Effects of Complex Formation on the Oxidation of Reduced N-Heteroaromatics

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The liquid-phase oxidation of reduced N-heteroaromatics with molecular oxygen was studied. Selective oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline (THQ) and 1,2,3,4-tetrahydroquinaldine (THQD), respectively, to quinoline and quinaldine occurred in glacial acetic acid solutions. In pyridine as the solvent, 1,2,3,4-tetrahydroisoquinoline (THIQ) reacted with oxygen to yield 1,2-dihydroisoquinoline. No reaction with oxygen was observable with the solvent–reactant systems reversed for the above compounds. The oxidizability of these compounds is discussed together with independently established evidence for hydrogen-bonded interactions and salt formation with the solvents for the nonreactive systems.

Evidence available in the literature indicates that the liquid phase oxidation of hydrocarbons and of oxygen-, sulfur-, and nitrogen-containing organic compounds with molecular oxygen occurs *via* free-radical intermediates.[2a] Although the exact nature of the initiation step in autoxidations is still unsettled, the evidence is in favor of chain-reaction steps propagated by free-radical intermediates. For most free-radical processes the influence of polar factors is relatively minor, although the formation of complexes between chlorine atoms and aromatic solvents has been found to alter the selectivity of attack in the photochlorination of 2,3-dimethylbutane.[2b] Other systems where π-complex formation between polar free radicals and aromatic solvents had been proposed to account for changes in reactivity were reviewed by Stefani and Szwarc.[3] Recently, Russell and Bridger[4] suggested that polar transition states account for the low reactivity of phenyl free radicals with molecular oxygen compared with alkyl or benzylic-type radicals.

The reaction of nitrogen-containing heteroaromatics with oxygen, where polar interactions with solvent media may be expected to be significant, have not been studied extensively to date. In the present investigation the liquid phase oxidation of the partially reduced N-heteroaromatics, 1,2,3,4-tetrahydroquinoline (THQ), 1,2,3,4-tetrahydroquinaldine (THQD), and 1,2,3,4-tetrahydroisoquinoline (THIQ) was studied employing both acidic and basic solvents: glacial acetic acid and pyridine, respectively. Such nitrogen-containing molecules are of some interest as constituents of petroleum and shale oils. The oxidation of the carbocyclic analog (tetralin) of these N-compounds has been shown to occur *via* free-radical chain paths.[5–7] The reaction involves oxygen attack at carbon–hydrogen bonds β with respect to the aromatic moiety of tetralin leading to the formation of tetralin hydroperoxide and tetralone in successive reaction stages. It was expected that the presence of nitrogen would lead to altered chemical reactivity, as a result of interactions with polar solvent media.

Results and Discussion

Oxidizability in Acidic and Basic Media.—Acetic acid and pyridine solutions of THQ and THQD on the one hand, and those of THIQ on the other hand exhibited contrasting behavior in their ability to react with molecular oxygen under the conditions studied in this investigation. In acetic acid solutions at 115–117° both THQ and THQD reacted smoothly with oxygen yielding the corresponding aromatic compounds, quinoline and quinaldine. The nearly quantitative conversion of THQ to quinoline is illustrated by the typical reaction curves of Figure 1. Only trace carbonyl compounds could be detected by infrared spectroscopy. Similarly, a 60% conversion of THQD to quinaldine was obtained in 4 hr. when a solution of THQD in acetic acid was oxidized at 117°. No evidence was found for attack by oxygen at the methyl substituent. The addition of small amounts of cobalt(II) bromide, a known catalyst for the liquid phase oxidation of aromatic molecules, resulted in higher reaction rates without any effect on the products of oxidation. Typical results for the catalyzed oxidation of THQ are presented in Figure 2. Since the rates of both catalyzed and uncatalyzed oxidation reactions were found to be dependent on the rate of agitation over a wide range of stirring speeds, no attempt was made to determine reaction rate constants and kinetic parameters for these diffusion-controlled reactions.

Under similar experimental conditions, but employing pyridine as the solvent for THQ or THQD, no reaction could be detected in experiments of extended duration. As will be discussed later, the lack of reactivity of these weakly basic nitrogen compounds in basic pyridine media suggests that complexing with the solvent stabilizes them against reaction with oxygen.

The effects of the acidic and basic solvent media were found to be reversed in the oxidation of THIQ. The basicity of this reduced N-heteroaromatic should be similar to that of a secondary amine, making it a much stronger base than the THQ ring structure where the unshared pair of electrons is conjugated with the aromatic system. In acidic media solutions of THIQ remained unreactive up to about 118°. In pyridine solutions of THIQ, however, reaction with oxygen again resulted in dehydrogenation, leading to the formation of the dihydro compound, 1,2-dihydroisoquinoline, as shown by the results in Figure 3. Only trace carbonyl infrared absorption was found in the reaction systems.

Complex Formation.—Interaction with the solvent *via* stabilized complex formation may be suggested as a reasonable hypothesis to account for the opposite effects found in the oxidation behavior of the compounds studied. Thus, THQ (or THQD) could form a hydrogen-bonded complex with the more basic solvent pyridine, which would be stabilized against reaction

(1) (a) Process Research Division; (b) Analytical Research Division.

(2) (a) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 397, and references cited therein; (b) G. A Russell, *J. Am. Chem. Soc.*, **79**, 2977 (1957).

(3) A. P. Stefani and M. Szwarc, *ibid.*, **84**, 3661 (1962).

(4) G. A. Russell and R. F. Bridger, *ibid.*, **85**, 3765 (1963.)

(5) A. Robertson and W. A. Waters, *Trans. Faraday Soc.*, **42**, 201 (1946).

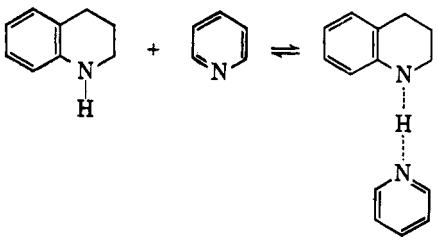
(6) A. Robertson and W. A. Waters, *J. Chem. Soc.*, 1574 (1948).

(7) G. A. Russell, *J. Am. Chem. Soc.*, **77**, 4583 (1955).

with oxygen but would remain uncomplexed and hence reactive in acidic media. In contrast with this behavior, the stronger base THIQ is not expected to complex with pyridine, but could yield an acetate salt complex in excess glacial acetic acid.

A. Hydrogen Bonding and Resistance to Oxidation.—Infrared spectroscopic examination of solutions of THQ in pyridine and of THIQ in pyridine showed significant differences which could be correlated with the reactivity of these heterocycles toward oxygen in pyridine solutions. Infrared evidence for hydrogen bonding was obtained only for the unreactive THQ–pyridine system. In contrast, blends of THIQ in pyridine showed no infrared spectral changes; *i.e.*, no evidence of N–H bonding interaction could be obtained.

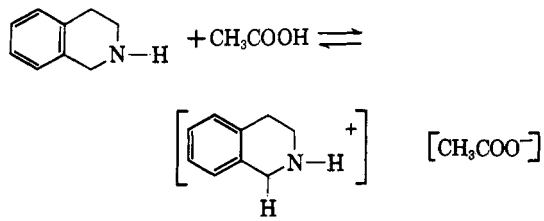
As the oxidation experiments in this study were performed at concentrations corresponding to a pyridine/THQ mole ratio of 17:1, the spectroscopic studies indicate that all of the THQ would have been H-bonded at least at room temperature. The complexing between THQ and pyridine presumably involves the hydrogen atom bonded to the nitrogen atom of THQ and the nitrogen atom of pyridine.



(1)

Based on the assumption that the stoichiometry of the intermolecular hydrogen bonding between pyridine and THQ is 1:1 as written in reaction 1, the equilibrium constant was calculated from the spectroscopic measurements presented in Figure 4. Using an iterative procedure, the unknown molar extinction coefficient of the hydrogen-bonded complex was calculated to be 71.3 l. mole^{-1} cm.$^{-1}$. The mean value of the equilibrium constant K at room temperature for the complex of eq. 1 was computed to be 0.62 l. mole^{-1}, with a standard deviation of 0.13 l. mole^{-1}. Thus the equilibrium constant is similar to the value reported for the hydrogen bonding of pyrrole with pyridine,[8] but somewhat smaller than the latter, presumably because THQ is more basic than pyrrole.

B. Salt Formation and Resistance to Oxidation.—In accord with the nonoxidizing behavior, THIQ was found to form a stable acetate salt in glacial acetic acid which was soluble in excess acetic acid. The stoichiometry of salt formation was found to be in 1:1 molar proportions, and the infrared evidence for the ionic character of the salt suggested its formation *via* reaction 2.



(2)

(8) H. J. Wimette and R. L. Linnell, *J. Phys. Chem.*, **66**, 545 (1962).

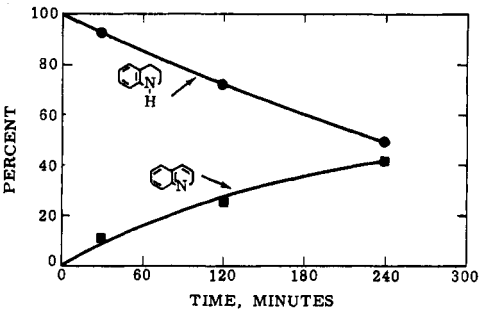


Figure 1.—Oxidation of THQ in acetic acid solution: temperature, 117°; stirring speed, 1350 r.p.m.; concentrations given as fraction of original reactant.

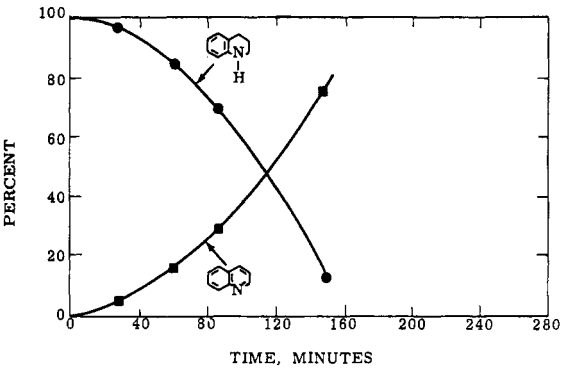


Figure 2.—Oxidation of THQ in acetic acid solution catalyzed by Co(II) Br_2: temperature, 118°; stirring speed, 500 r.p.m.; concentrations given as fraction of original reactant.

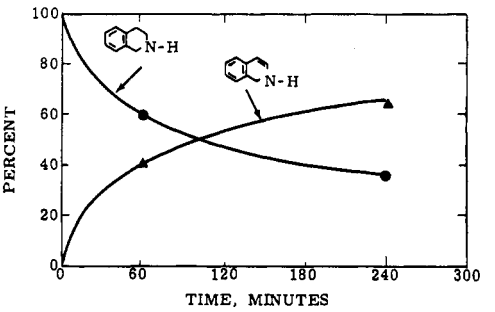


Figure 3.—Oxidation of THIQ in pyridine solution: temperature, 112°; stirring speed, 500 r.p.m.; concentrations expressed as fraction of original reactant.

In contrast, blends of THQ and acetic acid in CCl_4 did not yield a salt. Infrared analyses of the solutions indicated no consumption of acetic acid and 85% recovery of THQ. The latter result may be due to an absorbance intensity effect of THQ bands in the acidic medium, or possibly to some soluble salt formation.

THQD which was found oxidizable in acetic acid solution exhibited no salt formation in the acid. However, in pyridine solutions of THQD a new N–H band appeared at 3300 cm.$^{-1}$ of the infrared spectrum, similar to the H-bonded complex of THQ with pyridine. At a pyridine–THQD mole ratio of 15:1, the band at 3300 cm.$^{-1}$ reached a constant absorbance value. Thus, again it may be assumed that the oxidation of THQD in excess pyridine solvent could not occur due to hydrogen bonding with the solvent.

Reactivity with Oxygen.—Several conclusions may be inferred from the measurements of hydrogen-bonded complex and salt formation tendencies and the observations of the oxidizability of the N-compounds in

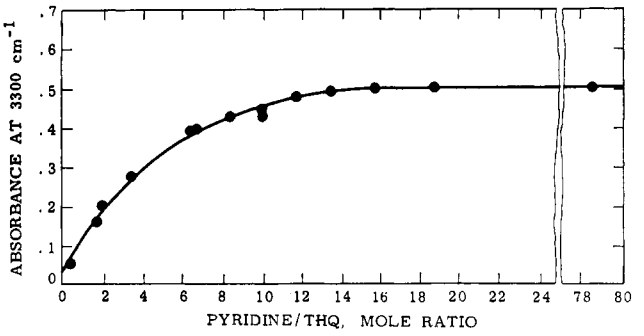


Figure 4.—Complex formation between THQ and pyridine at room temperature (thickness of infrared absorption cell, 0.1 mm.).

these studies. These results, discussed previously, are summarized in Table I.

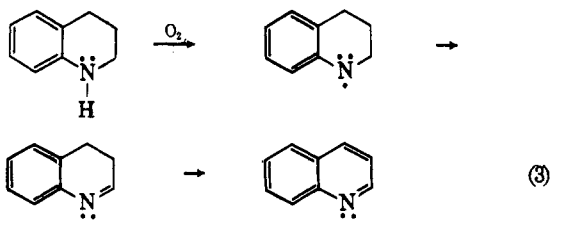
TABLE I

SUMMARY OF RELATIONSHIP BETWEEN OXIDIZABILITY AND COMPLEX FORMATION

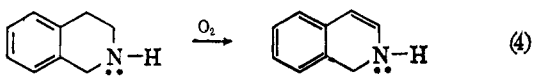
Compd.	Oxidizable in pyridine	Hydrogen bonding with pyridine	Product
Tetrahydroquinoline	No	Yes	H-bonded complex
Tetrahydroisoquinoline	Yes	No	1,2-Dihydroisoquinoline
Tetrahydroquinaldine	No	Yes	H-bonded complex

	Oxidizable in acetic acid	Salt formation with acetic acid	Product
Tetrahydroquinoline	Yes	No	Quinoline
Tetrahydroisoquinoline	No	Yes	Salt
Tetrahydroquinaldine	Yes	No	Quinaldine

It appears that the formation of the hydrogen-bonded complex between THQ (or THQD) and excess pyridine solvent is sufficient to prevent attack of the heterocycle by molecular oxygen up to fairly elevated temperatures. A tentative rationalization of this finding may be made by assuming that oxygen or a free radical can abstract a hydrogen atom bonded to the nitrogen of THQ in acetic acid solutions. However, in pyridine solutions the N–H bond is made unavailable for reaction because of hydrogen bonding. Oxidative dehydrogenation in acetic acid could lead to the formation of a relatively unstable cyclic imine which is expected to dehydrogenate to quinoline, as indicated in reaction 3.



Salt formation with the acidic solvent appears to stabilize THIQ against reaction with oxygen. In pyridine as the solvent, however, the same species are free to react. While the detailed mechanism of reaction 4 is not known, it is reasonable to assume that further



oxidative dehydrogenation of the 1,2-dihydroisoquinoline product should not occur, because it is a much weaker base than the original reactant THIQ, due to the conjugation of the unshared pair of electrons at the N-atom with the 3,4-double bond and the phenyl ring structure. In other words, the basicity of 1,2-dihydroisoquinoline is expected to be on the order of THQ or aniline, so that the 1,2-dihydroisoquinoline product in pyridine should be stabilized against reaction with oxygen due to H-bonding with the solvent.

Experimental

THQD and THIQ reagents were obtained from Aldrich Chemical Co., Milwaukee, Wis. The THQ reagent used in the experiments was supplied by K and K Laboratories, New York, N. Y. All reagents were further purified by distillation under reduced pressure. Impurities if present in the purified materials were below the levels of detectability by infrared absorption spectrometry. Reagent grade pyridine and glacial acetic acid solvents were used without further purification.

The oxidation experiments were performed under atmospheric pressure using stirred three-necked Pyrex reactor flasks of 250-ml. capacity, equipped with thermowells for measuring the temperature. A two-way valve arrangement allowed the gas inlet to the reactor to be connected to a supply of nitrogen gas for purging before the oxidation experiments. Solutions of 16.0 g. of N-compound in 150.0 ml. of solvent were placed in the reactor which was heated to reaction temperature in a thermostated mineral oil bath. To prevent entrainment of the solution in oxidation experiments performed near the boiling points of the solvents, a reflux condenser cooled with ice water was attached to the reactor outlet. Oxidation at a desired temperature was started by switching the nitrogen flow to oxygen. Wet-test gas meters were used to record the flow rates of inlet and outlet gases. The reactor contents were sampled periodically, by withdrawing 5-ml. aliquots of the reaction mixtures with a hypodermic syringe through a self-sealing neoprene diaphragm. Quenched pyridine solutions containing oxidation products and unreacted material were quantitatively analyzed by infrared absorption spectrophotometry. Samples of acetic acid solutions were first neutralized with excess 30% aqueous sodium hydroxide solution. Both reactants and products could be quantitatively extracted with carbon tetrachloride from the neutralized solutions. The carbon tetrachloride extracts were then also analyzed by infrared absorption spectrophotometry.[9] Similar procedures were employed for control experiments in the absence of oxygen using a nitrogen atmosphere. All solutions stayed stable in the control runs.

Identification of Reaction Products.—Quantitative aspects of the infrared analysis of quinoline produced in the oxidation of THQ in acetic acid solutions have been published elsewhere.[9] THQ has characteristic infrared absorption bands at 1351, 1308, 1260, 1092, and 711 cm.$^{-1}$, while the bands corresponding to quinoline are at 1429, 1370, 1135, and 938 cm.$^{-1}$.

The identity of the oxidation product of THIQ in pyridine solution, 1,2-dihydroisoquinoline, was confirmed by mass spectroscopy. Major m/e peaks were found at 130 and 131, indicative of a dihydroisoquinoline. The 3,4-dihydroisoquinoline isomer was ruled out by comparison of the published infrared absorption spectrum of this compound (Sadtler No. 16690) with the spectrum of the product. The published spectrum of 3,4-dihydroisoquinoline shows prominent absorption bands at 1640, 1205, 751, and 690 cm.$^{-1}$. These bands of the 3,4-isomer are absent from the product spectrum, which showed principal infrared absorption bands at 1370, 1177, 766, 730, and 879 cm.$^{-1}$. The isomeric assignment as 1,2-dihydroisoquinoline was then made by comparison of the product spectrum with that published for 1,2-dihydro-2-methylisoquinoline (Sadtler No. 12115). Further evidence for the 1,2-isomer was provided by the strong N–H absorbance at 3410 cm.$^{-1}$ in the product spectrum which of course would be absent from the spectrum of 3,4-dihydroisiquinoline.

Evidence for Complex Formation.—Blends of THQ (or THQD) in pyridine and of THIQ in pyridine were prepared (carbon tetrachloride was a diluent in some of the blends in order to keep the

(9) H. Pobiner, *Appl. Spectry.*, **17**, 79 (1963).

dilution effect constant). A new band with a maximum at 3300 cm.$^{-1}$ appeared in the infrared spectra of these solutions. Individual solutions of THQ or (THQD) in CCl_4 and of pyridine in CCl_4 did not exhibit absorption at this wave length. Significantly, the 3300-cm.$^{-1}$ band was independent of the normal N–H stretching mode of THQ (or THQD) at 3420 cm.$^{-1}$. In this region of the infrared spectrum, the 3300-cm.$^{-1}$ band was assigned to an intermolecular H-bonded complex between THQ (or THQD) and pyridine.

The tetrahydroquinoline–pyridine interaction was investigated by adding increments of pyridine to fixed amounts of THQ. As additional H-bonded complex formation occurred, the absorbance at 3300 cm.$^{-1}$ increased to a constant value, as shown in Figure 4. From a pyridine–THQ mole ratio of 12:1, the absorbance value remained constant up to a pyridine–THQ mole ratio of 79:1. Measured absorbances were corrected where necessary for dilution with carbon tetrachloride.

For the THIQ–acetic acid system, the tendency for salt formation was demonstrated with synthetic blends of THIQ and acetic acid in carbon tetrachloride. An insoluble salt was precipitated and the filtrate was analyzed by infrared spectroscopy for uncombined THIQ and acetic acid. The stoichiometry of THIQ and acetic acid for salt formation was found to be in 1:1 molar proportions. This stoichiometry was confirmed with different blends in which one of the two reactants was present in excess, thus assuring complete removal of the other component from solution. Thus, when an excess of acid was present, as in the oxidation experiments, all of the THIQ was presumably converted to the acetate salt which would not react with oxygen.

The isolated THIQ–acetic acid salt was analyzed. Its infrared spectrum was identified as that of an acetate salt. New COO^- bands at 1640 and 1590 cm.$^{-1}$ replaced the acid carbonyl absorption at 1720 cm.$^{-1}$. (This feature is indicative of the ionic character of the salt.)

Acknowledgment.—The authors wish to thank Drs. A. Schriesheim and T. J. Wallace of Esso Research and Engineering Company for fruitful discussions.

The Production of 3-Benzylidene-6-isobutylidene-2,5-dioxopiperazine, 3,6-Dibenzylidene-2,5-dioxopiperazine, 3-Benzyl-6-benzylidene-2,5-dioxopiperazine, and 3,6-Dibenzyl-2,5-dioxopiperazine by a Variant of *Streptomyces noursei*[1]

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3-Benzylidene-6-isobutylidene-2,5-dioxopiperazine (I), 3,6-dibenzylidene-2,5-dioxopiperazine (II), 3-benzyl-6-benzylidene-2,5-dioxopiperazine (III), and 3,6-dibenzyl-2,5-dioxopiperazine (IV) were isolated from broth cultures of a streptomycete. II and IV are both known substances, and the isolated materials were identified by comparison with authentic samples. The hydrogenation sequence II → III → IV effectively establishes the structure of III, a new compound. Evidence is presented that I has the indicated structure.

Streptomyces noursei variant No. 5286 which yields the antibiotic phalamycin[3] produces also four dioxopiperazines to which the following structures are assigned: 3-benzylidene-6-isobutylidene-2,5-dioxopiperazine, 3,6-dibenzylidene-2,5-dioxopiperazine, 3-benzyl-6-benzylidene-2,5-dioxopiperazine, and 3,6-dibenzyl-2,5-dioxopiperazine. The organism was grown for 4 days with shaking in a yeast extract broth.[4,5] The whole culture at pH 7.5–8.0 was extracted with ethyl acetate. Colored matter and other impurities in the dry extractives were removed with small volumes of chloroform, 70% ethanol, and acetone in succession. Chloroform was then percolated through the remaining solids thereby taking out I and II. These products, after removal of the solvent by distillation *in vacuo*, were separated from each other by extraction of the first into glacial acetic acid from which it was precipitated by dilution with water. To separate III and IV that remained after the chloroform treatment, many fractional recrystallizations from 2-propanol, chloroform, and acetone in succession were employed. For the final recrystallizations acetone or methanol were the solvents of choice. The progress in separation was followed by analysis of the infrared spectra and in the later stages by melting point determinations. This paper presents the evidence for the identification of the four compounds.

Results

3-Benzylidene-6-isobutylidene-2,5-dioxopiperazine (I).—The structure of I is supported by the following data. Upon hydrogenation with 10% palladium–carbon as catalyst, I added 2 molar equiv. to form 3-benzyl-6-isobutyl-2,5-dioxopiperazine (V). This hydrogenated I had the infrared spectrum and melting point of authentic V (leucylphenylalanine anhydride). Acid hydrolysis of 1 mole of the hydrogenated natural product yielded 1 mole each of phenylalanine and leucine. Furthermore, in the degradation products of the acid hydrolysis of I itself, phenylpyruvic acid and ammonia (2 moles/mole) were observed; and, on basic hydrolysis, benzaldehyde, isobutyraldehyde, and ammonia were released. The ultraviolet spectrum with maxima at 234 and 318 mμ is consistent with the conjugated carbonyl system. Infrared data give evidence for N–H, monosubstituted benzene, ethylenic and lactam C=O groupings, and, as in the other compounds of this study, absence of OH. I had the same infrared spectrum as "albonoursin"[6] which is reported to be 3-benzylidene-6-isobutylidene-2,5-dioxopiperazine. The mixture of the two showed no depression of the melting point.

(1) Presented in part as a dissertation by C. Kelley in partial fulfillment of the Degree of Doctor of Philosophy, Rensselaer Polytechnic Institute, 1961.

(2) Rensselaer Polytechnic Institute, Troy, N. Y.

(3) R. Brown and E. L. Hazen, *Antibiot. Chemotherapy*, **3**, 818 (1953).

(4) The cultures were kindly supplied by Mrs. Joan Brennan and Mr. Edward Lapa.

(5) No dioxopiperazine derivatives were isolated from the yeast extract used for the broth.

(6) A. S. Khokhlov and G. B. Lokshin, *Tetrahedron Letters*, **No. 27**, 1881 (1963); and personal communication. We are indebted to Dr. Khokhlov for a sample of "albonoursin."