18α-ursane skeleton) or of δ-amyrenol [olean-13(18)-en-3β-ol].[12] There is nothing in the literature to indicate that acetic acid alone affects lupeol or lupenone.

On balance of the evidence it is then reasonable to assume that the isolated oleanane derivative was not an artifact, but occurred as such in the plant. This would be well in line with the postulate of Ruzicka[13] that the cation IX functions as the biogenetic precursor of all pentacyclic terpenes having a six-membered ring E, including taraxerol.

Experimental

The melting points were taken in open Pyrex capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semimicrotube, with chloroform as the solvent.

Extraction of *Samadera indica*.—The ground, dried bark (39 kg.) of *Samadera indica* was extracted by refluxing for 2 hr. with 234 l. of 95% ethanol. This was repeated twice more with fresh portions of 95% ethanol. The ethanol solution was reduced to a volume of 3 l. and then dried in trays under vacuum at 40° to give 1.871 kg. of dark brown tarry material. This material was stirred three times with 12 l. of warm (55°) hexane for 15-min. periods and the total hexane solution was evaporated to 2 l. After washing with two 1.5-l. portions of 90% ethanol and backwashing the ethanol solutions with 2 l. of hexane, the hexane solutions were concentrated to about 500 ml. After standing for 2 days at room temperature, large needles had deposited which were collected and washed with absolute ethanol. Chromatography on Merck acid-washed alumina and elution with hexane gave, after two recrystallizations from 95% ethanol, 27.9 g. (0.07% of bark) of lupenone (I), m.p. 166–169°. Further recrystallization raised the melting point to 170–171°, $[\alpha]_D$ +58.7° (*c* 0.83); lit.[14] m.p. 170.5–171.2°, $[\alpha]_D$ +57.6°.

Anal. Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found: C, 85.19; H, 10.93.

The oxime had m.p. 278–287.5° (lit.[14] m.p. 267°).

Anal. Calcd. for $C_{30}H_{49}NO$: C, 81.94; H, 11.23; N, 3.19. Found: C, 82.11; H, 10.55; N, 3.17.

The 2,4-dinitrophenylhydrazone had m.p. 218.5–220° (lit.[14] m.p. 214°).

Anal. Calcd. for $C_{36}H_{52}N_4O_4$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.38; H, 8.50; N, 9.51.

Reduction of the ketone with sodium borohydride in methanol gave crude **lupeol (II)**, which, after two recrystallizations from ethanol, had m.p. 212–214°, $[\alpha]^{22}_D$ +27.1° (*c* 0.96); lit.[14] m.p. 215–216°, $[\alpha]_D$ +27.2°.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.31; H, 11.75.

The acetate melted at 218–219° and had $[\alpha]^{22}_D$ +37.8° (*c* 0.696); lit.[14] m.p. 220°, $[\alpha]_D$ +47.3.

The hitherto undescribed 2,4-dinitrobenzoate was prepared from lupeol with 2,4-dinitrobenzoyl chloride and pyridine (17 hr., room temperature), m.p. 286–287°.

Anal. Calcd. for $C_{37}H_{52}N_2O_6$: C, 71.58; H, 8.44; N, 4.51. Found: C, 71.65; H, 8.32; N, 4.75.

On catalytic hydrogenation (platinum, ethanol, uptake 1 mole/mole), lupeol gave pure lupanol (III): m.p. 202–203°, $[\alpha]^{23}_D$ −14.7° (*c* 0.856); lit.[15] m.p. 206°, $[\alpha]_D$ −17.8°.

The 90% ethanol solution obtained from the above distribution with hexane was taken to dryness. The residue (125 g.) was chromatographed on 2 kg. of Merck acid-washed alumina and 1.5-l. fractions were collected. Fractions 2–4 (benzene) gave a large amount of oil from which was obtained, after recrystallization from ethanol, an additional 6 g. of lupenone. Fractions 5–10 (benzene) gave 8.38 g. of oily crystals. After four recrystallizations from ethanol, 1.03 g. of **18α-oleanan-19α-ol-3-one** (IV) was obtained: m.p. 240–244°, $[\alpha]^{22}_D$ +27.5° (*c* 1.07); lit.[5] m.p. 229–233°, $[\alpha]^{22}_D$ +21°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.40; H, 11.33.

The 2,4-dinitrophenylhydrazone had m.p. 268–270°.

Anal. Calcd. for $C_{36}H_{54}N_4O_5$: C, 69.42; H, 8.74; N, 9.00. Found: C, 69.52; H, 8.57; N, 9.22.

Attempted acetylation with acetic anhydride–pyridine at room temperature gave only starting material.

18α-Oleanone-3,19-dione (V).—A solution of chromic anhydride (30 mg.) in glacial acetic acid (1 ml.) and 1 drop of water was added dropwise to 18α-oleanan-19α-ol-3-one (99 mg.) dissolved in glacial acetic acid (10 ml.). The mixture was kept at room temperature for 32 hr. and then worked up in the usual way. Two recrystallizations of the crude product from absolute ethanol gave 18α-oleanana-3,19-dione (47 mg.): m.p. 251–254°, $[\alpha]^{22}_D$ +73.7° (*c* 0.95); lit.[5] m.p. 249–252°, $[\alpha]^{20}_D$ +70°.

Anal. Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.71; H, 10.69.

18α-Oleanana-3β,19α-diol (VI).—A solution of 18α-oleanan-19α-ol-3-one (106 mg.) in ethanol (15 ml.) was added dropwise to a stirred solution of 207 mg. of sodium borohydride in 4 ml. of ethanol. The mixture was then heated at reflux for 3 hr. After cooling, it was acidified with 10% acetic acid and diluted with water. The resulting precipitate was collected (69 mg.). The filtrate was concentrated to remove the ethanol and extracted with chloroform. The chloroform solution was washed with sodium bicarbonate and water, dried over sodium sulfate, and evaporated to give an additional 32 mg. of material. The combined solids, after two recrystallizations from methanol–chloroform, gave 72 mg. of 18α-oleanana-3β,19α-diol: m.p. 248–249°, $[\alpha]^{24}_D$ −0.7° (*c* 1.08); lit.[5] m.p. 249–249.5°, $[\alpha]^{20}_D$ −3°.

Anal. Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.07; H, 11.64.

The 3-monoacetate, prepared by overnight treatment of the diol with acetic anhydride, after purification melted at 255.5–257° and had $[\alpha]^{20}_D$ +6.1° (*c* 0.87); lit.[5] m.p. 249–250°, $[\alpha]^{20}_D$ +7°.

Anal. Calcd. for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 78.97; H, 11.16.

18α-Oleanana-3β,19β-diol 3-Acetate.—A saturated ether solution of lithium aluminum hydride (2 ml.) was added to a solution of the crude dione V (27 mg.) in tetrahydrofuran (4 ml.), and the mixture was heated under reflux for 2 hr. The excess lithium aluminum hydride was decomposed by the addition of a saturated sodium sulfate solution. The organic layer was decanted and washed with 5% hydrochloric acid and saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to give 29 mg. of crude 18α-oleanana-3β,19β-diol (VII), m.p. 250–260°. The infrared spectrum showed the complete absence of any carbonyl absorption.

The crude diol was treated with 1 ml. of acetic anhydride and 2 ml. of pyridine overnight at room temperature. Purification of the crude product (25 mg.) by thin layer chromatography on activity V alumina with hexane–chloroform (1:1) and recrystallization of the eluted spot from methanol gave 7 mg. of 18α-oleanana-3β,19β-diol 3-acetate: m.p. 295–297°; lit.[5] m.p. 294.5–295°.

Anal. Calcd. for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 79.01; H, 11.23.

(12) For a summarizing account of the isomerization of lupeol by acids, see ref. 6, pp. 364–367.

(13) L. Ruzicka, *Proc. Chem. Soc.*, 341 (1959).

(14) In ref. 6, p. 331.

(15) In ref. 6, p. 332.

Synthesis and Stereochemistry of Hydrophenanthrenes. III.[1] The Reaction of 1,3-Dicyclohexyl-1-(1,2,3,9,10,10aβ-hexahydro-7-methoxy-2α-phenanthrylcarbonyl)urea with Sodium Alkoxides

ZOLTAN G. HAJOS, DAVID R. PARRISH, AND M. W. GOLDBERG[2]

Department of Chemical Research, Research Division, Hoffmann-La Roche, Inc., Nutley, New Jersey

Received March 16, 1965

During the course of the synthesis of hydrophenanthrene derivatives, a convenient method was required

(1) Part II of this series: Z. G. Hajos, D. R. Parrish, and M. W. Goldberg, *J. Org. Chem.*, **30**, 1213 (1965).

(2) Deceased Feb. 17, 1964.

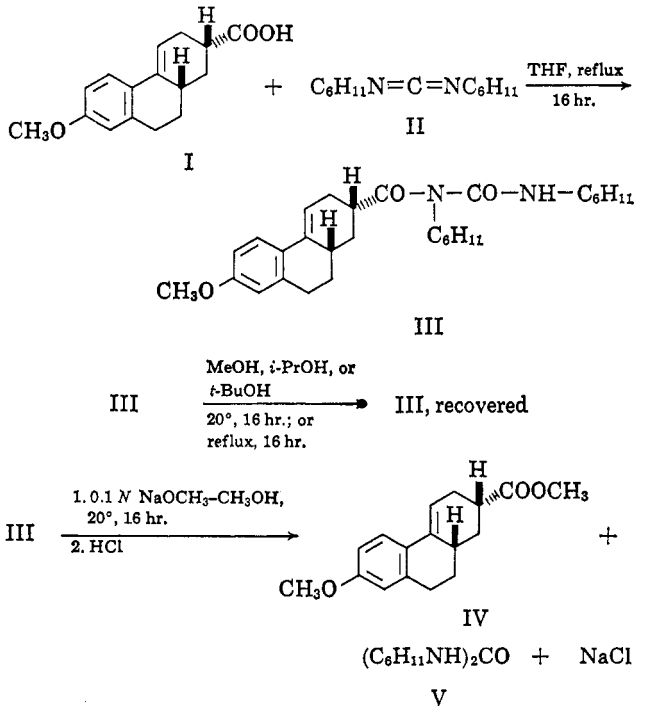
for the preparation of alkyl esters of 1,2,3,9,10,10aβ-hexahydro-7-methoxy-2α-phenanthrenecarboxylic acid (I).[1,3]

While the $\Delta^{4,4a}$ double bond of I is stable under neutral or basic reaction conditions, it rearranges readily to the $\Delta^{4a,10a}$ position with a trace of mineral acid.[4]

The methyl ester IV was therefore prepared from the unsaturated acid I with diazomethane.[1] In search for a more general esterification method, which would not involve rearrangement of the double bond, the acylurea III was prepared from the unsaturated acid I and dicyclohexylcarbodiimide II. Urea III was then treated with the corresponding alcohol (methanol, isopropyl alcohol, or *t*-butyl alcohol) at room temperature and also in tetrahydrofuran at reflux temperature, for 16 hr. In all instances, unchanged acylurea III was recovered, quantitatively. This was a somewhat surprising observation, since this reaction usually proceeds smoothly at room temperature[5a,b] with primary, secondary, as well as tertiary alcohols.[5b] The electrophilic character of the carbon atom of the carbonyl of the acid might play an important role.

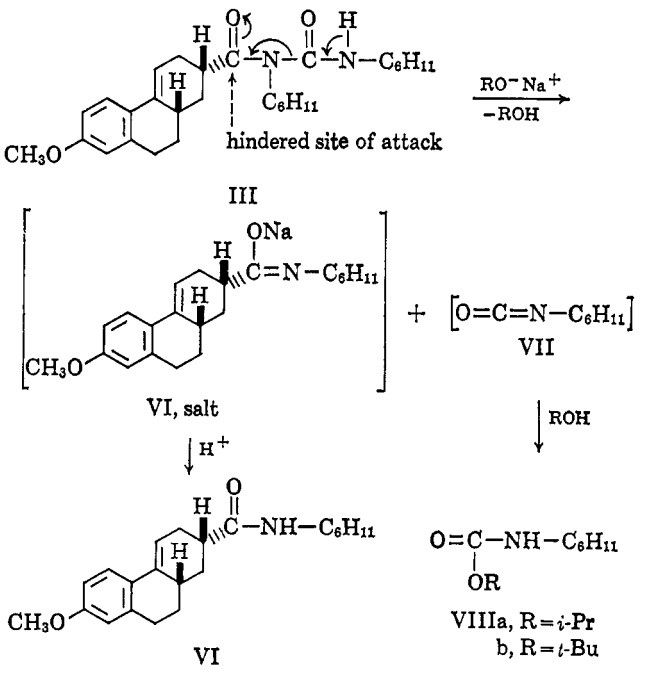
Stirring for 16 hr. at room temperature with 0.1 *N* sodium methoxide in methanol converted the acylurea III to the methyl ester IV in theoretical yield (Chart I). The ester IV was identical in every respect with the one obtained in the reaction of the unsaturated acid I with diazomethane.[1] Sodium alkoxides have been used previously to obtain esters from acylureas.[5a,6]

CHART I



The reaction of the acylurea III with 0.1 *N* sodium isopropoxide in isopropyl alcohol or with 0.1 *N* sodium *t*-butoxide in *t*-butyl alcohol did not give the expected esters of the unsaturated acid I. Instead, the N-acylaminocyclohexane (VI) and the corresponding cyclohexylcarbamic acid esters (VIIIa or b) were isolated. The same urethans (VIIIa or b) were obtained in the reaction of cyclohexyl isocyanate (VII) with isopropyl alcohol and *t*-butyl alcohol, respectively. Cyclohexyl isocyanate (VII) is the postulated intermediate in the reaction of the urea III with sodium isopropoxide or *t*-butoxide (Chart II).

CHART II



The mechanism of the urethan formation most probably involves a nucleophilic attack on the imide hydrogen. This could be due to increased steric interactions around the indicated carbonyl group toward the approaching bulky alkoxide ion (isopropoxide or *t*-butoxide). On the other hand, electronic factors, such as the relative nucleophilic strength of the attacking alkoxide ion cannot be excluded and might also play an important role. The reaction represents an interesting new cleavage of an acylurea with certain alkoxides to yield the corresponding amide and urethan. The desired esters were subsequently prepared in an excellent yield by Staab's imidazolide method of esterification.[1]

Experimental[7]

1,3-Dicyclohexyl-1-(1,2,3,9,10,aβ-hexahydro-7-methoxy-2α-phenanthrylcarbonyl)urea (III).—The unsaturated acid I (25.0 g.) and dicyclohexylcarbodiimide II (20.1 g.) were added to dry tetrahydrofuran (350 ml.). The mixture was refluxed and stirred for 16 hr. The solution was filtered to remove the small amount of dicyclohexylurea[8] impurity (V). The filtrate was concentrated to about half of its original volume *in vacuo*, and it yielded, on standing at room temperature for 16 hr., 20.9 g. of the acylurea III, m.p. 169–170°. Recrystallization from acetone gave analytically pure III: m.p. 170-170.5°; ultraviolet absorption, λ_{max}^{EtOH} 263 mμ (ε 20,200), 298 (3200); infrared absorption, ν_{max}^{KBr} 3340 (NH), 1680, and 1640 cm.$^{-1}$ (carbonyls).

(3) The unsaturated acid I and its derivatives described in this note are racemates. As a matter of convenience, only one enantiomeric series (10aβ-hydrogen) has been pictured.

(4) M. W. Goldberg and W. E. Scott, U. S. Patent 2,894,958 (July 14, 1959).

(5) (a) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953); (b) L. Peyron, *Bull. soc. chim. France*, 413 (1960).

(6) H. G. Khorana, *J. Chem. Soc.*, 2081 (1952).

(7) All melting points were determined in a Thomas–Hoover melting point apparatus and are corrected.

(8) H. G. Khorana, *Chem. Ind.* (London), 1087 (1955).

Anal. Calcd. for $C_{29}H_{40}N_2O_3$: C, 74.96; H, 8.68; N, 6.03. Found: C, 74.91; H, 8.35; N, 6.15.

1,2,3,9,10,10aβ-Hexahydro-7-methoxy-2α-phenanthrenecarboxylic Acid Methyl Ester (IV).—A suspension of the acylurea III (465 mg.) was stirred in 10 ml. of methanol, and 10 ml. of 0.1 *N* sodium methoxide in methanol was added over 15 min. Stirring was continued for 16 hr. at room temperature. Ice–water (10 ml.) was then added, and the cold solution was neutralized carefully with 2 *N* hydrochloric acid. Most of the methanol was removed *in vacuo*, and the solution was filtered from the dicyclohexylurea.[8] The filtrate was extracted with hexane. The extract was dried with sodium sulfate and evaporated *in vacuo* to yield 272 mg. of the methyl ester IV, m.p. 71–72°. The compound was identical in every respect with the previously described methyl ester.[1]

N-Cyclohexyl-1,2,3,9,10,10aβ-hexahydro-7-methoxy-2α-phenanthrylcarboxamide (VI), Cyclohexylcarbamic Acid Isopropyl Ester (VIIIa), and Cyclohexylcarbamic Acid *t*-Butyl Ester (VIIIb).—The acylurea III (4.65 g.) was suspended in 100 ml. of anhydrous isopropyl alcohol or *t*-butyl alcohol. A 0.1 *N* solution (100 ml.) of the sodium alkoxide in the corresponding alcohol was added, and the mixture was stirred at room temperature for 16 hr. with the exclusion of moisture. It was then neutralized with 2 *N* hydrochloric acid and evaporated to dryness *in vacuo*. The residue was broken up under hexane, and the hexane-insoluble amide VI was filtered. Recrystallization from ethanol gave analytically pure VI: m.p. 221–222°; ultraviolet absorption, λ_{max}^{EtOH} 264 mμ (ε 20,600), 298 (3200); infrared absorption, ν_{max}^{KBr} 3300 (NH), 1635 cm.$^{-1}$ (carbonyl).

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 78.12; H, 8.76; N, 4.25.

To obtain the urethans (VIIIa or b), the filtrate of the amide VI was evaporated *in vacuo*, and the solid residue was recrystallized from an appropriate solvent. Recrystallization from petroleum ether (b.p. 30–60°) gave analytically pure cyclohexylcarbamic acid isopropyl ester (VIIIa): m.p. 66.5–67.0°; infrared absorption, $\nu_{max}^{CHCl_3}$ 3450 (NH), 1706 (carbonyl), 1515 cm.$^{-1}$ (amide II).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.96; H, 10.11; N, 7.65.

Recrystallization from hexane gave analytically pure cyclohexylcarbamic acid *t*-butyl ester (VIIIb): m.p. 79–80°; infrared absorption, $\nu_{max}^{CHCl_3}$ 3450 (NH), 1705 (carbonyl), 1510 cm.$^{-1}$ (amide II).

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.20; H, 10.81; N, 7.00.

With sodium isopropoxide in isopropyl alchol, 3.4 g. of amide VI and 1.56 g. of urethan VIIIa (84.5%) were obtained. With sodium *t*-butoxide in *t*-butyl alcohol, 3.2 g. of amide VI and 1.6 g. of urethan VIIIb (80.3%) were obtained.

Cyclohexylcarbamic Acid Isopropyl Ester (VIIIa) and Cyclohexylcarbamic Acid *t*-Butyl Ester (VIIIb) from Cyclohexyl Isocyanate (VII).—The corresponding alcohol (10 ml.) was added to 12.5 g. of the isocyanate VII[9] and the reaction mixture was stirred at room temperature for 16 hr. Excess alcohol was evaporated *in vacuo*, and the dry residue was recrystallized from an appropriate solvent.

In the experiment with isopropyl alcohol, recrystallization from petroleum ether (b.p. 30–60°) gave 14.4 g. (78%) of the pure cyclohexylcarbamic acid isopropyl ester (VIIIa), which was identical in every respect with the compound described above.

The crude cyclohexylcarbamic acid *t*-butyl ester (VIIIb) was recrystallized from hexane to give 15.9 g. (80%) of the pure urethan (VIIIb), which was identical in every respect with the material obtained from the acylurea III with sodium *t*-butoxide in *t*-butyl alcohol.

Acknowledgment.—We wish to express our thanks to Mr. C. Parios for his technical assistance in this work. We are also indebted to Mr. S. Traiman for the infrared data, to Dr. V. Toome for the ultraviolet spectroscopic data, and to Dr. A. Steyermark for the microanalyses.

(9) Cyclohexyl isocyanate was obtained from K & K Laboratories, Inc., Plainview, N. Y.

3′-Deoxynucleosides. III.[1] 3′-Deoxyguanosine

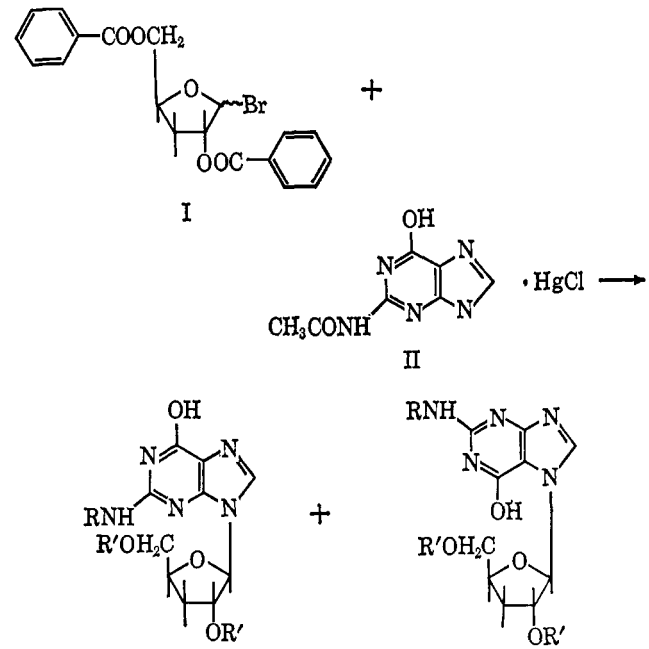
SUSAN R. JENKINS, FREDERICK W. HOLLY, AND EDWARD WALTON

Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey

Received March 16, 1965

In view of the biological activity[2] of 3′-deoxyadenosine (cordycepin) it seemed desirable to synthesize the 3-deoxyriboside of guanine, the other major purine component of nucleic acids. Although numerous guanine glycosides have been synthesized[3] by transformation of the purine moiety of other nucleosides, only one has been prepared from guanine. In this instance, a condensation of acetobromoglucose with chloromercuri-2-acetamidohypoxanthine (II) gave[4] not only 9-(β-D-glucopyranosyl)guanine but also the isomeric 7-(β-D-glucopyranosyl)guanine. We have synthesized 3′-deoxyguanine by a procedure in which 2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl bromide (I) was condensed with the chloromercuripurine II. Since a ribofuranoside and a glucopyranoside have both been prepared from II, it would appear that this procedure has general utility for the synthesis of guanine nucleosides.

When 2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl bromide (I)[1] was coupled with chloromercuri-2-acetamido-



III, R=CH_3CO; R′=C_6H_5CO IV, R=CH_3CO; R′=C_6H_5CO

V, R=H; R′=H VI, R=H; R′=H

(1) For paper II of this series, see E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, in press.

(2) (a) K. G. Cunningham, S. A. Hutchinson, W. Manson, and F. S. Spring, *J. Chem. Soc.*, 2299 (1951); (b) D. V. Jagger, N. M. Kredich, and A. J. Guarino, *Cancer Res.*, **21**, 216 (1961); (c) H. Klenow and S. Frederickson, Abstracts, the VIth International Congress of Biochemistry, New York, N. Y., 1964, p. 66; (d) E. A. Kaczka, E. L. Dulaney, C. O. Gitterman, H. B. Woodruff, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **14**, 452 (1964); (e) H. T. Shigeura and C. N. Gordon, *J. Biol. Chem.*, **240**, 806 (1965).

(3) See J. A. Montgomery and H. J. Thomas, *Advan. Carbohydrate Chem.*, **17**, 301 (1962).

(4) Z. A. Shabarova, Z. P. Polyakova, and M. A. Prokofev, *Zh. Obshch. Khim.*, **29**, 215 (1959).