

in excess of that required to convert the trialkylaluminum to dialkylaluminum chloride did not react further with the products.

To confirm this result, a solution of diisobutylaluminum chloride in cyclohexane was allowed to react with carbon tetrachloride. Periodic analysis of the hydrolyzable chloride showed no increase over seventy-two hours indicating that no isobutylaluminum dichloride,  $\text{RAlCl}_2$ , was formed.<sup>8</sup>

### Experimental

#### Reaction of Triisobutylaluminum with Carbon Tetrachloride.

To a mixture of 50 ml. of triisobutylaluminum (0.2 mole) and 100 ml. of heptane in a flame-dried 250 ml. three-necked flask equipped with a magnetic stirrer, a dropping funnel, a Vigreux column, and a thermometer, was added a solution of 6.45 ml. of carbon tetrachloride (0.067 mole) in 50 ml. of heptane. The solution was added dropwise over 2.5 hr., while the temperature was maintained at 30°. The solution was allowed to stir overnight, then distilled. Material boiling up to 40° (100 mm.), fraction A, 93 g., was collected in a Dry Ice-acetone cooled receiver. The remaining solvent was then removed *in vacuo* and the product distilled to yield, after a small forerun, 32.5 g. (92%), b.p. 93° (0.3 mm.) [lit.<sup>9</sup> b.p. 108° (1 mm.)].

Anal. Calcd. for  $\text{C}_8\text{H}_{18}\text{AlCl}$ : C, 54.4; H, 10.3; Cl, 20.1. Found: C, 54.1; H, 9.9; Cl, 19.4.

Fraction A, analyzed by g.l.c., was found to contain 1.65% isobutyl chloride, or 1.5 g. (25%).

**Effect of the Ratio of Triisobutylaluminum to Carbon Tetrachloride.**—In a 250 ml. three-necked flask, equipped as previously described, was placed 50 ml. of dry tetrachloroethylene. Then 25 ml. (0.1 mole) of triisobutylaluminum was added by means of a hypodermic syringe. A solution of 3.2 ml. (0.33 mole) of carbon tetrachloride in tetrachloroethylene (total volume, 25 ml.) was added at room temperature over 1 hr. The final solution was 0.1 M in aluminum.

Similarly, 9.7 ml. (0.1 mole) of carbon tetrachloride in tetrachloroethylene (total volume 25 ml.) was added to 0.1 mole of triisobutylaluminum in 50 ml. of tetrachloroethylene. The temperature of this reaction rose rapidly to over 100° during the early addition; the addition was, therefore, stopped and the reaction mixture cooled before continuing. The addition was completed over a period of 1 hr.

Both solutions were analyzed immediately after the addition was complete and then after several hours as follows. A 4-ml. aliquot was removed with a hypodermic syringe and added to 10-ml. of a 9:1 cyclohexane-1-butanol mixture. The resultant solution was extracted with 40 ml. of 5% sulfuric acid. The acid was washed twice with 10 ml. of ether, heated briefly on a steam bath to remove the traces of ether, transferred quantitatively to a 50-ml. volumetric flask, and diluted to volume with

5% sulfuric acid. The solution was analyzed for  $\text{Cl}^-$  potentiometrically. The results are in Table I.

**Stability of Isobutylaluminum Dichloride to Carbon Tetrachloride.**—A mixture of 19.4 ml. of diisobutylaluminum chloride (0.1 mole) and 75 ml. of cyclohexane was allowed to react with 4.9 ml. (0.05 mole) of carbon tetrachloride. Aliquots (4 ml.) of the mixture were analyzed for hydrolyzable chlorine periodically. No change in this value was observed over a period of 72 hr.

## A Reinvestigation of the Structure of "Cordycepic Acid"<sup>1a</sup>

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In 1957, Chatterjee, Srinivasan, and Maiti<sup>2</sup> reported the isolation of a new compound from the fungus *Cordyceps sinensis* (Berkeley) Saccardo. It was named "cordycepic acid," and was assigned the structure of a 1,3,4,5-tetrahydroxycyclohexanoic acid, isomeric with quinic acid, in which the hydroxyl groups in positions 3, 4, and 5 are all *trans* to the carboxyl group.

Since quinic acid can be formed enzymically<sup>3</sup> from 5-dehydroquinic acid, an intermediate in the biosynthesis of the aromatic amino acids, it was of interest to investigate the possible relation of "cordycepic acid" to this biosynthetic pathway.

The data presented by Chatterjee, *et al.*,<sup>2</sup> clearly ruled out the stereochemical configuration suggested for "cordycepic acid." Optical rotations were reported for both "cordycepic acid" and for the product of its acetylation, whereas the proposed structure has a plane of symmetry and is incapable of being optically active.

Authentic samples of *Cordyceps sinensis* (Berkeley) Saccardo were easily obtained with the aid of the detailed description given by Chatterjee, *et al.*<sup>2</sup> The ethanolic extract<sup>2</sup> of the fungus afforded a single compound, the highly water-soluble "cordycepic acid," as colorless needles, m.p. 166–168°. The yield was approximately 7%, as reported.<sup>2</sup> Acetylation of the product gave a compound having m.p. 122–123° and  $[\alpha]_{\text{D}}^{26} +29.7^\circ$  (*c* 0.46, EtOH); [lit.<sup>2</sup> m.p. 126° and  $[\alpha]_{\text{D}}^{26} +29.2^\circ$  (EtOH)]. It also was possible to prepare an isopropylidene derivative which was soluble in petroleum ether.<sup>2,4</sup>

Further investigation showed, however, that the structural assignment reported previously is completely erroneous. "Cordycepic acid" is neither a new compound nor an acid. It is in fact D-mannitol, considerable amounts of which are known to occur in various

TABLE I  
EFFECT OF RATIO OF TRIISOBUTYLALUMINUM TO CARBON TETRACHLORIDE ON FORMATION OF DIISOBUTYLALUMINUM CHLORIDE

Ratio <i>i</i> -Bu <sub>3</sub> Al:CCl <sub>4</sub>	Chloride concn., mmole/ml. <sup>a</sup>	
	3:1	1:1
Time, hr., 0	0.960	0.93
2	.960	.96
3	.960	1.01

<sup>a</sup> Theory for complete conversion of  $\text{R}_3\text{Al}$  to  $\text{R}_2\text{AlCl}$  is 1.00 mmole/ml.

(8) C. Eden and H. Feilchenfeld, *J. Phys. Chem.*, **66**, 1355 (1962), recently have suggested that triethylaluminum does not react with carbon tetrachloride. The small heat of reaction which they noted on mixing these two components and which they ascribed to impurities is probably due to the formation of diethylaluminum chloride; the effect is small because of the dilute solutions being used (3.5 mmoles/100 ml.). It seems improbable that there would be such a great difference in reactivity between triisobutylaluminum and triethylaluminum. It further would be a serious error to conclude from their results that triethylaluminum can be safely mixed in all proportions with carbon tetrachloride.

(9) J. E. Knap, R. E. Leech, A. J. Reid, and W. S. Tamplin, *Ind. Eng. Chem.*, **49**, 879 (1957).

(1) (a) This work was supported by grants from the American Cancer Society, the American Heart Association, and the National Institutes of Health of the U. S. Public Health Service; (b) Career Investigator of the American Heart Association.

(2) R. Chatterjee, K. S. Srinivasan, and P. C. Maiti, *J. Am. Pharm. Assoc.*, **46**, 114 (1957); M. W. Miller, "The Pfizer Handbook of Microbial Metabolites," McGraw-Hill Book Co., Inc., New York, N. Y., 1961, p. 147.

(3) S. Mitsuhashi and B. D. Davis, *Biochem. Biophys. Acta*, **15**, 268 (1954); D. B. Sprinson, *Advan. Carbohydrate Chem.*, **16**, 235 (1960).

(4) This solubility characteristic is incompatible with the proposed<sup>2</sup> structure. Shikimic acid, which has one less hydroxyl group than quinic acid, yields an isopropylidene derivative which is insoluble in petroleum ether.

fungi. "Tetraacetylcordycepic acid"<sup>2</sup> was identified as D-mannitol hexaacetate and the "acetyl derivative of cordycepic acid"<sup>2</sup> as 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol. The detailed evidence is presented in the Experimental section.

Proof that the original "cordycepic acid" is identical with the compound isolated in the present investigation was afforded by direct comparison, following the completion of this investigation, with a sample kindly furnished by Professor Chatterjee. The two materials were shown to be identical by mixture melting point and infrared spectrum.

#### Experimental<sup>5</sup>

"Cordycepic Acid."—The isolation followed the reported procedure.<sup>2</sup> The crude product was triturated with a little ethanol to remove a small fraction of highly colored material. The tan solid residue was dissolved in water and the solution was passed through a column of Dowex-50 (H<sup>+</sup>) and decolorized with charcoal. Evaporation to dryness under reduced pressure yielded white crystals of "cordycepic acid." In one case 37 g. of dried fungus yielded 2.5 g. (6.8%), whereas in another 106 g. of fungus yielded 9.5 g. (9%). Recrystallization was affected by solution in water and addition of ethanol, yielding long white needles, m.p. 166–168°;  $[\alpha]_D^{25} +40.3^\circ$  (*c* 2.29, 5% aqueous ammonium molybdate). The optical rotation in water was too small for convenient measurement.

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>O<sub>6</sub>: C, 39.54; H, 7.74; O, 52.68. Found: C, 39.36; H, 7.70; direct O, 52.51.

This "cordycepic acid" exhibited no acidic properties. Its infrared spectrum (in potassium bromide) showed no absorption in the carbonyl region, but had very intense bands at 2.95–3.10 μ (O–H), 9.25 and 9.82 μ (C–O). Calculated on the basis of molecular formula C<sub>8</sub>H<sub>14</sub>O<sub>6</sub>, 1 mole reacted with 5 moles of sodium periodate to yield 2 moles of formaldehyde (precipitated as the dimedon derivative). It was identified as D-mannitol by mixture melting point and comparison of infrared spectra [lit.<sup>6</sup> for D-mannitol gives m.p. 167°;  $[\alpha]_D +40.8^\circ$  (*c* 3.33, 6.67% aqueous ammonium molybdate)].

Acetylation of "Cordycepic Acid."—"Cordycepic acid" (369 mg.) was suspended in a mixture of 10 ml. of acetic anhydride and 10 ml. of dry pyridine and shaken mechanically at room temperature overnight. The solid dissolved. The acetic anhydride and pyridine were removed *in vacuo*, and 50 ml. of water was added to the residue which quickly crystallized. It was collected by filtration, washed thoroughly with water, and dried, to yield 847 mg. (96%), m.p. 121–122°. Two recrystallizations from benzene raised the m.p. to 122–123°;  $[\alpha]_D^{25} +25.3^\circ$  (*c* 7.18, chloroform).

*Anal.* Calcd. for C<sub>18</sub>H<sub>26</sub>O<sub>12</sub>: mol. wt., 434.4; C, 49.77; H, 6.03. Found: mol. wt., 420; C, 50.06; H, 5.66.

Lit.<sup>7</sup> for D-mannitol hexaacetate gives m.p. 122°;  $[\alpha]_D +25^\circ$  (*c* 1, chloroform). Identity of this compound as D-mannitol hexaacetate was further confirmed by mixture melting point with an authentic sample and comparison of infrared spectra (in chloroform and carbon tetrachloride).

Isopropylidene Derivative of "Cordycepic Acid."—"Cordycepic acid" (0.974 g.) was suspended in 300 ml. of 1% hydrogen chloride in dry acetone and stirred overnight. The solid dissolved. The solution was neutralized with silver carbonate, and the silver salts were filtered off. Evaporation of the filtrate under reduced pressure yielded an oil which crystallized readily. A cyclohexane solution of the crude product was filtered to remove insoluble material (70 mg.), and evaporated to yield 1.41 g. of crystals, m.p. 66.5–68°. Recrystallization from a minimum of hexane followed by sublimation at 0.5 torr (bath temp., ca. 90°) raised the m.p. to 67.5–68.5°;  $[\alpha]_D^{25} +12.7^\circ$  (*c* 9.68, abs. EtOH) [lit.<sup>8</sup> for 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol gives m.p. 68–70°;  $[\alpha]_D^{25} +12.5^\circ$  (*c* 9.6, abs. EtOH)].

(5) The melting points were determined on a Fisher-Johns melting point apparatus.

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(7) E. Pacsu and F. V. Rich, *J. Am. Chem. Soc.*, **55**, 3018 (1933).

(8) E. Fischer, *Ber.*, **28**, 1168 (1895); L. F. Wiggins, *J. Chem. Soc.*, 13 (1946).

The isopropylidene derivative was found to undergo slow hydrolysis in a moist acidic atmosphere. This may be responsible for the lower melting point reported previously.<sup>2</sup>

#### *gem*-Dinitro Esters. IV. Pyridine-Catalyzed Esterification of β-Dinitro Alcohols<sup>1</sup>

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β-Dinitro alcohols have been esterified with acids in the presence of trifluoroacetic anhydride or polyphosphoric acid<sup>2</sup> and with acid chlorides alone,<sup>3</sup> in an inert solvent,<sup>4</sup> in the presence of aluminum chloride by the method of Hill,<sup>5,6</sup> or by the use of the Schotten-Bauman reaction.<sup>7</sup> Low yields and mixtures are obtained from base-sensitive alcohols with the last method due to a reversal of the Henry<sup>8</sup> reaction.

Although β-nitro alcohols are dissociated by aqueous bases, they are not affected in the same way by pyridine in certain solvents, and are readily esterified by acid chlorides in this medium. The reaction is carried out in dichloromethane solution in the presence of equal molar quantities of pyridine, acid chloride, and alcohol. It is rapid in concentrated solutions and furnishes good yields of esters (Tables I and II) under mild conditions. The method is particularly advantageous with low boiling acid chlorides, such as phosgene, and for the preparation of esters from heat-sensitive alcohols and acid chlorides. A three-component complex appears to be the reactive intermediate whose fate is largely dependent on concentration.<sup>9</sup>

Good yields of simple esters are generally obtained from 2,2-dinitropropanol. 2-Nitro-1,3-propanediols yield diesters with acid chlorides derived from monobasic acids and mixtures of open-chain polymeric and cyclic esters with acid chlorides derived from dibasic acids, the latter predominating in the cases investigated. Thus, 2-nitrotrimethylene carbonates are the major products from 2-nitro-1,3-propanediols and phosgene, accompanied by smaller amounts of polymeric carbonates which have characteristic infrared absorption for open-chain carbonates.<sup>10</sup> They can be separated on the basis of the higher volatility of the cyclic carbonates.

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

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(4) M. B. Frankel, *J. Org. Chem.*, **23**, 813 (1958).

(5) M. E. Hill, *J. Am. Chem. Soc.*, **75**, 3020 (1953).

(6) C. O. Parker, W. D. Emmons, A. S. Pagano, H. A. Rolewicz, and K. S. McCallum, *Tetrahedron*, **17**, 92 (1962).

(7) M. H. Gold, E. E. Hamel, and K. Klager, *J. Org. Chem.*, **22**, 1665 (1957).

(8) L. Henry, *Compt. rend.*, **120**, 1265 (1895).

(9) H. E. Ungnade, E. D. Loughran, and L. W. Kissinger, *Tetrahedron*, to be published.

(10) Open-chain aliphatic carbonates have a broad C—O stretching band at 8.0 μ. The corresponding bands in the trimethylene carbonates are narrower and occur at 8.5 and 9.0 μ.