

Fig. 1.—The oxidation of calcium at 330, 350, 385 and 435°; parabolic plot.

The oxide that forms initially is dark colored and appears to adhere to the metal. For that reason and because the ratio of volumes of oxide to metal is so close to unity the author felt that the initial portion of the oxidation curve might be parabolic. The present study shows that such is the case.

Experimental

The method was the same as that used previously in this Laboratory.³ For the rapid oxidations a 500-cc. bulb was added to the system outside the furnace. The sample was a cube approximately 1 cm. on edge of electrolytic calcium, 99% pure, obtained from the A. D. Mackay Co., New York. Before each oxidation, the sample was abraded under carbon tetrachloride with 2/0 emery paper. The samples were heated for 100 min. *in vacuo* before oxygen was admitted to start the reaction.

Results and Discussion

The oxidation was studied for 100 min. from 330 to 475° at 20 cm. oxygen pressure. Typical oxidation curves are shown in Figs. 1 and 2. The curves obtained from 330 to 435° are shown in Fig. 1 on a parabolic plot. The oxidations below 435° obeyed the parabolic law for at least 100 min. At 435° the curve was not parabolic beyond the first five minutes.

The results above 425° are shown in Fig. 2. The oxidations had an induction period followed by a rapid rise to an approximately linear shape after about 50 min. The induction period presumably corresponds to the formation of the first,

(3) D. Cubicciotti, *THIS JOURNAL*, to be published.

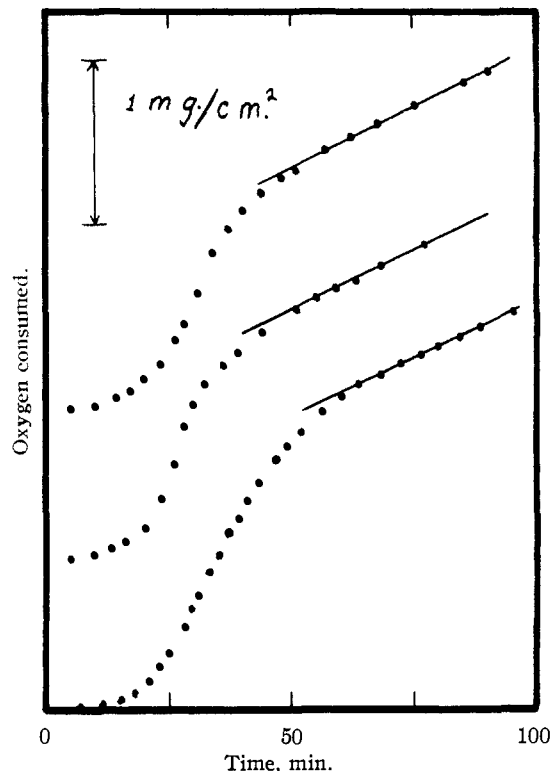


Fig. 2.—The oxidation of calcium at 425, 460 and 475°.

adherent film. The linear portion is expected since the volume ratio is less than unity. However it is difficult to understand the sudden rise in the curves.

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Cactus Alkaloids. II. Condensation of Mescaline with Formaldehyde by the Eschweiler-Clarke Reaction

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In previous work in this Laboratory¹ a tetrahydroisoquinoline base was obtained in an attempt to synthesize trichocereine, *i.e.*, N-dimethylmescaline, by methylation of mescaline with formic acid-formaldehyde. This base has now been characterized as N-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline. It is a new compound related to the *anhalonium* alkaloids, and can be expected to occur in nature, since it may be derived from anhaline by an N-methylation or from anhalidine by an O-methylation.

Only one reference to cyclization during the Eschweiler-Clarke reaction with phenethylamines has been found in the literature,² though the cyclizing action of formaldehyde with the aid of a

(1) L. Reti and J. A. Castrillón, *THIS JOURNAL*, **73**, 1767 (1951).

(2) J. S. Buck and R. Baltzy, *ibid.*, **64**, 2263 (1942), report that attempts to prepare 3,4-dimethoxyphenethylbenzylmethylamine from benzylhomoveratrylamine by this method, gave unsatisfactory results, probably owing to partial cyclization.

condensing agent such as hydrochloric acid is well known. In this particular case it can be explained by the presence of methoxyl groups in positions 3 and 5 which activate the 6-position in the ring. It must be remembered that phenethylamine,³ hordenine⁴ and 2,5-dimethoxyphenethylamine⁵ give the dimethyl tertiary amines in good yields.

The usual technique has been followed⁶ and after alkalization and extraction with ether, a new base was obtained in a 51% yield. Under more drastic conditions the yield was increased to 80%.

The base was isolated as its hydrochloride which was not identical with that of trichocereine. Since the structure of this last compound is well established, this fact suggested that the reaction had led to a tetrahydroisoquinoline derivative.

A definite proof was provided by the oxidation of the hydrochloride which gave N-methyl-3,4,5-trimethoxyphthalimide, identical with a synthetic sample.⁷

Experimental

Pure mescaline (1.95 g.), 97.5% by weight formic acid (2.20 g.) and 40% "formalin" (1.53 ml.) were heated on the steam-bath for 12 hours. The reaction mixture was diluted with 70 ml. of water and strongly alkalinized with 20 ml. of 20% sodium hydroxide solution. After 4 extractions with ether the aqueous solution was exhausted of alkaloid. The collected extracts were dried over anhydrous sodium sulfate and the ether removed. An oily, slightly yellowish base (1.12 g.) was obtained (yield 51.2%).

It was taken up in 18 ml. of acetone, filtered and 0.45 ml. of concentrated hydrochloric acid added. On cooling to 0° and scratching, a colorless hydrochloride crystallized. It was collected, washed three times with 5 ml. of cold acetone and dried, weight 0.67 g. A second crop of less pure hydrochloride was obtained from the mother liquors. The first crop was recrystallized twice from absolute alcohol, m.p. 215–216° (cor.); mixed with trichocereine hydrochloride m.p. 180°.

Anal. Calcd. for C₁₃H₁₉O₃N·HCl: C, 57.03; H, 7.36; OCH₃, 34.01; CH₃, 22.0. Found: C, 57.04; H, 7.49; OCH₃, 33.81; CH₃, 22.5.

Another experiment was carried out with a mixture of mescaline (0.86 g.), 93% in weight formic acid (1.81 g.) and 40% "formalin" (1 ml.) which was refluxed for eight hours in the oil-bath. Under these conditions 0.77 g. of the base was obtained (79.7%).

Methiodide.—The free base (0.19 g.), prepared from the hydrochloride, was dissolved in acetone (2 ml.) and methyl iodide added (0.1 ml.). A spontaneous exothermic reaction followed, and after 24 hours standing, the methiodide was filtered and washed 6 times with 1 ml. of acetone each time. Dry, it weighed 0.25 g., m.p. 210° (cor.). After three recrystallizations from alcohol a constant m.p. 215° (cor.), in agreement with that given by Späth,⁸ (211.5–212.5°) who prepared this compound from anhalinine, was reached.

(3) R. N. Icke, B. B. Wisegarver and G. A. Alles, "Organic Syntheses," Vol. XXV, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 89.

(4) Y. Raoul, *Compt. rend.*, **204**, 74 (1937).

(5) B. Baltzly and J. S. Buck, *THIS JOURNAL*, **62**, 161 (1940). Dr. R. Baltzly, in a private communication, kindly revealed to us the conditions used in their work, which were essentially those of Eschweiler (heating with formalin in a bomb). The Eschweiler-Clarke was tried by Baltzly and Buck on β -(2,5-dimethoxyphenyl)-propylamine and was found to give a product different from β -(2,5-dimethoxyphenyl)-propyl dimethylamine. It was also found that the Eschweiler-Clarke method gave tetrahydroisoquinolines in varying amounts and purity from homoveratrylamine.

(6) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *ibid.*, **55**, 4571 (1933).

(7) R. H. F. Manske and H. L. Holmes, *ibid.*, **67**, 95 (1945).

(8) E. Späth, *Monatsh.*, **42**, 113 (1921).

Anal. Calcd. for C₁₄H₂₂O₃N: C, 44.34; H, 5.84; OCH₃, 24.54. Found: C, 44.87; H, 5.57; OCH₃, 25.18.

The picrate was precipitated from the hydrochloride (0.20 g.) and picric acid (0.17 g.) in alcohol. When recrystallized three times from the same solvent, it had m.p. 135–137° (cor.).

Anal. Calcd. for C₁₃H₁₉O₃N·C₆H₃O₇N₃: N, 12.01. Found: N, 12.22.

Oxidation.—The hydrochloride (0.16 g.) was dissolved in water (50 ml.) and alkalinized with 2 ml. of 1 N sodium hydroxide. Permanganate solution (1.8%) was then added in small portions, finally with heating on the steam-bath. The total volume used up was 38 ml. The clear solution obtained after passing in sulfur dioxide was acidified with sulfuric acid and extracted thoroughly with chloroform. After evaporating the solvent, the residue (30 mg.) was taken up in hot water and filtered. This solution was concentrated to 1 ml. and the crystalline precipitate which separated was sublimed at 5 mm. pressure. A few milligrams of colorless needles melting at 125° (cor.) were collected. Mixed with an authentic sample of N-methyl-3,4,5-trimethoxyphthalimide, m.p. 127° (cor.), it melted at 126° (cor.).

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Steroid Tetrahydropyranyl Ethers

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In connection with other studies in this Laboratory¹ the synthesis and cleavage of tetrahydropyranyl ethers² of steroids have been investigated. This work was substantially completed before we learned of the similar work of Ott and co-workers.³ It has been found that the tetrahydropyranyl ether of cholesterol can be prepared in good yield by employing an excess of dihydropyran as the solvent. Following the same procedure, the tetrahydropyranyl ether of methyl Δ^5 -homocholenate was obtained in fair yield but the preparation of the ether of 3 β -hydroxy- Δ^5 -norcholesten-25-one gave erratic results. Good yields, in this latter case, could be obtained only when careful attention was paid to the addition of the acid catalyst (see Experimental). The yield was not improved in this instance by applying the procedure of Ott.⁴

Both dilute hydrochloric acid and catalytic amounts of *p*-toluenesulfonic acid in alcohol effected cleavage of the ether to the free sterol, though better yields were obtained when the sulfonic acid procedure was employed. It was found that when cholesteryl tetrahydropyranyl ether was refluxed with acetic acid or acetic anhydride as solvent for four hours, a mixture of cholesteryl acetate and the original ether was obtained. This mixture which had a constant melting point could not be separated by fractional crystallization. Treatment of the ether with boiling acetic acid or acetic anhydride for 24 hours or with acetic acid plus 1% hydrochloric acid gave the pure acetate in good yield.

In addition cyclohexyl tetrahydropyranyl ether was prepared in an orientating run.

(1) W. G. Dauben and H. L. Bradlow, *THIS JOURNAL*, **72**, 4248 (1950).

(2) (a) G. F. Woods and D. N. Kramer, *ibid.*, **69**, 2246 (1947); (b) W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948).

(3) A. C. Ott, M. E. Murray, R. L. Pederson and M. H. Kuizenga, Abstract of the 117th Meeting of the American Chemical Society, Philadelphia, Penna., 1950, p. 9K.

(4) We are indebted to Dr. Ott for details of their method.