

products occurring in initial stages of oxidation of paraffins and olefins. The results seem significant in that they indicate the "initial point of oxygen attack" in the gas-phase oxidation of hydrocarbons.

Experiments were carried out by mixing atom-rich hydrogen from a Wood's discharge tube with a hydrocarbon mixture. The gases reacted at 20° and products were condensed at liquid nitrogen temperature. Results (from experiments with hydrogen, hydrocarbon and oxygen in the ratio of 3:1:1; hydrogen about 60% dissociated; total pressure, 0.4 mm.; total gas velocity, 300-400 cm./sec.) in Table I show the main carbonyl products present from oxidation of C₄ hydrocarbons. Ratios of aldehyde or ketone to hydrocarbon as high as 0.20 resulted.

Hydrocarbon oxidized	Main carbonyl products
<i>n</i> -Butane	Acetaldehyde
Isobutane	Acetone, formaldehyde
1-Butene	Propionaldehyde, formaldehyde
1,3-Butadiene	Acrolein, formaldehyde, glyoxal

(Each product was definitely identified by precipitating with 2,4-dinitrophenylhydrazine, separation by fractional recrystallization and determination of melting points and mixed melting points with pure compounds.) The aldehyde or ketone first listed for each particular hydrocarbon was present in largest amount; some formaldehyde was also present in the *n*-butane products. Peroxides and other products were also present.

Insufficient evidence is available to determine the exact mechanism but the results clearly show that oxidation initially occurs at tertiary in preference to secondary and secondary in preference to primary C-H bonds. Oxidation occurs at a double bond if present.

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RESOLUTION OF AN ALIPHATIC TERTIARY ALCOHOL

Sir:

We wish to report the partial resolution of 2,4-dimethyl-4-hexanol (I, methylethylisobutylcarbinol), apparently the first successful resolution of an aliphatic tertiary alcohol in which the hydroxyl group is attached to the asymmetric carbon atom.¹

The racemic alcohol I, b. p. 152-153° (760 mm.); n_D^{18} 1.4277; n_D^{28} 1.4234, was synthesized according to Clarke² and converted to its hydrogen

(1) Paolini and Divizia, *Atti accad. Lincei*, (5) **23**, 171 (1914), have claimed the partial resolution of *dl*-linalool ($\alpha = 1.7^\circ$ instead of $\alpha = 20^\circ$ for the natural product) without furnishing evidence that the optical activity is due to resolved linalool rather than to a resolved impurity.

(2) Clarke, *THIS JOURNAL*, **30**, 1144 (1908), reported b. p. 151° (768 mm.); n_D^{18} 1.4286.

phthalate (II) by adding a benzene solution of the potassium salt of I to a benzene solution of phthalic anhydride according to the general procedure of Fuller and Kenyon.³ The liquid II was purified by crystallizing its barium salt, m. p. 84-86°, from ether-pentane.

Anal. Calcd. for C₂₂H₄₂O₈Ba·H₂O: C, 54.13; H, 6.25; Ba, 19.35. Found: C, 54.38; H, 6.54; Ba, 18.94.

The brucine salt from 139 g. of II, m. p. 139.5-140.5° (A), $[\alpha]_D^{28} - 7.8^\circ$ [$c = 6.3\%$],⁴ crystallized in heavy prisms from acetone. After a fourteen-step systematic fractional crystallization, the brucine salt, m. p. 141-142° (B), comprising the head fraction crystallized as tight, hemispherical pellets, $[\alpha]_D^{26} - 4.8^\circ$ [$c = 9.8\%$].⁴

Anal. Calcd. for C₃₉H₄₈O₈N₂: C, 69.62; H, 7.19; N, 4.16. Found: C, 69.91, 70.32; H, 7.04, 7.15; N, 4.59, 4.11.

On regeneration the brucine salt (B) gave II, $[\alpha]_D^{26} + 7.3^\circ$ [$c = 8.0\%$, $\alpha = 0.59^\circ$]. The curve obtained by melting mixtures of A and B showed a minimum at 136° indicating that A is a 1:1 compound of brucine -(+)-II and brucine -(-)-II.

The recovery of I was effected by adding an ethereal solution of 9.0 g. of II, $[\alpha]_D^{27} + 5.5^\circ$ [$c = 8.5\%$],⁴ to six equivalents of ethylmagnesium bromide. The optically active I (2.0 g.) had the following properties: b. p. 78-80° (52 mm.); 152° (760 mm.); n_D^{18} 1.4259; $[\alpha]_D^{27} - 2.6^\circ$ [$c = 5.1\%$, $\alpha = -0.13^\circ$].

Anal. Calcd. for C₈H₁₈O: C, 73.78; H, 13.93. Found: C, 73.55; H, 14.02.

During the preliminary distillation of the (-)-I there was formed some olefin, b. p. 112-115°, which showed no optical activity. A sample of II, 13.7 g., $[\alpha]_D^{28} - 2.7^\circ$ [$c = 5.1\%$],⁴ from the tail fraction gave (+)-I (2.7 g.), $[\alpha]_D^{28} + 1.5^\circ$ [$c = 5.9\%$, $\alpha = 0.09^\circ$]; b. p. 152° (760 mm.); n_D^{28} 1.4234.

The infrared spectra of racemic I, partially resolved (+)-I and partially resolved (-)-I were identical in all details between 700 and 4000 wave numbers. We are indebted to Professor Ralph S. Halford and to Mr. Abraham Savitzky for these measurements.

(3) Fuller and Kenyon, *J. Chem. Soc.*, **125**, 2304 (1924).

(4) All optical rotations were measured in 95% ethanol.

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WILLIAM VON E. DOERING
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PENICILLIN AMIDE

Sir:

In considering methods for obtaining the amide of penicillin, both the symmetrical anhydride¹ and a mixed penicillin anhydride were considered as

(1) Carpenter, *THIS JOURNAL*, **70**, 2964 (1948).

intermediates. Especially in view of the normal utilization of only one of the two acid moieties of an anhydride in amide formation, the latter approach was investigated.

At 5° equimolar quantities of acetyl chloride and sodium benzylpenicillin in acetyldimethylamine react rapidly to produce penicillin acetyl anhydride in 90-95% conversion. Dilution with neutral buffer precipitates the anhydride as a white gum. This may be isolated through chloroform extraction. While insoluble in water, the anhydride is rapidly hydrolyzed by contact with neutral buffer, yielding the theoretical amount of penicillin.

It undergoes reactions typical of anhydrides. With amines and other compounds the anhydride function reacts preferentially over the sensitive β -lactam ring. Further, the derivative of penicillin rather than acetic acid is formed predominantly. Thus the sixty-second addition of an acetyldimethylamine solution of anhydride to a cold, concentrated solution of ammonium phosphate at pH 8 forms a 60% over-all yield of penicillin amide and 35% of recoverable penicillin. The amide is readily isolated by extracting with chloroform and diluting this solution with Skellysolve A in the presence of dispersed aqueous buffer. The trihydrate separates as colorless needles, 22° extinction, m.p. 65°; slightly soluble in water, soluble in most organic solvents.

Anal. Calcd. for $C_{16}H_{19}N_3O_3S \cdot 3H_2O$: C, 49.6; H, 6.50; H₂O, 14.0. Found: C, 49.7; H, 6.38; H₂O, 14.1.

Drying the trihydrate *in vacuo* and recrystallizing from acetone-benzene gives anhydrous rods, parallel extinction, m.p. 161°. Contact with water immediately transforms this modification to the trihydrate. The molecular weight has been confirmed by iodometric² assay, which shows both forms have the theoretical amount of "activity," *viz.* 1530 and 1790 units/mg. Stability of the amide in neutral solution and toward acid and alkali is similar to that of penicillin.

Biologically the amide shows marked antibiotic properties *per se*, without evidence of hydrolysis to penicillin. While approximately one-half to one-quarter as active as penicillin against normal staphylococci (serial dilution), it exhibits profound resistance to penicillinase, the penicillin-destroying enzyme elaborated by many penicillin-resistant organisms. Apparently the amide forms a complex with this enzyme without undergoing inactivation. Animal blood exhibits antibiotic activity after oral or parenteral administration. No evidence of toxicity has been elicited, even after large doses in mice.

Other acid halides up to octadecanoyl have been used to produce anhydrides. Most lower ones are colorless oils but the higher ones are white waxes, insoluble but very slowly hydrolyzed to penicillin by contact with neutral buffer. Derivatives of

many amino compounds, as amino acids and dialkylaminoalkylamines, have been prepared. Methanol gives the methyl ester. With sodium penicillin other types of reactive halides, as phenacyl chloride, produce the corresponding esters. These are crystalline and stable, but hydrolyze to penicillin in the presence of water.

The therapeutic implications of these findings are being explored. Details of the above reactions and products will be reported in a separate publication.

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RECEIVED OCTOBER 20, 1948

FRACTIONATION OF LANTHANUM AND NEODYMIUM NITRATES BY SOLVENT EXTRACTION

Sir:

Appleton and Selwood¹ reported a separation factor of 1.06 (in favor of neodymium) for a single extraction of an aqueous solution of lanthanum and neodymium thiocyanates with *n*-butyl alcohol. Fischer and co-workers more recently used solvent methods for purifying scandium² and for the fractionation of hafnium from zirconium,³ although earlier claims for solvent fractionation of the rare earths⁴ were not followed up. In spite of the success of chromatographic methods of separating the rare earths, we think continued investigation of these solvent methods may uncover techniques of merit.

Preliminary measurements of the distribution of lanthanum, cerium, and neodymium nitrates between water and *n*-hexyl alcohol⁵ revealed relationships analogous to those encountered for thorium nitrate.⁶ The mole fraction of $R(NO_3)_3$ in the alcohol was proportional to approximately the fourth power of the mole fraction of R^{3+} in the aqueous phase. Thus very concentrated aqueous phases are necessary for appreciable extraction into the alcohol, and the yield is easily washed out of the separated alcohol with water.

We carried out batch extractions of aqueous solutions of lanthanum and neodymium nitrate mixtures with *n*-hexyl alcohol at room temperature. A spectrophotometric method was used to determine neodymium, and the total oxides were determined by ignition. All percentages of oxides are expressed relative to the total oxides in a nitrate sample. Aqueous phases were kept about 90% saturated in the total nitrates. Two single extractions showed:

- (1) Appleton and Selwood, *THIS JOURNAL*, **63**, 2029 (1941).
- (2) Fischer and Bock, *Z. anorg. allgem. Chem.*, **249**, 146 (1942).
- (3) Fischer and Chalybaeus, *Z. anorg. Chem.*, **255**, 79 (1947), and Fischer, Chalybaeus and Zumbusch, *ibid.*, **258**, 277 (1948).
- (4) Fischer, Dietz and Jübermann, *Naturwissenschaften*, **25**, 348 (1937).
- (5) J. A. Peterson, B. S. Thesis, University of Wisconsin, 1948; directed by Prof. Norris F. Hall.
- (6) Rothschild, Templeton and Hall, *J. Phys. Colloid Chem.*, **52**, 1006 (1948).

(2) Alicino, *Ind. Eng. Chem., Anal. Ed.*, **18**, 619 (1946).