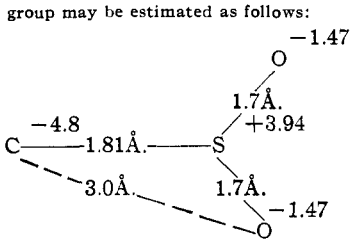
the chemical reactions from which the parallel between sulfone and carbonyl groups has been drawn are ionic reactions. An example is ionization of a hydrogen atom on an adjacent carbon atom.

$$R{-}\underset{X}{\overset{R}{C}}{-}H + :B \rightleftharpoons R{-}\underset{X}{\overset{R}{C^-}}: + BH^+$$

The influence of the substituent X on the course of this reaction, as on many other polar reactions, is undoubtedly due to a combination of two independent effects, a simple electrical effect and resonance or mesomeric interaction. The reaction as written will be favored if either or both effects stabilize the anion more than the undissociated molecule. An electrical effect will accomplish this stabilization if the group X has permanent dipoles with the positive poles directed toward the anionic carbon atom. The carbonyl group and, to a greater extent, the sulfonyl group are each of this character and both would thus favor ionization as indicated.[15] In addition, the unsaturation of the carbonyl group would permit an added mesomeric stabilization by allowing the negative charge to spread out in part to the oxygen atom. Since the evidence presented herein indicates that the sulfonyl group has little or no conjugative properties to a free radical, the close similarity in chemical properties of carbonyl and sulfonyl compounds in ionic reactions suggests that the strong electrical effect of the sulfonyl group is about equal to the combined electrical and resonance effects of the carbonyl group in stabilizing an adjacent carbanion.[15]

In view of these considerations indicating that a charge on an atom can be stabilized both by electrical and by mesomeric or resonance interaction, it would seem that stabilization of a free radical (or an excited) state is a much more nearly unequivocal criterion of mesomeric effects than is stabilization of a polar state.

(15) The direct coulombic stabilization of a carbanion by a sulfone group may be estimated as follows:



$(-4.8 \times 3.94/1.8 + 2(4.8 \times 1.47)/3.0) \times 14.45 = 60$ kcal./mole.

A similar calculation for the carbonyl group gives $(-4.8 \times 1.93/1.54 + 4.8 \times 1.93/2.5) \times 14.45 = 33$ kcal./mole. To attain approximately equivalent stabilization of the carbanion, the carbonyl group must therefore provide at least 25 kcal./mole more resonance stabilization than the sulfone group.

Summary

The copolymerization ratios for methyl vinyl sulfide with styrene and methyl acrylate and for methyl vinyl sulfone with styrene and vinyl acetate have been determined.

The low monomer reactivity of methyl vinyl sulfone supports the view that the sulfur–oxygen bonds are best described as semi-polar rather than covalent double bonds.

Copolymerization data and ultraviolet spectra indicate strong conjugative properties of a sulfide sulfur, interpreted in terms of mesomerism involving expansion of the sulfur octet.

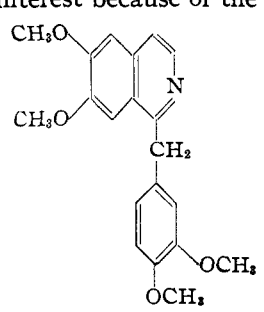
NOTRE DAME, INDIANA RECEIVED NOVEMBER 6, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

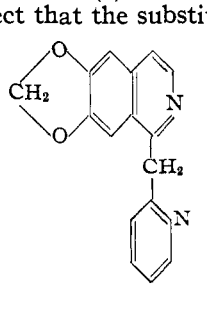
The Synthesis of a Pyridyl Analog of Papaverine

BY C. R. NOLLER* AND M. AZIMA

It has been pointed out previously[1,2] that compounds in which a pyridyl group replaces the dimethoxyphenyl group of papaverine (I) would be of interest because of the effect that the substitution might have on the physiological properties of the compound, and because of the possibility that such compounds might show antimalarial activity. Previous attempts to prepare 1-(α-picolyl)-6,7-methylenedioxyisoquinoline (II) have been unsuccessful, because it has not been possible to dehydrogenate the 3,4-dihydro or the 1,2,3,4-tetrahydro derivative without scission of the side chain.[1,2]



I



II

Determination of the absorption spectrum of the 3,4-dihydro derivative indicated that it was 1-(α-picolyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (III), whereas the corresponding phenyl analog is 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (IV).[2]

A possible explanation of the greater stability of the exocyclic structure for III as compared with IV is that proton bonding between the two nitrogen atoms is possible for III as indicated in formula V. If such is the case, the β-picolyl deriv-

* Harvard University Visiting Lecturer 1938–1939.

(1) Clemo, McIlwain and Morgan, *J. Chem. Soc.*, 610 (1936).

(2) Bills and Noller, THIS JOURNAL, **70**, 957 (1948).

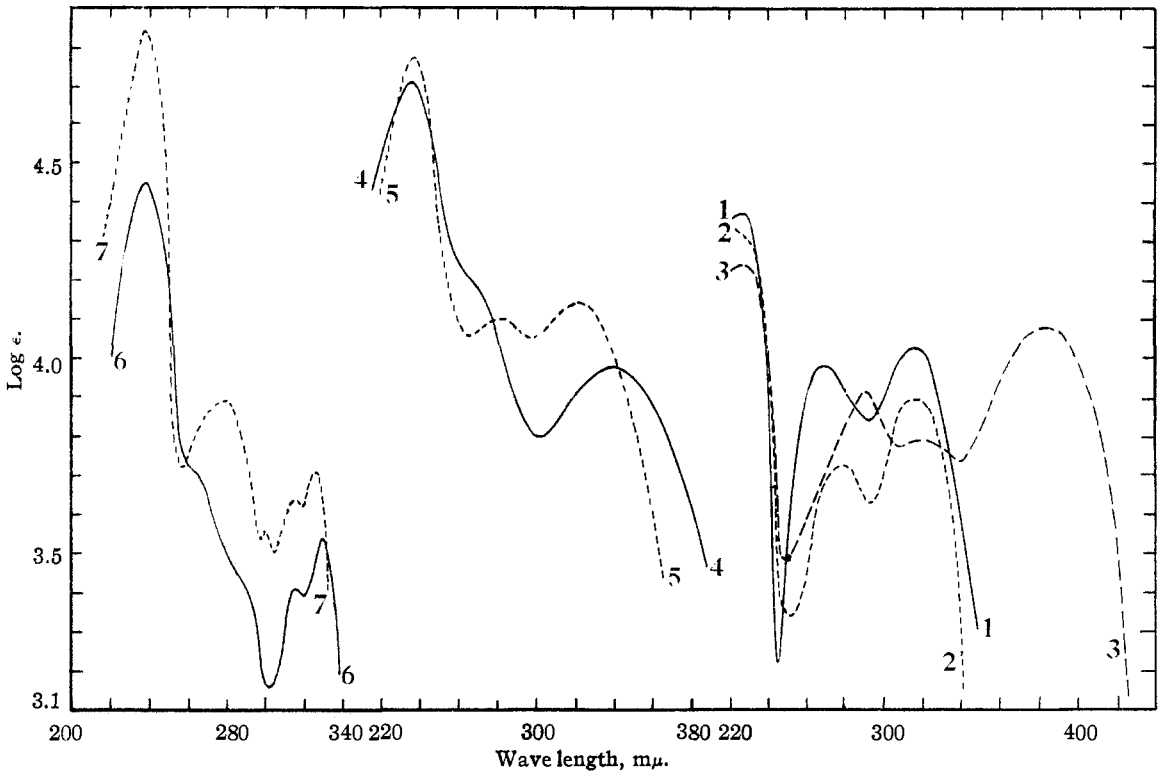
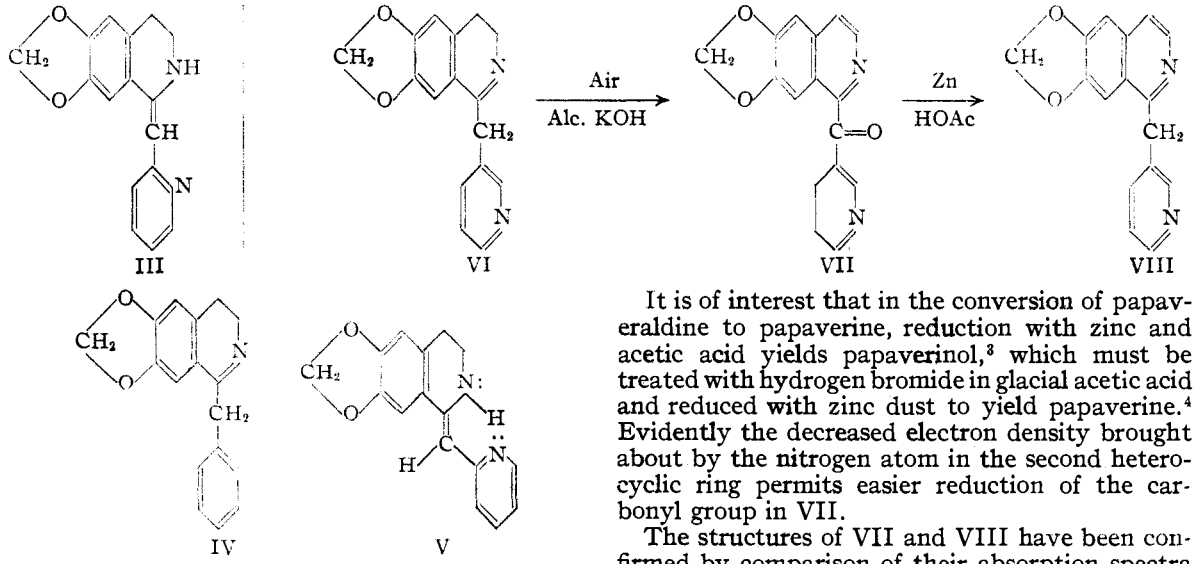


Fig. 1.—Ultraviolet absorption spectra in 95% alcohol. Curve 1, structure VI; curve 2, structure IV[2]; curve 3, structure III[2]; curve 4, structure VII; curve 5, papaveraldine; curve 6, structure VIII; curve 7, papaverine (I)

ative should have the normal structure (VI) since intramolecular proton bonding is not possible.



We have synthesized VI and find that the absorption spectrum indicates that it has the normal structure (Fig. 1, Curve 1). While it has not been possible to dehydrogenate VI directly to the isoquinoline, the action of air in alcoholic potassium hydroxide solution converted VI into the keto isoquinoline (VII) which was reduced with zinc and acetic acid to 1-(β-picolyl)-6,7-methylenedioxyisoquinoline (VIII).

It is of interest that in the conversion of papaveraldine to papaverine, reduction with zinc and acetic acid yields papaverinol,[3] which must be treated with hydrogen bromide in glacial acetic acid and reduced with zinc dust to yield papaverine.[4] Evidently the decreased electron density brought about by the nitrogen atom in the second heterocyclic ring permits easier reduction of the carbonyl group in VII.

The structures of VII and VIII have been confirmed by comparison of their absorption spectra (Curves 4 and 6) with those of papaveraldine and papaverine (Curves 5 and 7). A sufficient quantity of VIII is being prepared to determine whether it has antimalarial or antispasmodic activity. It is hoped also to convert it into the

(3) Stuchlik, *Monatsh.*, **21**, 813 (1900).

(4) Buck, Perkin and Stevens, *J. Chem. Soc.*, **127**, 1462 (1925).

diquaternary salt and to test the latter for curare activity.

ADDED TO PROOF.—1-(β-Picolyl)-6,7-methylenedioxyisoquinoline was examined for antispasmodic activity by Dr. R. H. Dreisbach of the Department of Pharmacology of Stanford University Medical School. A 2% solution in propylene glycol was diluted with water to give solutions of the desired concentration. The compound relaxes previously untreated rabbit ileum (small intestine) and also antagonizes spasm induced by barium chloride. The concentration required to produce these effects is from two to five times greater than the concentration of papaverine required to produce the same effects. Thus a concentration of 0.002% was somewhat less effective in relaxing untreated intestine than a concentration of 0.001% of papaverine.

Experimental

N-(β-Pyridylacetyl)-homopiperonylamine.—β-Pyridyl methyl ketone was prepared by the procedure of Hurd and Webb[5] and converted to methyl β-pyridylacetate by the Willgerodt reaction using the procedure of Hartmann and Bosshard.[6] The ester was condensed with homopiperonylamine[2] by the procedure reported previously for the α-pyridyl derivative.[2] The product was crystallized from carbon tetrachloride to a constant melting point of 100–100.5°; yield 65%.

Anal.[7] Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.55; H, 5.56.

1-(β-Picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (VI).—The above amide was cyclized by the procedure of Clemo, McIlwain and Morgan.[1] The product was crystallized from cyclohexane to a constant melting point of 117–119° (dec.); yield 89%.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30. Found: C, 72.65; H, 5.23.

The **dihydrochloride** of the base was prepared by adding an alcoholic solution of hydrogen chloride to an ether solution of the base. After crystallization from alcohol-ether, the light yellow crystals decomposed at 204°.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O_2$: Cl, 20.92. Found: Cl, 20.82.

1-Nicotinyl-6,7-methylenedioxyisoquinoline (VII).—A modification of the procedure used by Buck, Haworth and Perkin[8] for the preparation of papaveraldine was followed in which the intermediate dihydro derivative was not isolated. A solution of 2.5 g. of 1-(β-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline in 25 cc. of a 10% solution of potassium hydroxide in methyl alcohol was refluxed on the steam-bath for one hour. The solvent was evaporated by allowing a stream of air to pass over the solution, the solvent being renewed five times during the process. The resulting crystalline mass was filtered and recrystallized from methyl alcohol to give a yellow product weighing 1.4 g. and melting at 176–177°. The mother liquors gave another 0.12 g. making a total yield of 60%. Further recrystallizations did not change the melting point.

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.06. Found: C, 69.34, 69.38; H, 3.75, 3.69; N, 9.52.

1-(β-Picolyl)-6,7-methylenedioxyisoquinoline (VIII).—A solution of 0.25 g. of 1-nicotinyl-6,7-methylenedioxyisoquinoline in 2.5 cc. of glacial acetic acid was stirred on the steam-bath while 1.2 g. of zinc powder was added over a period of three hours. The reaction mixture was filtered, the residue washed with hot water, and the zinc precipitated from the combined filtrates by passing in hydrogen sulfide. The filtrate was concentrated on the steam-bath, neutralized with sodium carbonate, an excess of ammonia added, and the mixture extracted with chloroform. After removal of the chloroform the residue was crystallized from petroleum solvent (b. p. 55–85°) to give 0.15 g., m. p. 133–135° (63%). This product resisted further reduction on treating with hydrogen bromide in acetic acid solution and adding zinc dust. Recrystallization did not raise the melting point.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58. Found: C, 72.43; H, 4.72.

Attempts to prepare this compound directly by the dehydrogenation of 1-(β-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (VI) with Raney nickel, Raney nickel and nitrobenzene, or by oxidation with nitric acid[9] were unsuccessful.

Absorption Spectra.—All of the absorption spectra were determined on freshly prepared solutions in 95% alcohol that had been distilled from potassium hydroxide. A Beckman Quartz Spectrophotometer, Model DU, was used. It was found that the intensities of the absorption maxima of some solutions decreased fairly rapidly on standing without change in the positions of the maxima.

Summary

1-(β-Picolyl)-6,7-methylenedioxyisoquinoline (VIII), a pyridyl analog of papaverine, has been synthesized.

(5) Hurd and Webb, THIS JOURNAL, **49**, 551 (1927).

(6) Hartmann and Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941).

(7) All microanalyses by C. W. Koch, Albany, Calif.

(8) Buck, Haworth and Perkin, *J. Chem. Soc.*, **125**, 2176 (1924).

(9) Rodionov and Yavorskaya, *J. Gen. Chem.* (U. S. S. R.), **11**, 446 (1941); *C. A.*, **35**, 6592 (1941).

STANFORD, CALIFORNIA RECEIVED MARCH 8, 1949

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Calculation and Determination of the Buttressing Effect for the Racemization of 2,2',3,3'-Tetraiodo-5,5'-dicarboxybiphenyl

BY MARTIN RIEGER AND F. H. WESTHEIMER*

I. Introduction

Recently Westheimer and Mayer[1] developed a method for calculating the activation energy for the racemization of optically active biphenyl derivatives. In principle, the energy by which the planar configuration of a particular ortho substituted biphenyl exceeds that of the twisted form is expressed in terms of the force constants for the vibrations of the molecule and the van der Waals potential function for the interaction of the atoms which form the ortho substituents attached to the biphenyl skeleton. The activation energy for the racemization must be the minimum value of the excess energy of the planar form. The method, although approximate, involves no arbitrary parameters; it has been successfully applied[2] in calculating the activation energy for the racemization of 2,2'-dibromo-4,4'-dicarboxybiphenyl.

* Harvard University Ph.D. 1935.

(1) Westheimer and Mayer, *J. Chem. Phys.*, **14**, 733 (1946).

(2) Westheimer, *ibid.*, **15**, 252 (1947).