holley, Jr., and E. J. Huber, Jr., *THIS JOURNAL*, **73**, 5577 (1951).

The value in the table for the heat of combustion of lanthanum metal as used must be corrected for the impurities present. If it is assumed that the oxygen is present as La_2O_3 , that the nitrogen is present as LaN which burns to $\text{N}_2\text{O}_5(\text{s})$ and La_2O_3 , that the carbon exists as free graphite which burns to CO_2 , and that the other impurities are negligible, the corrected value for the heat of combustion of lanthanum is found to be 6439.2 joules/g. Actually the carbon probably exists as lanthanum carbide, but the heat of formation of this compound is not available. Essentially we are taking its heat of formation as zero. For the small amount of carbon present this does not introduce an error of any consequence.

The uncertainty to be attached to this value must include the uncertainty in the energy equivalent. When this is included the value becomes 6439.2 ± 2.9 joules/g. There are small additional unknown uncertainties due to the corrections for the impurities.

Composition of the Lanthanum Oxide.—The La_2O_3 formed was tan in color. A Debye X-ray pattern showed only lines of hexagonal La_2O_3 . Analysis by the "active oxygen" method of Barthauer and Pearce⁸ gave a formula of $\text{La}_2\text{O}_{3.001}$. This analysis was made on run No. 2 in which the combustion was assumed to be complete.

Heat of Formation of La_2O_3 .—The heat of combustion reported above gives, for the reaction in the bomb, a value of $\Delta E_{24.6}^\circ = -1789.1 \pm 0.8$ kjoules/mole. The correction of this value to 25° is less than the uncertainty in the result. To obtain the heat of formation it is necessary to correct for the deviation of oxygen from the perfect gas law and to convert from ΔE to ΔH . Using Rossini and Frandsen's⁹ value of $(\partial\Delta E/\partial P)_{301^\circ\text{K}} = -6.51$ joules/atm./mole for oxygen and taking $\Delta H = \Delta E + \Delta(PV)$, we have for the heat of formation of La_2O_3 , $\Delta H_{25}^\circ = -1793.1 \pm 0.8$ kjoules/mole. In defined calories this is -428.57 ± 0.19 kcal./mole. This value differs by about 6.4% from the value of -458 kcal./mole selected by the National Bureau of Standards.¹⁰

Acknowledgments.—The authors are appreciative of the courtesy of Dr. F. H. Spedding of the Ames Laboratory, A. E. C., through whom the lanthanum metal was obtained. They also wish to express their appreciation of the valuable assistance of F. H. Ellinger, R. D. Gardner, O. R. Simi, E. Cramer and W. G. Smiley in performing most of the analytical work.

(8) G. L. Barthauer and D. W. Pearce, *Ind. Eng. Chem.*, **18**, 479 (1946).

(9) F. D. Rossini and M. Frandsen, *J. Research Natl. Bur. Standards*, **9**, 733 (1932).

(10) Selected Values of Chemical Thermodynamic Properties, N. B. S. Circular 500, 1952, p. 351.

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The Isolation of Desacetylneoprotoveratrine from *Veratrum Viride* Ait.

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A further investigation of the more hydrophilic ester alkaloids of *Veratrum viride* Ait. has resulted in the isolation of a new hypotensively active triester, desacetylneoprotoveratrine; m.p. 182–183°, $[\alpha]_{24}^{\text{D}} -9.6 \pm 2$ (c 1.0 in py.). Mild alkaline hydrolysis afforded protoverine, acetic acid, (levo) α -methylbutyric acid and α -methyl- α,β -dihydroxybutyric acid. On the basis of the hydrolysis products and analytical data, the empirical formula $\text{C}_{39}\text{H}_{61}\text{O}_{14}\text{N}$ was established.

Except for the absence of an acetyl group, it seemed probable that the new ester was structur-

ally identical with neoprotoveratrine.¹ A similar relationship has been demonstrated in the germin ester series (germitrine \rightarrow germerine,² neogermitrine \rightarrow germidine,³ germanitrine \rightarrow germanidine⁴) where in each case a labile acetyl group is lost upon subjecting the triester to methanolysis. For this reason, neoprotoveratrine was treated with methanol and a compound was obtained which proved to be identical with the triester, desacetylneoprotoveratrine, isolated directly. The ease with which the acetyl group was removed from neoprotoveratrine suggests the possibility that desacetylneoprotoveratrine may be of secondary rather than primary origin.

Pharmacology.⁵—The hypotensive activity of desacetylneoprotoveratrine was found to be 1.0 μg . [0.72 – 1.64].⁶

Experimental⁸

Countercurrent Separation of the "Amorphous Bases" of *Veratrum Viride* Ait.—The amorphous bases (30 g.) remaining after the removal of protoveratrine and neoprotoveratrine as described in our previous publication⁴ were subjected to an 8-plate Craig countercurrent distribution using benzene–2 M acetate buffer pH 5.5 (1500 ml. per phase, lower phase moving). The material recovered from tube 8 (6.4 g.) was then distributed on a 24-plate countercurrent machine using benzene–2 M acetate buffer pH 6.9 (450 ml. per phase, lower phase moving).

Desacetylneoprotoveratrine.—The material recovered from tubes 22–24 (2.25 g.) was dissolved in benzene with heating. On standing, desacetylneoprotoveratrine separated as clusters of needles (0.7 g.); m.p. 182–183° (vac.), $[\alpha]_{24}^{\text{D}} -9.6 \pm 2$ (c 1.0 in py.), $+9.8 \pm 2$ (c 0.89 in CHCl_3). For analysis the sample was dried at 120° (2 mm.) to constant weight.

Anal. Calcd. for $\text{C}_{39}\text{H}_{61}\text{O}_{14}\text{N}$: C, 61.00; H, 8.01; N, 1.83; equiv. wt., 767.89. Found: C, 60.47; H, 8.40; N, 1.76; equiv. wt., 777.

In a volatile acid determination 8.185 mg. required 2.01 ml. of 0.01 N $\text{Na}_2\text{S}_2\text{O}_3$ or 1.87 equivalents.⁹

Hydrolytic Cleavage of Desacetylneoprotoveratrine to Protoverine, Acetic Acid, (levo)- α -Methylbutyric Acid¹⁰ and α -Methyl- α,β -dihydroxybutyric Acid.—Desacetylneoprotoveratrine (0.48 g.) was hydrolyzed in the same manner as that reported for neoprotoveratrine,⁴ yielding protoverine,¹¹ m.p. 193°; $[\alpha]_{24}^{\text{D}} -16.2 \pm 2$ (c 1.03 py.). On admixture with an authentic sample of protoverine, no melting point depression was observed.

The acid fraction when treated in the same manner as re-

(1) M. W. Klohs, R. Arons, M. D. Draper, F. Keller, S. Koster, W. Malesh and F. J. Petracek, *THIS JOURNAL*, **74**, 5107 (1952).

(2) Josef Fried, Howard L. White and O. Wintersteiner, *ibid.*, **72**, 4621 (1950).

(3) J. Fried, P. Numerof and N. H. Coy, *ibid.*, **74**, 3041 (1952).

(4) M. W. Klohs, M. D. Draper, F. Keller, S. Koster, W. Malesh and F. J. Petracek, *ibid.*, **74**, 4473 (1952).

(5) The pharmacological tests were carried out under the supervision of Dr. R. O. Bauer of the Riker pharmacology section.

(6) Expressed as micrograms per kilogram of anesthetized dog per minute required for a 10-minute intravenous infusion to lower the mean arterial blood pressure 30% when administered according to a previously described assay procedure.⁷ The bracketed numbers express the 95% confidence limits.

(7) George L. Maison and J. W. Stutzman, *Arch. Intern. Pharmacodynamic*, **85**, 357 (1951).

(8) All melting points are corrected. We are indebted to Dr. Adalbert Elek for the micro analyses and to C. H. Stimmel for equivalent weight determinations.

(9) It has previously been shown⁴ that α -methyl- α,β -dihydroxybutyric acid is non-volatile under the conditions of the volatile acid determination.

(10) The specific rotation of the volatile acids from desacetylneoprotoveratrine indicated the presence of one mole of (levo) α -methylbutyric acid.

(11) By hydrolyzing for longer periods of time, isoprotoverine rather than protoverine was obtained.