and the nonidentity of 2,4-hexadiene adducts. The sharp crystallization and ready sublimation of the adducts eliminated polymeric materials from consideration.

The n.m.r. spectrum (60 Mc., deuterioacetone solution, TMS internal standard) of the cyclobutane adduct II from 4-methylpentadiene showed peaks at 326 (doublet, $J = 8$), 269 and 200 (apparent ABX pattern), and −110 (singlet) in the expected ratio (1:1:2:6) for vinylic, ring, and allylic methyl protons. The spectrum of the cyclohexene adduct I showed singlet peaks at 351, 201, and 97. The isomeric adducts from 2,4-hexadienes gave identical spectra, 355, 209, 97, with a splitting constant of 7 c.p.s. for CHCH₃. Adducts from other dienes were examined in CDCl₃ solution and the following shifts were observed: trans-pentadiene, 345, 185, 93; 2-chlorobutadiene, 360, 192; 2,3-dichlorobutadiene, 205. The adduct from cyclohexadiene proved to be too insoluble to obtain an adequate spectrum in suitable solvents.

Rate and Competition Experiments.—Competitive reactions and fade time observations were made by adding 0.64 g. (0.005 mole) of powdered TCNE to a solution of 0.10 mole of diene, or of each of two dienes, in 5 ml. tetrahydrofuran. "Fade time" was noted by visual comparison to an arbitrary standard corresponding to an estimated two-thirds reaction. When the solution was colorless, solvent and diene were evaporated. The observed yield in each case was essentially quantitative. Assumed second-order rate constants were calculated from fade times by the relation $k = 1/T_F$ for the concentrations employed. Relative rates were determined by infrared comparison of the crude products (Primol mull) with synthetic mixtures and calculation assuming the reactions to be first order in diene, $k_A/k_B = (\log A_0/A_0 - X_A)/(\log B_0/B_0 - X_B)$, where X_A and X_B are the fractions of the respective adducts found. Observed results are shown in Table

TABLE II
COMPETITIVE REACTIONS OF DIENES WITH TCNE

1,3-Dienes A	B	Fade time,[a] min.	Adduct composition, X_A
3-Methyl-trans-penta-	2-Methyl-trans-penta-	< 1	0.40 ± 0.05
trans,trans-2,4-Hexa-	2-Methyl-trans-penta-	< 1	0.20 ± 0.04
2,3-Dimethylbuta-	3-Methyl-trans-penta-	< 1	0.32 ± 0.02
2-Methylbuta-	trans,trans-2,4-hexa	< 1	0.09 ± 0.02
2-Methylbuta-	trans-Penta-	1	0.40 ± 0.02
4-Methylpenta-	2-Methylbuta-	4	< 0.05[b]
cis,trans-2,4-Hexa-	4-Methylpenta-	960	0.11 ± 0.04[b]
3-Methyl-cis-penta-	cis,trans-2,4-Hexa-	4000	0.33 ± 0.06
cis-Penta-	cis,trans-2,4-Hexa-	360/57°	< 0.05

[a] See Experimental for definition and conditions. [b] Composition including both adducts from 4-methylpentadiene, see ref. 27.

II.[27] Absolute rates, Table I, were calculated from relative rates, where available and the fade time observations with isoprene and with 4-methylpentadiene as time standards for the fast and slow series, respectively.

(27) Reaction products for 4-methylpentadiene were analyzed for cyclobutane adduct and corrected for cyclohexene adduct on the basis of data given in ref. 6.

Dihydrophthalic Acid Derivatives as Diels–Alder Dienes[1,2]

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The conversion of phthalic and terephthalic acids and/or esters to dienes suitable for use in the Diels–Alder reaction has been reexamined and a number of such reactions have been carried out. In two instances tetracyanoethylene (TCNE) affords relatively stable π-complexes but no true adducts. Conversion of a number of the adducts to amides and nitriles also is reported.

We have described elsewhere exploratory work[1] involving the Diels–Alder reaction, using cyclic conjugated dienes bearing electron-withdrawing substituents (e.g., nitrile, ester). Whereas the nitrile group proved too deactivating for the usual type of Diels–Alder reaction, the ester group proved to be more tractable. The present paper reports similar work with cyclic conjugated dienes bearing two ester groups, both conjugated with the dieneic system and isolated from it. Three principal conjugated dienes, dimethyl cyclohexa-3,5-diene-trans-1,2-dicarboxylate (I), dimethyl cyclohexa-2,6-diene-1,2-dicarboxylate (II), and dimethyl cyclohexa-1,3-diene-1,4-dicarboxylate (III) were investigated; and in addition the compound (IV) previously assigned the structure[3] dimethyl cyclohexa-1,4-diene-1,4-dicarboxylate but shown in the sequel to be the isomeric conjugated 1,5-diene also was found to enter into the Diels–Alder reaction by isomerization to III.

Preparation of the Dienes.—Compound I was prepared by esterification (diazomethane) of the free

dibasic acid (Ia) obtained by 3% sodium amalgam reduction of phthalic acid[4,5]; and compound IIa was prepared by the thermal isomerization of Ia.[6] The ester, II, was prepared from IIa by acid-catalyzed reaction with methanol.

In view of the structural problem encountered with III and IV, physical examination of the acid and esters Ia, IIa, I, and II was undertaken in order to confirm the structures assigned.[4,5] The infrared and ultraviolet spectra are entirely consistent, I having an unconjugated ester (1750 cm.⁻¹) and II a conjugated ester (1730 cm.⁻¹) in the infrared spectrum while Ia exhibits an ultraviolet spectrum almost identical with that of cyclohexa-1,3-diene and IIa shows absorption at a longer wave length. The n.m.r. spectra likewise are consistent, Ia showing four vinyl protons and two tertiary α-protons. A nearly identical spectrum was obtained for the corresponding ester I, with the addition of the methoxyl line.

The structure of I is further confirmed by the n.m.r. spectra of its adducts with various dienophiles, all of which show two vinyl protons and complete absence of

(1) Previous paper in this series, P. Scheiner, K. K. Schmiegel, G. Smith and W. R. Vaughan, J. Org. Chem., 28, 2960 (1963).

(2) Work supported by a research grant (CY 5406) from the National Cancer Institute to The University of Michigan.
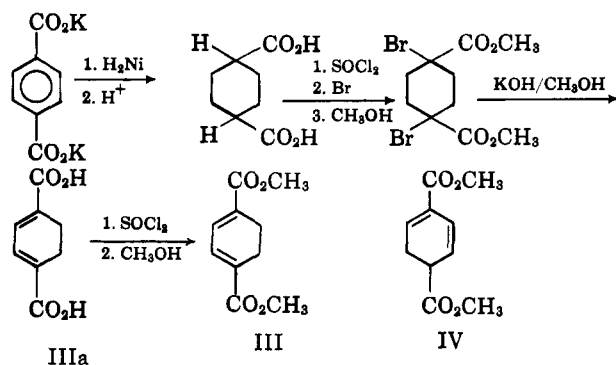
(3) A. von Baeyer, Ann., 251, 276 (1889).

(4) A. von Baeyer, ibid., 269, 189 (1892).

(5) A. Neville, J. Chem. Soc., 89, 1745 (1906), has resolved this acid in order to confirm the structure.

(6) A. von Baeyer, Ann., 269, 190 (1892).

methylene protons (except for X where they are expected). No true adducts were obtained from II, which rules out the alternative structure, dimethyl cycohexa-1-3-diene-1,6-dicarboxylate, which has been shown to possess diene activity in the Diels–Alder reaction.[7]

There appeared to be considerable difficulty in the preparation of III and IV and the corresponding free dibasic acids, IIIa and IVa. Initially compound III was obtained by the following reaction sequence.[8]

CO$_2$K $\xrightarrow{\text{1. H}_2\text{Ni} \ \ 2. \text{H}^+}$ H–CO$_2$H (with H, CO$_2$H) $\xrightarrow[\text{3. CH}_3\text{OH}]{\text{1. SOCl}_2 \ \ 2. \text{Br}}$ Br–CO$_2$CH$_3$ (with Br, CO$_2$CH$_3$) $\xrightarrow{\text{KOH/CH}_3\text{OH}}$

CO$_2$K / CO$_2$H

CO$_2$H $\xrightarrow[\text{2. CH}_3\text{OH}]{\text{1. SOCl}_2}$ CO$_2$CH$_3$ ... CO$_2$CH$_3$

IIIa ... **III** ... **IV**

Subsequent attempts to repeat the whole sequence, with one exception, invariably produced IV. This led us to examine the relationship between the dienes III and IV, whereupon it was found that IV rearranges partially to III either in methanol containing a trace of sodium methoxide or simply thermally (sublimation). Likewise, on standing at room temperature for long periods of time, IV → III (partially).

Reconversion of III to IV was achieved by treatment of III or a mixture of III and IV with refluxing aqueous potassium hydroxide[9] for 3.5 days, followed by cooling in an ice bath and acidification to pH 2 with concentrated hydrochloric acid. The dried precipitate was next heated for 30 min. with phosphorus pentachloride and then treated with cold absolute methanol. The product was pure IV.

The distinction between III and IV is readily made on the basis of melting points which are sharp and distinctive when the two esters are pure; and, while dimethyl terephthalate could not be demonstrated as a third component by v.p.c., microanalysis rules out appreciable contamination as does n.m.r. analysis of samples of III and IV in which the two distinctive lines (τ 1.83, 6.02) of dimethyl terephthalate are lacking absolutely. Both III and IV always gave two bands on v.p.c. analysis, though these were of different intensities, the position of the stronger band being reversed in the spectra of analytical samples of III and IV. Thus isomerization occurs on the column, a not unexpected phenomenon in view of the thermal isomerization noted previously.

The reaction of III with TCNE afforded a stable complex V but no true adduct, and with maleic anhydride the expected adduct VI was formed. But surprisingly IV also formed a TCNE complex (IV· 3TCNE) and reacted with maleic anhydride to give the same adduct VI as from III (mixture melting point

showed no depression, identical infrared spectra). The n.m.r. spectrum of VI shows but three sharp lines in the ratios 2:6:2 at τ 3.17 (vinyl), 6.07 (methoxyl), 6.22 (alpha to carbonyl), and the ultraviolet spectrum is transparent above 240 mμ with only slight end absorption below 240 mμ. Thus VI clearly is the normal adduct of III and maleic anhydride.

The formation of VI from IV is understandable in view of the ready interconversions III ⇌ IV, if one assumes that, in spite of an unfavorable electronic condition in III, its geometry is considerably better for Diels–Alder reaction than that of the alternative conjugated diene (1,5) for the system which could be formed from the accepted structure for IV (1,4-diene[3]). However, the formation of a TCNE complex, albeit a rather unusual one, from the accepted structure of IV suggested more extensive spectrophotometeric examination of IV to be in order, especially since its infrared spectrum shows a distinct shoulder at 1712 cm.$^{-1}$ on the 1730-cm.$^{-1}$ carbonyl band even though but one band (1652 cm.$^{-1}$) obviously attributable to carbon-carbon double bond appears.

The ultraviolet data for IV, along with III, dimethyl terephthalate, and methyl cyclohexene-1-carboxylate, are collected in Table I. The resemblance of IV to dimethyl terephthalate is as notable as is its lack of resemblance to methyl cyclohexene-1-carboxylate, but until now there has been no question as to the proper structure of IV.

TABLE I
ULTRAVIOLET SPECTRA[a]

Compound[b]	λ_{max} mμ	log ϵ
Dimethyl terephthalate	240	4.188
	285	3.090
	398.5	3.016
III	309	4.051[c]
IV	240[d]	4.069
	286	3.107
	294	3.090
Methyl cyclohexene-1-carboxylate	218.5	4.006

[a] A double-beam Cary Model 11 spectrophotometer was used. [b] In absolute ethanol, compensated with this solvent. [c] R. H. Burnell and W. I. Taylor, J. Chem. Soc., 3636 (1954), give ϵ 27,300 (log ϵ 4.36). [d] H. C. Brill, Philippine J. Sci., 11, 59 (1916) [Chem. Abstr., 10, 2876 (1916)], reports 2415 Å. and 2875 Å. without ϵ values.

The n.m.r. data for III, IV, and dimethyl terephthalate are collected in Table II.[10] The spectrum of III is essentially as expected with two normal vinyl protons, four methylene protons, and six methoxyl protons. And likewise the spectrum of dimethyl terephthalate is as expected with four equivalent aromatic protons and six methoxyl protons. However, the spectrum of IV is unusual. Integration shows three vinyl protons, two of which appear at an anomalously low field and as a single sharp line, six methoxyl protons in two sharp lines of equal intensities, one proton alpha to ester, and two methylene protons. Clearly such a spectrum cannot belong to the originally assigned structure for

(7) J. Kazan and F. D. Greene, private communication; results kindly communicated prior to publication by Professor Greene.
(8) P. C. Guha and G. D. Hazra, J. Indian Inst. Sci., 22A, 263 (1939); Chem. Abstr., 34, 2822 (1940).
(9) A. von Baeyer, Ann., 251, 280, 303 (1889).

(10) The authors are indebted to Dr. Norman le Bel and Dr. Merle Emerson of the Department of Chemistry, Wayne State University, for the initial high resolution spectra on III and IV (60 Mc., Varian HR 60 instrument) and for helpful discussion of their significance. These data appear in Table II in parentheses, numerical differences being attributable to alignment, design, and calibration differences in the Varian A 60 instrument used for the duplicate and other data in the table.

TABLE II

N.M.R. DATA[a] FOR DIMETHYL TEREPHTHALATE DERIVATIVES

Compound	Vinyl (or aromatic)	Methoxyl	Other
Dimethyl terephthalate	1.834 [4] sharp	6.02 [6] sharp	None
III	(2.94 [2]) broad	(6.23 [6]) sharp	(7.83 [4]) slight fine structure
IV	1.72 [2] sharp	5.97 [3] sharp	6.13 [buried]
	(1.93 [2]) sharp	(5.98 [3]) sharp	(6.17) [partly buried]
	2.83 [1] ⎱ fine structure (2.97 [1]) ⎰	6.16 [3] sharp (6.17 [3]) sharp	6.80 [2] ⎱ fine structure (6.78 [2]) ⎰
VI	3.17 [2] sharp	6.07 [6] sharp	6.22 [2] sharp 7.75–8.70 broad with much fine structure

[a] Spectra obtained by Mr. B. E. Wenzel of this department with Varian A-60 n.m.r. spectrometer, deuteriochloroform solution, internal tetramethylsilane. Values in parentheses obtained with HR-60, cf. ref. 10. All values given in τ.

IV,[3] which would have two essentially equivalent vinyl protons, four methylene, and six equivalent methoxyl protons. Nor could it belong to the alternative 2,5-diene which would have four equivalent vinyl protons, two alpha to ester, and six equivalent methoxyl protons. It is, however, consistent with dimethyl cyclohexa-1,5-diene-1,4-dicarboxylate, if the anomalous position and lack of splitting for the two vinyl protons at lowest field is accepted. Microanalysis, line positions for dimethyl terephthalate, and integration of the spectrum of IV rule out any significant contribution from traces of the aromatic ester. Thus we assign the 1,5-dieneic structure to IV, and we suggest that the anomalous n.m.r. character of the two vinyl protons is in some obscure manner connected with the rather "aromatic" character of its ultraviolet spectrum.

In two instances π-complexes (V and VII) with TCNE were formed with dienes (III and IV), and in another (with I) a true adduct (VIII) was formed. The latter is colorless and characteristically shows no conjugated nitrile absorption in the ultraviolet spectrum, whereas both V and VII show conjugated nitrile absorption about the same as for TCNE itself. Table III confirms the π-complex character of V; note the appearance of a longer wave-length band in the complex (λ_1) and the increase in log ϵ values. The analytical data for VII suggest the formula, IV·3TCNE, and the color is visually indistinguishable from that of V.

TABLE III

ULTRAVIOLET SPECTRA FOR V AND TCNE

Concn. $(M)^a$ × 10⁴	λ_1 (312 mμ)	λ_2 (277.5 mμ)	λ_3 (248 mμ)
Complex[a]	log ϵ	log ϵ	log ϵ
0.458	3.958	4.202	4.184
0.916	3.956	4.193	4.184
TCNE			
0.940	None	4.105	4.008

[a] As 1:1 complex in methylene chloride. For general characteristics of π-complex formation with TCNE, cf. R. E. Menifield and W. D. Phillips, J. Am. Chem. Soc., 80, 2778 (1958). The λ_1 band here is significant. Attempts to convert V to a true adduct in methanol solution resulted in dissociation and conversion of III to IV.

Compound II failed entirely to react under Diels–Alder conditions. The acid corresponding to I (Ia) also failed to give Diels–Alder adducts, and TCNE oxidized it to phthalic acid, isolated as the anhydride. Compound I itself, however, readily reacted with TCNE and in this instance a colorless, true adduct (transparent in ultraviolet between 240 and 340 mμ with weak end absorption < 240 mμ) was formed

(VIII). Thus among the four dienes investigated only I showed sufficient reactivity under Diels–Alder conditions to warrant further study.[11]

The reactions of I with various dienophiles were carried out under the conditions and with the yields reported in Table V (Experimental). The problem of precise configurational assignments is not simple and depends in large part on the stereochemistry of I. The trans configuration of I has been established,[5] and the lack of conjugation of the ester groups with the dienic system is clear from the ultraviolet spectrum.

The adduct with maleic anhydride (XIII) has an ultraviolet spectrum like that of VIII and for both VIII and XIII this rules out addition in the form of dimethyl 1,3-cyclohexadiene-1,2-dicarboxylate which would lead to a conjugated ester.

The presence of two vinyl protons and no methylene protons (except X) in all n.m.r. spectra of I adducts (Table IV) supports this argument and also precludes addition in the form of dimethyl 1,3-cyclohexadiene-1,6-dicarboxylate. Finally the integrity of the trans ester relationship during Diels–Alder reactions is indicated by the sterically more favorable trans configuration for ridid α,β-diester, and by the facile conversion of XVI to a triamide (XVIc) via triacid and triacid chloride, no anhydride being formed when the triacid was treated with thionyl chloride. Likewise the adducts show two methyl ester bands in the n.m.r. spectra.

The remaining configurational problems involve the mode of addition. In the absence of conclusive evidence it may be assumed that steric interactions will govern it, since the reaction times in each case (Table V) imply thermodynamic control. Thus substituents in the dienophiles should orient themselves to minimize such interactions. This is of importance chiefly where trans dienophiles are involved (IX, XI), and the preferred adduct structures (>50% isolated) may be represented as the following.
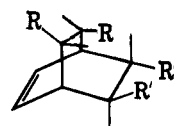
IX, R = CO₂CH₃; R' = CN
XI, R = CO₂CH₃; R' = CO₂C₂H₅

(11) The previously mentioned adduct VI obtained from both III and IV with maleic anhydride was converted to the diacid with the expectation of oxidative decarboxylation with lead tetraacetate, but the experiment proved abortive.

TABLE IV

N.M.R. DATA FOR ADDUCTS OF I[a]

Compound	Vinyl	Methoxyl[b] endo	exo		Other
VIII	3.24 (2) multiplet	6.18 (3)	6.10 (3)	5.70–6.25 (3)	6.75 (1)
IX	3.47 (2) multiplet	6.24 (3)	6.17 (3)	6.40–7.14 (5)	7.14 (1)
X	3.2–3.9 (2) complex, diffuse multiplet	6.30 (1.5) 6.32 (1.5)	6.25 (3)	6.38–7.30 (5)	7.5–9.0 (2)[c]
XI	3.65 (2) multiplet	6.30 (3)	6.21 (3)	6.07–7.25 (6)	5.85 (4)[d] quartet 8.70 (3), 8.77 (3)[e] triplets
XIII	3.59 (2) multiplet	6.26 (3)	6.18 (3)	6.02–6.60 (2)	6.68–7.07 (4)
XIV	3.48 (2)	6.18 (3)	6.11 (3)	5.85–6.45 (3)	6.51 (1), 6.80 (1)

[a] Values given in τ; internal tetramethylsilane (TMS) reference in deuteriochloroform, Varian A-60 spectrometer. Spectra prepared by Mr. B. E. Wenzel of this department. [b] The carbomethoxyl endo to the double bond is assigned the higher τ value since it should be the more shielded of the two, cf. L. M. Jackman, "Applications of Nuclear Magnetic Resononce Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 129, and also ref. 7. [c] This diffuse band represents methylene protons in the two isomers. [d] Methylene protons of the two ethoxyl groups. [e] Methyl protons of the two ethoxyl groups, one slightly shifted due to different shielding in cis and trans positions.

When a cis difunctional dienophile is used, it is reasonable to assume preferential endo addition in accordance with the observation[7] that, not unexpectedly, the endo isomer is thermodynamically favored in a bicyclo[2.2.2]octene system.

Thus XII–XIV have the general following structure
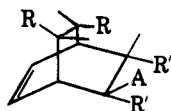
wherein A is hydrogen (XII, XIII) or chlorine (XIV), R' is ester or carbonyl, and R is carbomethoxy.

The n.m.r. spectrum of X shows three bands attributable to CH_3O protons, two of which are of approximately equal intensity and together equal the intensity of the third. Analysis by v.p.c. proved unsatisfactory (decomposition), and in its absence the n.m.r. spectrum may be interpreted as arising from a 1:1 mixture of two adducts (microanalysis satisfactory), most likely the endo and exo isomers. A more diffuse vinyl n.m.r. absorption than for the other bicyclo[2.2.2]octenes is observed, as would be expected.
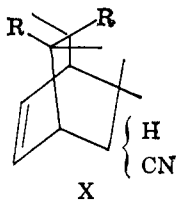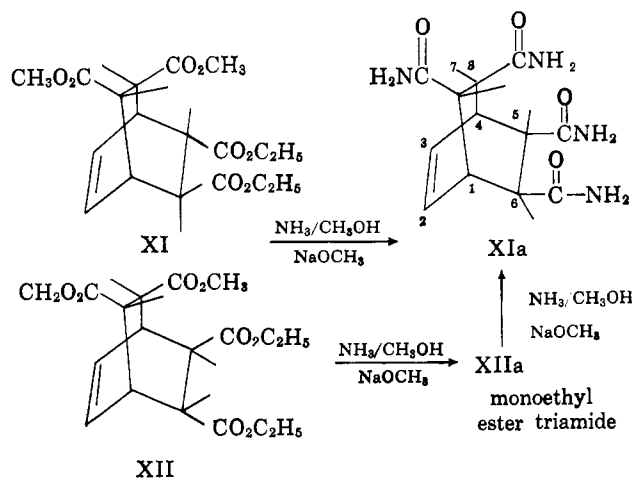

There remain to be discussed the subsequent transformations of the adducts XI, XII, and XIV. These are represented in Charts I and II.

The production of XIa from both XI and XII is not surprising, since the trans–trans arrangement is sterically favored, and the conditions[12] are such as to favor epimerization of an ester with an α-hydrogen.

The reactions represented by Chart II were carried out in order to obtain the nitriles XVId and XVIb for investigation of potential cytostatic activity. They are straightforward except for the conversion of XV to XVI, which is a typical dehalogenative decarboxylation

CHART I

(fragmentation) and was carried out as described elsewhere.[1,13]

Experimental[14,15]

Cyclohexa-3,5-diene-*trans*-1,2-dicarboxylic Acid (Ia).—The procedure of von Baeyer[4] was slightly modified, and a 50% yield was obtained by 3% sodium amalgam reduction of phthalic acid in sodium acetate–buffered 50% acetic acid, m.p. 209°, lit.[4,16] 210°; infrared, 1710, 1675 cm.$^{-1}$; ultraviolet, λ_{max} 253 mμ (log ϵ 3.557), cyclohexa-1,3-diene λ_{max} 257 mμ (log ϵ 3.557), both in ethanol; n.m.r. (acetone-d_6, internal TMS), four vinyl protons (τ 3.99), two tertiary α-protons (τ 6.21), both lines being sharp with slight fine structure.

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.27; H, 4.75.

The acid was converted to the dimethyl ester I by treatment with ethereal diazomethane, b.p. 83–85° (0.3 mm.); infrared, 1750, 1650, 1690 cm.$^{-1}$; n.m.r. (CDCl$_3$) internal TMS), four vinyl protons (τ 4.10, multiplet), two tertiary α-protons (τ 6.25, doublet with some fine structure), six methoxyl protons (τ 6.22, sharp singlet).

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.10; H, 6.07.

Reactions of I with Various Dienophiles.—Data are collected in Table V.

(12) P. B. Russell, *J. Am. Chem. Soc.*, **72**, 1853 (1950).

(13) W. R. Vaughan and R. L. Craven, *ibid.* **77**, 4629 (1955).

(14) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(15) Melting and boiling points are uncorrected. N.m.r. spectra were obtained with Varian A 60 spectrometer by Mr. B. E. Wenzel of this department.

(16) E. A. Pasquinelli, *Anales asoc. quim. arg.*, **31**, 181 (1943).

TABLE V

ADDUCTS WITH DIMETHYL CYCLOHEXA-3,5-DIENE-*trans*-1,2-DICARBOXYLATE (I)

	Moles/mole diene[a]	Time, hr.	Recrystg. solvent	Yield, %	M.p. or b.p. (mm.), °C.	Compound	Calcd. C	H	N	Found C	H	N
VIII[b] TCNE	1/1	48	Benzene	75	172–173	C₁₆H₁₂N₄O₄	59.26	3.73	17.28	59.32	3.80	17.35
IX Fumaronitrile	2/1	115[c]	*n*-Butyl ether	54	132.5	C₁₄H₁₄N₂O₄	61.31	5.15	10.20	61.54	5.20	10.22
X Acrylonitrile	3/1	144	Liquid	36	142–144 (0.1 mm.)	C₁₂H₁₅NO₄	62.64	6.07	5.62	62.53	6.14	5.32
XI Diethyl fumarate	1/1	138	Liquid	48	200 (1.5 mm.)	C₁₈H₂₄O₈	58.69	6.57		58.71	6.63	
XII Diethyl maleate	1/1	72	Liquid	37	180 (0.3 mm.)	C₁₈H₂₄O₈	58.69	6.57		58.76	6.55	
XIII[b] Maleic anhydride	1/1	68	Ethanol	69	115.5–116.0[c]	C₁₄H₁₄O₇	57.14	4.80		57.23	4.86	
XIV Chloromaleic anhydride	1/1	90	Benzene	59	141–142	C₁₄H₁₃ClO₇	51.10	3.79		51.21	4.04	

[a] Reactions run on steam bath without solvent. [b] This compound is transparent in the ultraviolet region between 240 and 340 mμ with only slight end absorption down to 220 mμ. [c] 1 ml. of benzene/ml. of diene.

CHART II
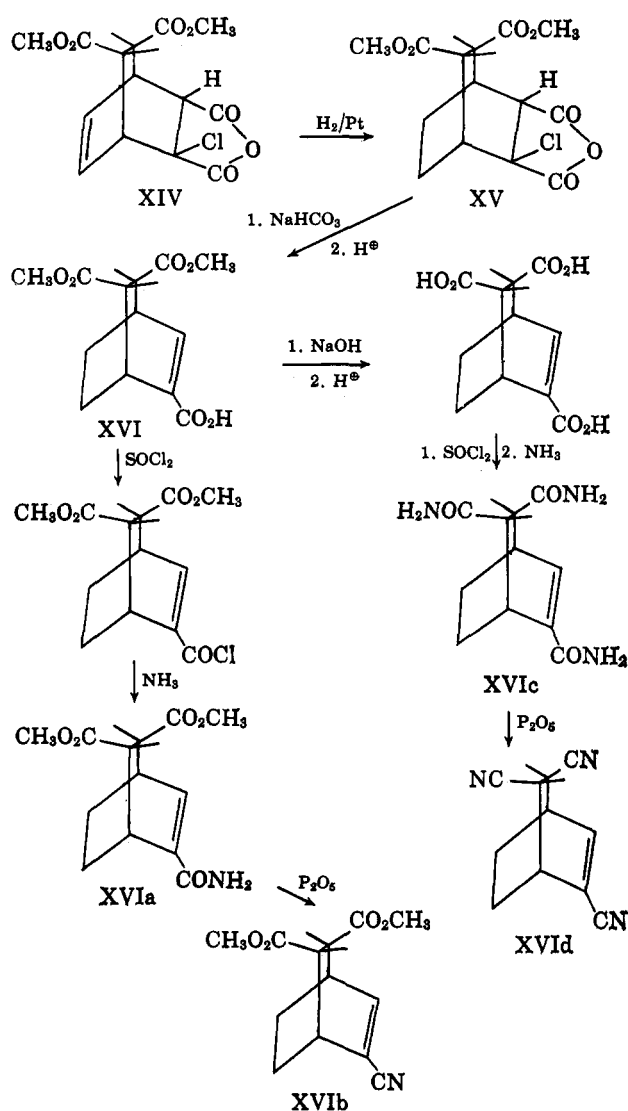
Dimethyl Cyclohexa-2,6-diene-1,2-dicarboxylate (IIg).—Thermal rearrangement of Ia by boiling in aqueous solution for 9–10 hr. provided IIa, m.p., 215°, in agreement with the reported[6] value; infrared, 1705, 1690 cm.⁻¹; ultraviolet, λmax 273 mμ (log ε 2.972) in ethanol.

Anal. Calcd. for C₈H₈O₄: C, 57.14; H, 4.80. Found: C, 57.29; H, 4.69.

Conversion of IIa to the dimethyl ester (II) was accomplished by means of absolute methanol and an acid catalyst (4% added concentrated hydrochloric acid) in 80–88 % yields, b.p. 90° (0.3 mm.); infrared, 1740, 1650, 1690 cm.⁻¹; ultraviolet, λmax 274 mμ (log ε 3.013).

Anal. Calcd. for C₁₀H₁₂O₄: C, 61.21; H, 6.17. Found: C, 61.34; H, 6.23.

The foregoing acid (IIa) and its dimethyl ester (II) were inactive in the Diels–Alder reaction with maleic anhydride, diethyl maleate, diethyl fumarate, fumaronitrile, acrylonitrile, and dimethyl acetylenedicarboxylate. A red-brown TCNE complex of undetermined composition was obtained but could not be converted into a true adduct. The dianion of the acid also was inactive.

Dimethyl Cyclohexa-1,3-diene-1,4-dicarboxylate (III).—The acid (IIIa) was prepared by the procedure of Guha and Hazra[8] (m.p. above 360°), and the dimethyl ester (III) was prepared from it by treatment with thionyl chloride and then methanol, m.p. 84–85°, lit.[8,9] 78–85°. Vapor phase chromatography at 200° of the analytical sample using silicone oil on Chromasorb or silicone gum rubber gave evidence of contamination only by IV.

Anal. Calcd. for C₁₀H₁₂O₄: C, 61.21; H, 6.17. Found: C, 61.03; H, 6.20.

Dimethyl Cyclohexa-1,5-diene-1,4-dicarboxylate (IV).—Hydrolysis of 5.0 g. of III by refluxing in a solution of 5.6 g. of potassium hydroxide in 5.0 ml. of water for 3.5 days,[9] followed by cooling in an ice bath and acidification with concentrated hydrochloric acid to pH 2 afforded a white precipitate (IVa) which was washed well with water and dried *in vacuo* over phosphorus pentoxide. Conversion of 2.0 g. of IVa to the dimethyl ester (IV) was accomplished by gentle warming with a threefold excess (9.9 g.) of phosphorus pentachloride for 30 min. followed by dropwise addition of excess (20 ml.) of absolute methanol to the ice-cooled reaction mixture. Further cooling afforded a white precipitate which was refrigerated for several hours and subsequently washed with cold absolute methanol. Recrystallization from ethyl acetate yielded IV, m.p. 129.5–130.5°, lit.[17] 128.4–129.4°. The infrared spectrum shows bands at 1712 (s), 1730 (sh), 1652 cm.⁻¹.

Anal. Calcd. for C₁₀H₁₂O₄: C, 61.21; H, 6.17. Found: C 61.17; H, 6.27.

Vapor phase chromatography of an analytical sample showed contamination only by a small amount of III.

Interconversions of III and IV.—Whenever the 1,5-diene (IV) was subjected to heat, either in methanol containing a trace of sodium methoxide, or on vacuum sublimation, substantial quantities were converted into the 1,3-diene (III). The change was followed by v.p.c. which revealed, as might be expected, that even analytical samples of IV (1° melting range) afforded appreciable amounts of III. On standing for long periods of time, samples of IV slowly rearranged to give appreciable III. Conversion in the opposite direction was achieved as reported in the preparation of IV.

Tetracyanoethylene Complex with III (V).—A mixture of 4.0 g. of III and 3.0 g. of tetracyanoethylene (TCNE) in 10 ml. of benzene was heated on the steam bath for 114 hr. after which time 20 ml. of additional benzene was added, the solution warmed on the steam bath and then filtered. On cooling, the filtrate deposited a dark yellow solid (4.8 g.) which was recrystallized from benzene, affording yellow crystals, m.p. 120–140°. Sublimation at 95° (0.2 mm.) gave bright yellow needles (V) with the same melting range, which was not improved by repeated recrystallizations from benzene.

Anal. Calcd. for C₁₆H₁₂N₄O₄: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.30; H, 3.61; N, 17.29.

Repetition of this experiment and treatment of the product with methanol resulted in the appearance of a deep red color and partial solution of V. The mixture was gently heated for a few

(17) M. T. Bogert and C. P. Harris, *J. Am. Chem. Soc.*, **41**, 1683 (1919).

minutes until complete solution was effected, and on cooling there was obtained a white crystalline product, m.p. 130–131°, which did not depress the melting point of IV and which possessed the same infrared spectrum as IV.

Spectrographic data relating to V are reported in Table III.

Reaction of IV with TCNE (VII).—A recrystallized sample of IV (∼ 2 g.) was added to a solution of 1.61 g. of resublimed TCNE in boiling methylene chloride whereupon a yellow color developed. After all of IV was added the color was orange; boiling was continued for 1 hr. Next the warm solution was filtered and concentrated under reduced pressure, cooled, and the yellow precipitate collected after standing at 0° for 48 hr., 1.9-g. canary yellow crystals, m.p. 160–176° after sublimation. Further purification was unsucessful.

Anal. Calcd. for $C_{28}H_{12}N_{12}O_4$ (IV · 3 TCNE): C, 57.93; H, 2.08; N, 28.96. Found: C, 57.92, 57.87; H, 2.00, 1.71; N, 29.56.

1,4-Dicarbomethoxybicyclo[2.2.2]oct-5-ene-endo-2,3-dicarboxylic Anhydride (VI).—A mixture of 35 g. of III and 18.8 g. of maleic anhydride was heated at 155° for 64 hr. and then cooled and triturated with ether, whereupon a solid was obtained and filtered off. After being throughly washed with ether, the product was recrystallized from a small volume of benzene giving needles (29.1 g., 55 %), m.p. 191.5°. The infrared spectrum showed both anhydride (1865, 1780 cm.$^{-1}$) and ester (1745 cm.$^{-1}$) bands, and with C–C double bond at 1620 cm.$^{-1}$. The compound is transparent in the ultraviolet from 240 to 340 mμ with only very weak end absorption down to 220 mμ.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 57.34; H, 5.03.

Hydrogenation of the adduct VI over Adams' catalyst in dioxane for 27 hr. afforded a white solid which on recrystallization from benzene afforded cubes (VIa), m.p. 158°, which gave negative tests for unsaturation.

Anal. Calcd. for $C_{14}H_{16}O_7$: C, 56.75; H, 5.44. Found: C, 56.77; H, 5.38.

Hydrolysis of the reduced adduct was accomplished by heating in 20% potassium bicarbonate solution on the steam bath for 20 min. with occasional stirring. The resultant solution was cooled and acidified with concentrated hydrochloric acid and then allowed to stand in the refrigerator for 2 hr. The precipitate was filtered and carefully washed with water and then dried in an air stream at room temperature to give a white powder (VIb), m.p. 177–178° (95%). The infrared spectrum lacked anhydride absorption.

Anal. Calcd. for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.62; H, 5.95.

An attempt to effect oxidative decarboxylation[18] was abortive.

By reaction of 11.5 g. of IV with 5.77 g. of maleic anhydride in 30 ml. of benzene on the steam bath for 139 hr., followed by evaporation of the benzene, addition of 40 ml. of ether, and cooling in the refrigerator for 3 hr., there was obtained 12.1 g. of a white solid. After recrystallization from ethanol the product (10.6 g. of white needles) melted at 190.5–191.0° and failed to depress the melting point of VI obtained from III and maleic anhydride. Likewise the infrared spectrum was identical with that of VI.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found C, 56.96; H, 4.96.

Hydrogenation of this adduct as for VI afforded the same product, 1,4-dicarbomethoxybicyclo[2.2.2]octane-2,3-dicarboxylic anhydride (VIa).

Reaction of Ia with Tetracyanoethylene.—A solution of the diene Ia (2.0 g.) and TCNE (1.6 g.) in 25 ml. of tetrahydrofuran was refluxed for 16.5 hr. Evaporation of the solvent afforded a brown gum which on trituration with nitromethane yielded a solid (m.p. 205–208°), which was recrystallized from water to give white plates, m.p. 209°, which was undepressed on admixture with Ia and which possessed an infrared spectrum identical with that of Ia. The nitromethane was evaporated from the filtrate and the brown gummy residue was treated with a hot 2:1 benzene–petroleum ether (b.p. 60–75°) mixture. Filtration and cooling of the filtrate afforded a yellow solid, m.p. 196–197°, which was crystallized from chlorobenzene to give a small quantity of yellow crystals (0.23 g., m.p. 198°); this proved to be TCNE (mixture melting point and superposable infrared spectra). Evaporation of the filtrate gave a solid which was recrystallized

from petroleum ether to give white needles (0.32 g., m.p. 129–130°). A mixture melting point determination and infrared analysis showed this to be phthalic anhydride, and more of this substance was recovered from the gum remaining after the benzene–petroleum ether extraction (0.40 g.). The residual gum was not further examined.

Bicyclo[2.2.2]oct-2-ene-endo-5,7-exo-6,8-tetracarboxamide (XIa).—Ammonolysis of XII (3.7 g.) was accomplished by allowing it to stand at room temperature for 12 days in 250 ml. of ammonia-saturated (cold) absolute methanol containing a trace of sodium methoxide.[12] Work-up at the end of this period afforded a monoethyl ester triamide (XIIa).

Anal. Calcd. for $C_{14}H_{19}N_3O_5$: C, 54.36; H, 6.19; N, 13.59. Found: C, 54.81; H, 6.01.

The ammonolysis was repeated on XIIa, and after 9 days the methanol was evaporated, leaving a gummy solid which upon trituration with ether afforded a white product which was recrystallized from aqueous methanol (1:2), 1.8 g., m.p. 290–293° dec. (red color).

Anal. Calcd. for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.51; H, 5.64; N, 19.82.

Conversion of XI to XIa.—Ammonolysis of XI (4.5 g.) was accomplished as for XII, including interruption, at which point infrared analysis showed the process to be incomplete. After the additional 9 day-period the product was worked up and recrystallized from aqueous methanol (2:3), white needles, 2.1 g., m.p. 289–300° dec. (red color). A mixture melting point with XIa showed no depression, and potassium bromide pellet infrared spectra[19] of products from XI and XII were superimposable.

Anal. Calcd. for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.42; H, 5.55; N, 20.00.

2-Chloro-trans-5,6-dicarbomethoxybicyclo[2.2.2]octane-2,3-dicarboxylic Anhydride (XV).—Compound XIV (25 g.) was hydrogenated at 3 atm. in 400 ml. of glacial acetic acid for 24 hr. at room temperature over 0.8 g. of Adams' catalyst. The residue after filtration and evaporation of the filtrate was crystallized from 3:1 benzene–petroleum ether (60–75°), m.p. 110°; yield was nearly quantitative, unsaturation tests negative.

Anal. Calcd. for $C_{14}H_{15}ClO_7$: C, 50.80; H, 4.54. Found: C, 50.90; H, 4.51.

trans-5,6-Dicarbomethoxybicyclo[2.2.2]oct-2-ene-2-carbonitrile (XVIb).—An 8.8-g. sample of XVI prepared from XV by treatment with hot sodium bicarbonate[1] was refluxed with 35 ml. of thionyl chloride, the excess of which was distilled, and the residual acid chloride was added dropwise to 50 ml. of ice-cooled 35% ammonium hydroxide solution. Stirring was continued for an additional 1.5 hr., and after standing 24 hr. in the refrigerator, the mixture was filtered. The residue was washed with water, dried *in vacuo*, and crystallized from benzene to give colorless crystals of XVIa, 6.3 g., m.p. 145°. The infrared spectrum showed both ester and amide bands.

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.40; H, 6.49; N, 5.31.

A 6.0-g. sample of XVIa was refluxed with 60 ml. of thionyl chloride for 28 hr. and then allowed to stand at room temperature for 31 hr. Evaporation of the excess thionyl chloride left a light brown oil which was distilled to give a light yellow oil, 4.7 g., b.p. 131–134° (0.16 mm.). The product was cloudy but resisted all attempts at crystallization, and two additional distillations did not remove the turbidity.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.38; H, 6.13; N, 5.50.

Bicyclo[2.2.2]oct-2-ene-2-trans-5,6-tricarbonitrile (XVId).—A 14.5-g. sample of XVI was stirred with 55 ml. of 20% aqueous sodium hydroxide at room temperature for 113 hr. and then the solution was acidified with concentrated hydrochloric acid and allowed to stand in the refrigerator for 2 hr., whereupon a white solid precipitated, was collected by filtration, washed with water, and dried *in vacuo* to give 8.6 g. of a white powder, m.p. 225–227°. A small sample of this was recrystallized from 1:1 ethyl acetate–petroleum ether (60–75°). The product, m.p. 228.5°, showed no ester absorption in the infrared spectrum; and, although microanalysis for carbon and hydrogen showed too much of each, 8.0 g. of the crude triacid was refluxed for 64 hr. with 75 ml. of thionyl chloride. Evaporation of the excess thionyl chloride afforded a light yellow oil which was added dropwise with stirring to 200 ml. of ice-cooled 35% ammonium hydroxide solu-

(18) C. A. Grob, M. Onta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).

(19) Very kindly obtained by Mr. B. E. Wenzel of this department.

tion. The mixture was stirred for an additional 2 hr. and then was allowed to stand for 2 days in the refrigerator. The solid was collected by suction filtration, washed with water, and dried *in vacuo*, 6.1 g., m.p. 287–289°. Recrystallization proved difficult, solubility in petroleum ether, benzene, tetrahydrofuran, chloroform, and water being poor, but it was finally effected from absolute methanol containing a few drops of absolute ethanol, in which this triamide (XVIc) is more soluble, m.p. 260.0–261.2° dec. (red color).

Anal. Calcd. for $C_{11}H_{15}N_3O_3$: C, 55.58; H, 6.37; N, 17.71. Found: C, 55.42; H, 6.46; N, 17.62.

Finally a 0.24-g. sample (1 mmole) of XVIc was very finely

ground in a mortar and placed in a vacuum sublimation apparatus along with 1.14 g. of phosphorus pentoxide (8 mmoles) and a number of glass beads. The components were intimately mixed by agitation for several minutes, and then the apparatus was heated slowly to 130° and finally to 160° at 0.005 mm. Heating was continued for 3 hr., during which time the mixture became dark brown and some of the phosphorus pentoxide sublimed along with the product (50.0 mg., crude). The crude sublimate was recrystallized from absolute methanol to which was added a trace of water, m.p. 129.0–130.5°.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.27; H, 4.92. Found: C, 71.94; H, 5.07.

Synthetic Studies of Potential Antimetabolites. IX. The Anomeric Configuration of Tubercidin
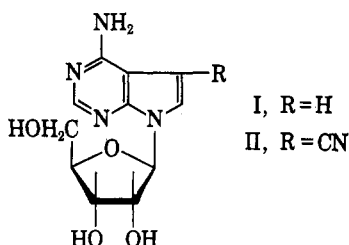
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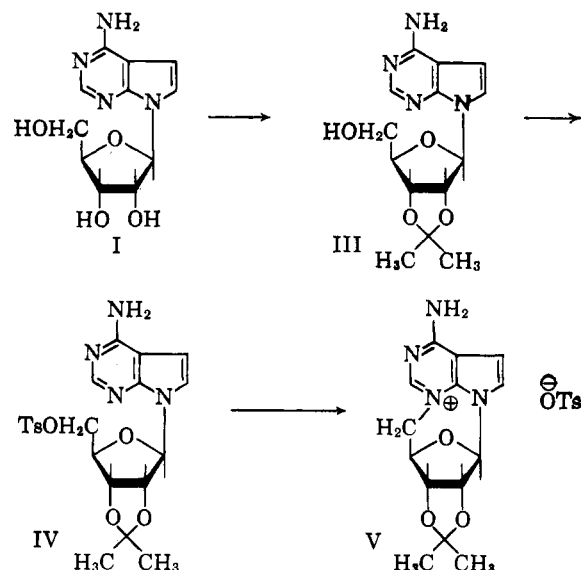
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The glycosyl center of the antibiotic nucleoside, tubercidin (I), has been established as β-D on the basis of a series of reactions. The nucleoside I was converted to 2,3-O-isopropylidenetubercidin (III) which was in turn converted to the 2,3-O-isopropylidene-5-O-p-tolylsulfonyl derivative IV. Treatment of IV with boiling acetone gave rise to a water-soluble, intramolecularly quaternized nucleoside V. 3-(2,3-O-Isopropylidene-5-O-p-tolyl-sulfonyl-β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (IX) was prepared and converted to X by intramolecular alkylation. The chromatographic properties and spectral characteristics of V were compared with those of X and VII (the latter is the similar intramolecularly quaternized derivative in the adenosine series).

The antibiotic nucleoside, tubercidin, was isolated from *Streptomyces tubercidicus* by Anzai and Marumo[2] and has been assigned the 4-amino-7-D-ribofuranosyl-7H-pyrrolo[2,3-d]pyrimidine structure (I).[3] This is the first example of the natural occurrence of a pyrrolo-[2,3-d]pyrimidine ring system. Because of its unique structure, tubercidin as well as toyocamycin (5-cyano-tubercidin, II)[4] has attracted interest. The establish-

ment of the structure of I[3] was based on degradative work, elementary analyses, and spectral examination, and is quite reasonable. However, assignment of the β-D configuration[3] to the anomeric carbon atom in I was not unequivocal. Since we are interested in the total synthesis of I and in the preparation of potential antimetabolites containing this ring system, we have felt it mandatory to establish unequivocally the configuration at the glycosyl center of tubercidin. The present paper reports an investigation on the glycosyl linkage.

Tubercidin (I) was converted to the 2,3-O-isopropylidene acetal III in almost quantitative yield by a reported procedure.[5] Paper chromatography of the product gave in three solvent systems (1-butanol–

(1) Part VIII of this series: Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, *Chem. Pharm. Bull.* (Tokyo), **11**, 1091 (1963).

(2) K. Anzai and S. Marumo, *J. Antibiotics* (Tokyo), *Ser. A*, **10**, 20 (1957).

(3) S. Suzuki and S. Marumo, *ibid.*, **14**, 34 (1961).

(4) K. Ohkuma, *ibid.*, **14**, 343 (1961).

(5) A. Hampton and D. I. Magrath, *J. Am. Chem. Soc.*, **79**, 3250 (1957).

water, ethanol–ammonia–water, and water) a single spot whose R_f values were 0.16, 0.38, and 0.43, respectively. These ultraviolet-absorbing spots on paper chromatograms failed to give a positive test with the periodate spray reagent.[6] The ultraviolet absorption spectrum of the spot was very similar to that of tubercidin (I), see Fig. 1, indicating that the chromophore of I was not appreciably affected on conversion of I to III. On the basis of these facts, the product was assigned the 2,3-O-isopropylidene structure III, although elementary analyses were not done because of the small amount of the material available. The compound III was then converted to the 5-O-p-tolyl-sulfonate IV with p-toluenesulfonyl chloride in pyridine. The ultraviolet absorption maximum of IV was

(6) A combination spray of 2% aqueous metaperiodate, followed by the benzidine spray (benzidine–glacial acetic acid–absolute ethanol, 500 mg./200 ml./80 ml.).