lyzed with potassium iodide. This chloride likewise failed to react with either the silver or sodium salt of phenyl-2-thienylacetic acid. Esters were therefore prepared, (I) by action of an acid chloride on the basic alcohol in benzene solution, (II) by ester exchange[12] with methyl esters using sodium methoxide as catalyst in refluxing *n*-heptane and (III) by direct esterification of an acid with the alcohol in refluxing benzene with gaseous hydrogen chloride. This latter method was used when acid chlorides could not be made or were not available and in those cases where methyl esters were unstable toward sodium methoxide.

Hydrohalides were prepared by conventional methods or obtained as products of the esterifications. Quaternary salts were best prepared in acetonitrile solutions from free bases and the desired alkyl halide.

The preliminary antispasmodic screening data reported herein were graciously supplied by Dr. A. M. Lands and co-workers in the Pharmacological Research Laboratories. All activities were obtained by means of the Magnus technique against acetylcholine induced spasms in isolated strips of rabbit jejunum and are recorded as relative activities in comparison to atropine at 100%.

## Experimental

**Methyl Phenyl-2-thienylglycolate.**—A solution of 37.4 g. (0.1595 mole) of phenyl-2-thienylglycolic acid, 300 cc. of anhydrous methanol and 5 cc. of 98% sulfuric acid was refluxed for 17 hours. The excess methanol was removed by distillation and the red residue treated with water. The insoluble ester was extracted with ether, the extract back washed once with dilute sodium bicarbonate solution and then dried with anhydrous magnesium sulfate. After filtration and removal of solvent by distillation the deep red colored residual oil was distilled; yield of light straw colored oil 29.3 g. (74%), b.p. 109–113° (0.02–0.03 mm.), $n^{25}D$ 1.5694.

*Anal.* Calcd. for $C_{13}H_{12}O_2S$: sapn. equiv., 248.3. Found: sapn. equiv., 250.3.

**Methods of Esterification. I. With Acid Chlorides.**—Equimolar quantities of an acid chloride and 3-(1-methylpiperidyl)-carbinol were refluxed in a benzene solution. Invariably the crystalline ester hydrochloride separated out during this process.

**II. With Methyl Esters.**—A solution of a methyl ester and an equivalent quantity of 3-(1-methylpiperidyl)-carbinol in *n*-heptane (b.p. 98°) was placed in a flask connected to a water separator with 0.5 g. of sodium methoxide. Ester exchange was readily observed as liberated methanol separated from the refluxing mixture. The free crude basic ester was obtained by first removing the solvent by distillation *in vacuo* and then treating the residue with dilute sodium carbonate solution. The insoluble oil was extracted with ether and the extract dried with anhydrous magnesium sulfate. After filtration the ether was removed by distillation leaving the oily base in crude form for conversion to either a hydrohalide or quaternary salt.

**III. With Acids.**—A mixture of equimolar quantities of acid and 3-(1-methylpiperidyl)-carbinol with benzene was placed in a flask fitted with a submerged gas inlet tube, water separator, condenser, etc. Hydrogen chloride was bubbled into the reaction at a moderate rate while refluxing. The rate of esterification was readily followed by the separation of water. Usually the theoretical amount collected within 15 hours depending somewhat upon the rate of gas introduction. Hydrochlorides of the basic ester were isolated in yields ranging from 50 to 60% by usual methods.

**Acknowledgment.**—The author wishes to thank Mr. M. E. Auerbach and Mr. K. D. Fleischer and their staffs for the analytical data reported herein.

RENSSELAER, NEW YORK

(12) A. R. Surrey, THIS JOURNAL, **70**, 2190 (1948).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

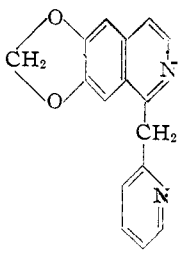
# The Synthesis of a 4-Pyridyl Analog of Papaverine

BY C. R. NOLLER AND E. A. WUNDERLICH

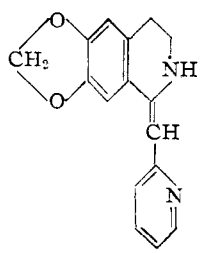
RECEIVED JANUARY 18, 1952

Comparison of the ultraviolet absorption spectrum of 1-(4-pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline with those of the 2- and 3-pyridyl isomers indicates that the stability of the exocyclic form of the 2-isomer, and possibly its resistance to dehydrogenation, is the result of proton bonding between the two nitrogen atoms. The 4-pyridylmethyl isomer undergoes very rapid autoxidation to 1-isonicotinyl-3,4-dihydro-6,7-methylenedioxyisoquinoline. The latter compound has been converted to the papaverine analog, 1-(4-pyridylmethyl)-6,7-methylenedioxyisoquinoline, which has practically no spasmolytic activity.

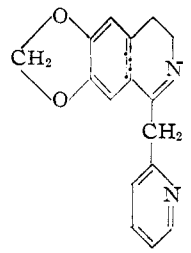
During attempts to synthesize 1-(2-pyridylmethyl)-6,7-methylenedioxyisoquinoline (I), the ultraviolet absorption spectrum of the intermediate 3,4-dihydro derivative indicated that it was 1-(2-pyridylmethylene)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (II) rather than the expected 1-(2-pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (III).[1] Later the 3-pyridylmethyl analog was synthesized,[2] and its absorption spectrum indicated that it has the expected structure, namely, that of 1-(3-pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (IV).



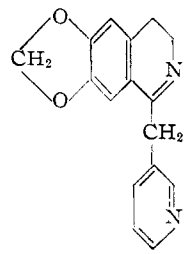
I



II



III

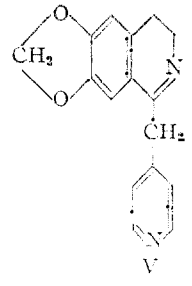


IV

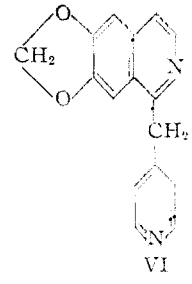
(1) J. L. Bills and C. R. Noller, THIS JOURNAL, **70**, 957 (1948).
(2) C. R. Noller and M. Azima, *ibid.*, **72**, 17 (1950).

Whereas II could not be converted to I,[1] IV readily was oxidized to the papaveraldine analog which was reduced to the papaverine analog.[2] The greater stability of II as compared with III was ascribed to the possibility of proton bonding between the two nitrogen atoms in II.[2] Such proton bonding is not possible in the corresponding isomeric structure for IV.

Since the hydrogen of the methylene group of III would be expected to ionize more readily than that of IV, which also might account for the greater stability of II, it became of interest to synthesize the corresponding 4 derivative (V). In this compound the methylene hydrogen might be expected to be almost as acidic as that in III, but proton bonding again is not possible. It was of interest also to determine whether V could be converted into the papaverine analog, VI, and if so, to compare the physiological properties of VI with those of the corresponding 3-pyridylmethyl derivative.

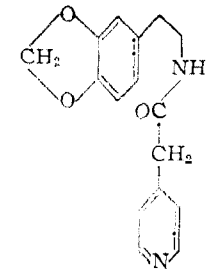


V

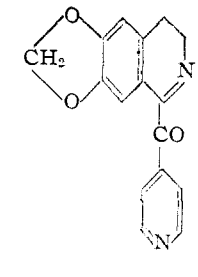


VI

4-Pyridylacetamide was synthesized from 4-vinylpyridine by the Willgerodt reaction.[3] The amide was condensed directly with homopiperonylamine[2] by heating in tetralin solution to give N-(4-pyridylacetyl)-homopiperonylamine (VII). When this compound was cyclized with phosphorus oxychloride by the usual procedure, the product was 1-isonicotinyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (VIII).



VII



VIII

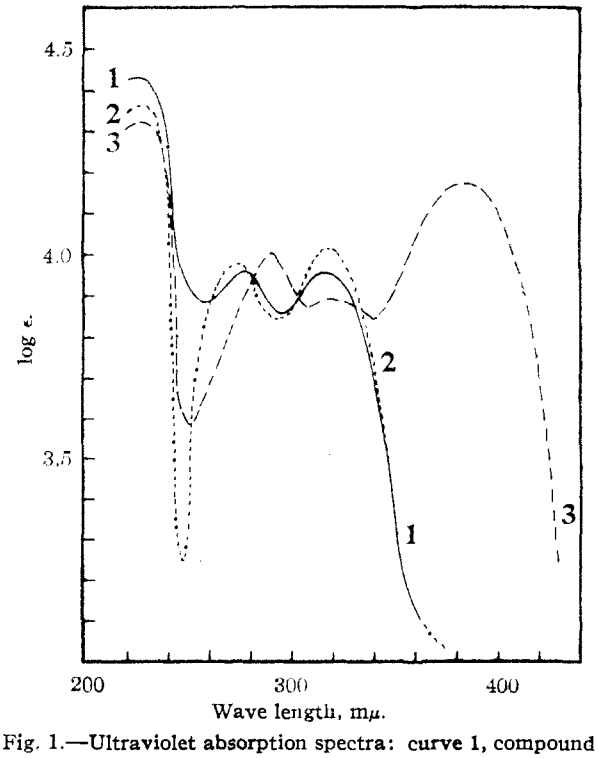
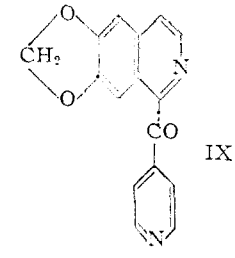



Fig. 1.—Ultraviolet absorption spectra: curve 1, compound V; curve 2, compound IV[2]; curve 3, compound II[1].

(3) M. Carmack and D. F. De Tar, *ibid.*, **68**, 2033 (1946).

The marked ease of oxidation of certain benzyldihydroisoquinolines has been noted previously.[4] Since it was desirable to obtain the unoxidized dihydro derivative to determine whether it contained an endo- or an exocyclic double bond, the cyclization and purification was carried out in a nitrogen atmosphere. Even under these conditions oxidation was not prevented entirely, but it was possible to obtain a small amount of an impure product, the absorption spectrum of which (curve 1, Fig. 1) was very similar to that of IV (curve 2, Fig. 1) and entirely different from that of II (curve 3, Fig. 1). Hence it seems likely that the structure of II is associated with proton bonding within the molecule.

The oxidized product, VIII, was dehydrogenated to the papaveraldine analog, IX, by drawing air through an alkaline solution in methyl alcohol. Reduction with zinc in acetic acid[2] gave the papaverine analog, VI. The absorption spectra (curve 1, Fig. 2 and curve 1, Fig. 3) are compared with those of previously recorded analogs.



IX

We wish to thank Dr. R. H. Dreisbach of the Department of Pharmacology of Stanford University Medical School for testing the antispasmodic activity of 1-(4-pyridylmethyl)-6,7-methylenedioxyisoquinoline (VI) for us. It produced only a slight diminution in activity of previously untreated rabbit small intestine (ileum) at a concentration of 0.01%. The effect was less than that produced by papaverine at a concentration of 0.001%. Thus the activity is even less than that of the 3-isomer.[2]

## Experimental

**4-Pyridylacetamide.**—A mixture of 22.0 g. of freshly distilled 4-vinylpyridine, purchased from Reilly Tar and Chemical Corporation, 25 g. of flowers of sulfur, 35 g. of concentrated aqueous ammonia and 15 cc. of purified dioxane was heated in a sealed glass tube for 4.5 hours at 165°.

(4) J. S. Buck, R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 2176 (1924); J. S. Buck, THIS JOURNAL, **52**, 3610 (1930); A. Lindenmann, *Helv. Chim. Acta*, **32**, 69 (1949).

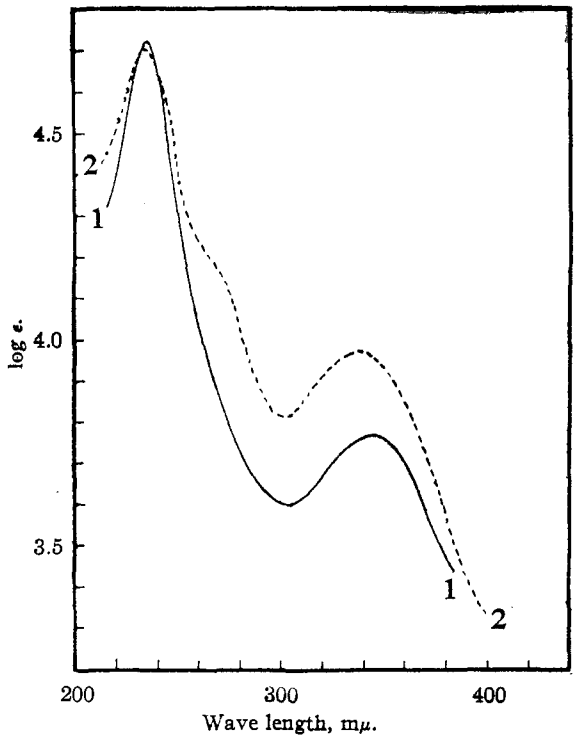



Fig. 2.—Ultraviolet absorption spectra: curve 1, 1-isonicotinyl-6,7-methylenedioxyisoquinoline (IX); curve 2, 1-nicotinyl-6,7-methylenedioxyisoquinoline.[2]

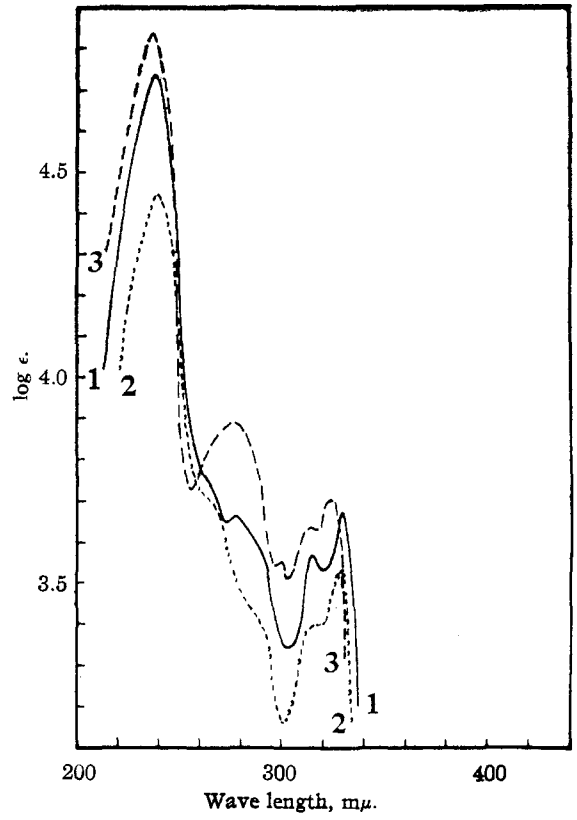



Fig. 3.—Ultraviolet absorption spectra: curve 1, 1-(4-pyridylmethyl)-6,7-methylenedioxyisoquinoline (VI); curve 2, 1-(3-pyridylmethyl)-6,7-methylenedioxyisoquinoline[2]; curve 3, papaverine.[2]

After cooling, the tube content was evaporated to dryness under reduced pressure from a water-bath kept below 70° to prevent darkening of the product. The residue was extracted with four 50-cc. portions of boiling water. The combined water extracts were decolorized with Norit and evaporated to dryness under reduced pressure. The white residue was dissolved in chloroform and precipitated by the addition of petroleum solvent (b.p. 55–85°). The yield was 12.7 g. (45%) of white crystals melting at 138–141°. A sample prepared for analysis by crystallizing five times from ethyl acetate and drying at 80° and 20 mm., melted at 141–142°.[5]

*Anal.*[6] Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92. Found: C, 61.75; H, 6.04.

Comparable yields were obtained from 4-pyridyl methyl ketone. Reducing the amount of sulfur, using an iron autoclave, omitting the dioxane, or heating at higher temperatures or for a longer time gave reduced yields. No 4-pyridylacetic acid ever was obtained. Its decomposition to 4-methylpyridine evidently proceeds at a faster rate than the hydrolysis of 4-pyridylacetamide.

**N-(4-Pyridylacetyl)-homopiperonylamine (VII).**—In a 25-cc. flask equipped with an air condenser were placed 3.6 g. (0.021 mole) of homopiperonylamine,[1] 2.9 g. (0.021 mole) of 4-pyridylacetamide and 12 cc. of tetralin as a high-boiling medium. The flask was heated in an oil-bath at 200° for two hours. Crystallization was induced by cooling and scratching the walls of the flask. After standing overnight in the cold room at 0°, the product was filtered, dissolved in hot carbon tetrachloride, and decolorized with Norit. On cooling the filtrate, 3.3 g. (0.016 mole, 73%) of white crystals separated which melted at 107–110°. After five crystallizations from carbon tetrachloride and drying at 80° and 20 mm., it melted at 110–111°.

*Anal.* Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.40; H, 5.58.

**1-(4-Pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (V) and 1-Isonicotinyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (VIII).**—A solution of 4.2 g. of N-(4-pyridylacetyl)-homopiperonylamine (VII) in 20 cc. of phosphorus oxychloride was refluxed by heating with an oil-bath at 120° for 40 minutes. The reaction mixture was poured onto cracked ice and the free base liberated by the addition of a saturated solution of sodium carbonate. A dark gum separated which adhered to the sides of the beaker. The gum and the aqueous emulsion were each extracted with four 50-cc. portions of chloroform, and the combined chloroform extracts were dried over sodium sulfate in a nitrogen atmosphere. After removing the chloroform, the residue was extracted with boiling cyclohexane under a nitrogen atmosphere. On cooling the cyclohexane solution, a few bright crystals melting at 134–140° separated. The absorption spectrum determined immediately after solution in ethyl alcohol (curve 1, Fig. 1) indicated that the compound was 1-(4-pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (V). All attempts to isolate a pure substance were unsuccessful, the final product always being that in which the methylene group had been oxidized to a carbonyl group.

When the cyclohexane extraction was carried out in air light yellow crystals were obtained, melting at 155–158°. After crystallizing four times from cyclohexane and drying at 80° and 20 mm., it melted at 158–159.5°. Analysis indicated that it was 1-isonicotinyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (VIII).

*Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32. Found: C, 68.66; H, 4.37.

**1-Isonicotinyl-6,7-methylenedioxyisoquinoline (IX).**—A solution of 0.5 g. of 1-isonicotinyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (VIII) in 10 cc. of a 10% solution of potassium hydroxide in methyl alcohol was refluxed for one hour and then evaporated by drawing a stream of air over the solution. The solvent was renewed five times during the process. The organic material was extracted with hot methyl alcohol and allowed to crystallize to give 0.35 g. (70%) of a cream-colored product melting at 213–215°. After three crystallizations from methyl alcohol and drying at 80° and 20 mm., it melted at 215.5–216.6°.

(5) All melting points are corrected.

(6) All analyses are microanalyses by Microchemical Specialties, Berkeley, Calif.

*Anal.* Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62. Found: C, 69.12; H, 3.69.

**1-(4-Pyridylmethyl)-6,7-methylenedioxyisoquinoline (VI).**—A solution of 0.35 g. of 1-isonicotinyl-6,7-methylenedioxyisoquinoline (IX) in 5 cc. of glacial acetic acid was stirred on the steam-bath while 1.77 g. of zinc dust was added over a period of three hours. Acetic acid was added from time to time to keep the volume of the solution constant. At the end of three hours the mixture was filtered and the residue washed with 20 cc. of boiling water. After removal of zinc with hydrogen sulfide and washing the precipitate with hot water, the filtrate was concentrated on the steam-bath to 20 cc., neutralized with sodium carbonate, and an excess of aqueous ammonia added. The free base was extracted with six 10-cc. portions of chloroform, and the extract dried over sodium sulfate and evaporated to dryness. The residue was crystallized from petroleum solvent (b.p. 55–85°) to give 0.04 g. of white crystals, m.p. 167–169°. After three more crystallizations and drying at 80° and 20 mm., it melted at 171–173°.

*Anal.* Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58. Found: C, 72.31; H, 4.61.

**Absorption Spectra.**—All of the absorption spectra measurements were made on freshly prepared solutions in 95% alcohol that had been distilled from potassium hydroxide. The concentrations were approximately $4 \times 10^{-5}$ molar. A Beckman spectrophotometer, model DU, was used.

STANFORD, CALIF.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

# Mycomycin. II. The Structure of Isomycomycin, an Alkali-Isomerization Product of Mycomycin[1,2]

BY WALTER D. CELMER AND I. A. SOLOMONS

RECEIVED FEBRUARY 1, 1952

Isomycomycin, a crystalline alkali-isomerization product of the antibiotic mycomycin, has been prepared and characterized. The structure of isomycomycin has been deduced from chemical and physical evidence as 3,5-tridecadiene-7,9,11-triynoic acid, $CH_3C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}COOH$.

The antibiotic mycomycin, an elaboration product of *Norcardia acidophilus*,[3] has been previously isolated in crystalline form and characterized.[4] This unstable compound was shown to be an optically active, highly unsaturated carboxylic acid having the empirical formula $C_{13}H_{10}O_2$ and structure[1] 3,5,7,8-tridecatetraene-10,12-diynoic acid (I).

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}CO_2H$$

I

Mycomycin undergoes extensive rearrangement in normal aqueous alkali metal hydroxide solution at 27° involving an allene to acetylene isomerization accompanied by migration of existing acetylenic bonds. The rearranged acid, isomycomycin, has been assigned[1] the structure 3,5-tridecadiene-7,9,11-triynoic acid (II).

$$CH_3{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}CO_2H$$

II

It is the purpose of this paper to describe further the preparation and derived structure of isomycomycin.

The extreme instability of mycomycin at the *p*H of its alkali metal salts and in liquid ammonia[4] prompted further investigation of possible base-catalyzed rearrangement reactions. Attempts to isomerize mycomycin in alcoholic alkali[5] and in various amines invariably gave black tarry products. However, when an excess of aqueous potassium, sodium or lithium hydroxide is added to mycomycin, the crystalline salt of an isomeric acid separates from solution within a few minutes. Acidification of a dilute aqueous solution of this salt precipitates the free acid, designated "isomycomycin," which can be recrystallized from ether–hexane. Isomycomycin is about one-fourth as active *in vitro* as mycomycin against *Mycobacterium tuberculosis* H37Rv, however, the activity against the mycomycin assay organism, *B. subtilis*,[4] is extremely low. Like mycomycin, isomycomycin has the empirical formula $C_{13}H_{10}O_2$ and takes up eight moles of hydrogen upon catalytic hydrogenation, yielding *n*-tridecanoic acid, thus excluding the possibility of branching or ring structure in the original molecule and establishing the length of the carbon chain. However, unlike mycomycin, the isomeric compound is optically inactive and analyzes for one C-methyl group (mycomycin has none). Its infrared spectrum exhibits no allenic nor terminal acetylenic absorption. Isomycomycin reacts with diazomethane to give a crystalline methyl ester, which in contrast to mycomycin methyl ester, does not react with alcoholic silver nitrate, substantiating the absence of a $-C{\equiv}CH$ functional group.[6] The ester reacts smoothly with fused maleic anhydride at 70°, yielding a crystalline monoaddition product.

The infrared spectra (Fig. 1) of isomycomycin, its methyl ester and the maleic anhydride adduct of the methyl ester exhibit a strong absorption band near 2200 cm.$^{-1}$ which is interpreted as a disubstituted carbon–carbon triple bond stretching frequency.[7] It has been observed that compounds containing conjugated polyacetylenic linkages have well-defined ultraviolet absorption, with the long wave length maxima spacings (1900–2300 cm.$^{-1}$)

(1) First reported in a Communication to the Editor, THIS JOURNAL, 74, 1870 (1952).

(2) Presented before the Division of Organic Chemistry at the Milwaukee meeting of the American Chemical Society, April 2, 1952.

(3) E. A. Johnson and K. L. Burdon, *J. Bact.*, **54**, 281 (1947).

(4) W. D. Celmer and I. A. Solomons, Abstracts 121st ACS Meeting, Milwaukee, March–April, 1952; THIS JOURNAL, **74**, 2245 (1952).

(5) (a) T. Moore, *Biochem. J.*, **31**, 138 (1937); (b) J. P. Kass and C. C. Burr, THIS JOURNAL, **61**, 3292 (1939).

(6) A. Behal, *Ann. chim.*, **15**, 408 (1888).

(7) (a) H. W. Thompson, *J. Chem. Soc.*, 328 (1948); (b) J. H. Wotiz and F. A. Miller, THIS JOURNAL, **71**, 3441 (1949); (c) N. B. Colthup, *J. Optical Soc. Am.*, **40**, 397 (1950).