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Base-catalyzed Condensation of *o*-Nitroacetophenone. IV. Structure of Dehydro-derivative of Compound A, a Condensation Product

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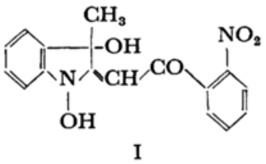
The alkaline hydrogen peroxide oxidation of compound A, $C_{17}H_{14}O_5N_2$, a base-catalyzed condensation product of *o*-nitroacetophenone, gave a dehydro compound, $C_{17}H_{12}O_5N_2$. The structure of the dehydro compound was deduced from the spectral data of its derivatives to be a (*o*-nitrobenzoyl)-1-hydroxycarbostyril. The forced hydrogenation of the dehydro compound gave 3-(*o*-aminobenzoyl)-4-methylcarbostyril, which was synthesized by the condensation of *o*-aminoacetophenone and ethyl *o*-nitrobenzoylacetate followed by reduction. Therefore, the dehydro compound proved to be 1-hydroxy-4-methyl-3-(*o*-nitrobenzoyl)carbostyril. On the other hand, the alkaline hydrogen peroxide oxidation of compound A methyl ether gave *o*-nitrobenzoic acid and 1-methoxy-3-methyldioxindole along with *o*-nitroacetophenone. These facts are explained by assuming a transition state which would be controlled by the presence of a hydrogen bonding.

In the first paper of this series,[2] the alkaline hydrogen peroxide oxidation of compound A(I),[3] $C_{17}H_{14}O_5N_2$, a base-catalyzed condensation product of *o*-nitroacetophenone, was reported to give dehydro-compound A, $C_{17}H_{12}O_5N_2$, with a loss of two atoms of hydrogen. A striking change of the ultraviolet absorption of compound A by the dehydrogenation implied that the compound had undergone a major reaction during the transformation.



I

Dehydro-compound A is a weak acid similar to compound A and has a broad band at 3145 cm⁻¹ in its infrared spectrum. In contrast to the latter, the dehydro compound shows carbonyl stretching absorptions at 1675 and 1600 cm⁻¹.

Methylation of dehydro-compound A with dimethyl sulfate and potassium carbonate gave a methyl ether, which lost both acidity and the 3145 cm⁻¹ band of the original compound. The 1600 cm⁻¹ carbonyl band of dehydro-compound A was shifted to 1647 cm⁻¹ during methylation.

On hydrogenation over palladium-on-carbon, dehydro compound A methyl ether absorbed three moles of hydrogen to yield a yellow amine, $C_{18}H_{16}O_3N_2$, melting at 220—222°C. This amine has a C-methyl group and a methoxyl group. Its ultraviolet spectrum has a new band at 384 mμ. Acetylation of the amine with acetic anhydride led to a monoacetyl derivative, $C_{20}H_{18}O_4N_2$, mp 202—203°C. In the ultraviolet spectrum of this compound, the 380 mμ band of the amine shifted by 40 mμ to a shorter wavelength (Fig. 1). Such a characteristic hypsochromic shift indicates that the original amine contains an *o*-aminobenzoyl

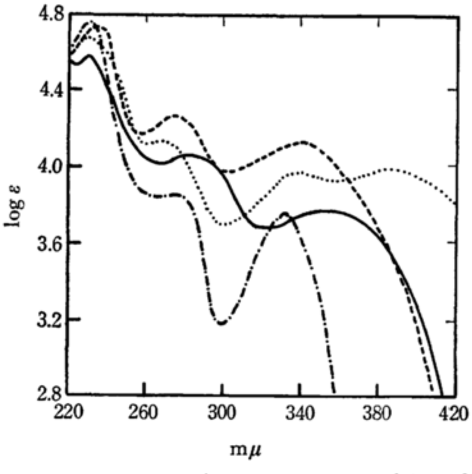


Fig. 1. UV spectra of dehydro-compound A methyl ether (II, OMe for OH) (——), amine VIII (······), amide IX (----) and its $NaBH_4$ reduction product (X) (-·-).

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[2] T. Sakan, K. Kusuda and T. Miwa, This Bulletin, **37**, 1678 (1964).

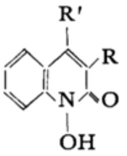
[3] T. Sakan, K. Kusuda and T. Miwa, *ibid.*, **38**, 18 (1965).

group;[4] therefore, dehydro-compound A should be an *o*-nitrophenyl ketone.

Reduction of the acetamido derivative with sodium borohydride gave a compound decomposing at 141—143°C. This compound was difficult to purify, but its infrared spectrum showed that the keto function of the *o*-acetamidobenzoyl group was reduced. All the compounds derived from dehydro-compound A have a set of triple absorption maxima (near 230, 280 and 340 mμ) as shown in Fig. 1. The spectral feature is characteristic of the carbostyril derivative;[5] consequently, dehydro-compound A was assumed to be an α-quinolone derivative. The carbonyl band (1647 cm^{-1}) of its methyl ether is in good accord with those (1661—1650 cm^{-1}) of α-quinolones.[5,6]

Providing that the carbostyril system still possesses a hydroxyl group on the nitrogen atom as proposed for compound A (I), dehydro-compound A would be a cyclic hydroxamic acid; the weak acidity as well as the carbonyl band (1600 cm^{-1}) of longer wavelength than those of usual α-quinolones may be attributed to the hydroxamic function.

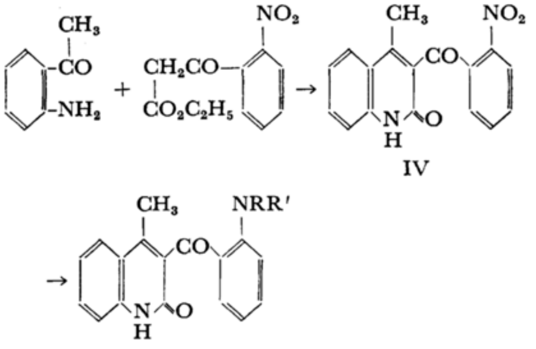
These facts suggest structure II or III for dehydro-compound A. Of these structures, the former appears to be more plausible, if the carbostyril ring is formed by the C_α-C_β ring fission of the indoline nucleus[7] with a β-methyl group in compound A (I).



II: R=*o*-Nitrobenzoyl, R′=CH_3
III: R=CH_3, R′=*o*-Nitrobenzoyl

In order to derive dehydro-compound A to a readily available compound, attempts were made to remove the hydroxyl group attached to the cyclic nitrogen atom. The methoxyl group of an *N*-methoxycarbostyril was reported to be removed by reduction with zinc and hydrochloric acid.[8] No reduction was carried out with the yellow amine, $C_{18}H_{16}O_3N_2$, derived from dehydro-compound A methyl ether. Catalytic hydrogenation over Raney nickel seemed promising, because such a hydrogenolysis of a 1-methoxyoxindole led to an oxindole;[3] however, this also failed with dehydro-compound A methyl ether. Forced hydrogenation of dehydro-compound A over Raney nickel at a hydrogen pressure of 80 atm and at a temperature of 115°C yielded a deoxy compound. Being difficult to purify, the product was acetylated immediately to produce a monoacetyl derivative, $C_{19}H_{16}O_3N_2$, mp 279—280°C, and a diacetyl derivative, $C_{21}H_{18}O_4N_2$, mp 218—220°C. Both of the acetyl derivatives on hydrolysis gave the same bright yellow amine, $C_{17}H_{14}O_2N_2$, decomposing at 277—279°C. Thus ultraviolet absorption spectra of the amine and its acetyl derivatives indicate the survival of the *o*-aminobenzoyl system through the hydrogenation process. The amine would be represented by formula V on the basis of the assumed preferential structure II for dehydro-compound A. This was proved to be the fact by the following synthesis of the amine.

Heating *o*-aminoacetophenone with ethyl *o*-nitrobenzoylacetate afforded 4-methyl-3-(*o*-nitrobenzoyl)carbostyril IV, which in turn was hydrogenated to the corresponding amine V. This amine was spectroscopically identical with the amine obtained by the high-pressure hydrogenation of dehydro-compound A. Acetylation of V gave a monoacetyl derivative VI, which was identified with the monoacetyl compound, $C_{19}H_{16}O_3N_2$, by a mixed melting point determination; consequently, the diacetyl compound, $C_{21}H_{18}O_4N_2$, was assumed to have the structure VII because of the absence of the amide II band in its infrared spectrum.



V : R, R′=H
VI : R=H, R′=$COCH_3$
VII: R, R′=$COCH_3$

The establishment of the structure of amine V excluded structure III for dehydro-compound A and evidently confirmed that dehydro-compound A is 1-hydroxy-4-methyl-3-(*o*-nitrobenzoyl)-2-quinolone. As a corollary, the C_{18}-amine derived from dehydro-compound A methyl ether, its acetyl derivative, and the sodium borohydride reduction product of the latter were assigned structures VIII,

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[4] The ultraviolet absorption maximum at 385 mμ of *o*-aminobenzophenone is shifted to 325 mμ by acetylation: P. Grammaticakis, *Bull. Soc. Chim. France*, **1953**, 93.

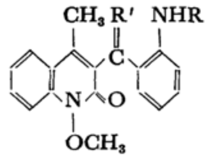
[5] B. Witkop, J. B. Patrick and M. Rosenblum, *J. Am. Chem. Soc.*, **73**, 2641 (1951).

[6] M. F. Grundon, N. J. McCorkindale and M. N. Rodger, *J. Chem. Soc.*, **1955**, 4284.

[7] Example of the ring enlargement of indoline nucleus through such a ring fission is found in literature.[4]

[8] F. A. Arndt, C. Ergener and O. Kutlu, *Chem. Ber.*, **86**, 962 (1953).

IX, and X, respectively.



VIII: R=H, R′=O
IX : R=Ac, R′=O
X : R=Ac, R′=H, OH

Formation of the dehydro compound from compound A may be explained as shown in Chart 1.

The oxidation of α,β-unsaturated ketones with alkaline hydrogen peroxide is a familiar reaction leading to epoxy ketones.[9] The reaction was proposed to be stereoselective and to proceed through a transition state controlled by the overlap of the pi-orbitals of the enolate anion.[10] In this case, the transition state is presumed to involve the overlap of p (or pi)-orbital on the α-carbon atom with the vacant orbital which is developing in the S_N2 reaction on the peroxide oxygen atom.[11] The hydrogen bondings shown in XII would force the transition state to assume a conformation where the overlap required for the formation of the epoxide ring is apparently impossible (Fig. 2-a). Therefore, another alternative nucleophilic substitution shown in XII may occur at the β-carbon atom of the indoline nucleus, if we assume a transition state shown in Fig. 2-b which leads to the formation of a cyclopropane ring in XIII.

The importance of the hydrogen bonding in the above rearrangement was substantiated by the alkaline hydrogen peroxide oxidation of the methyl

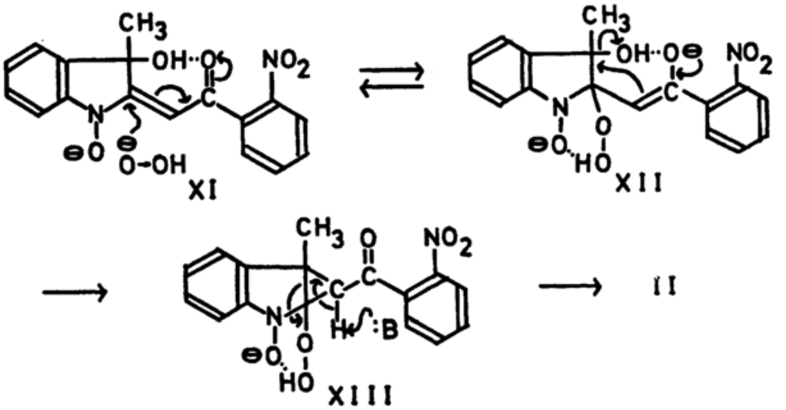


Chart 1

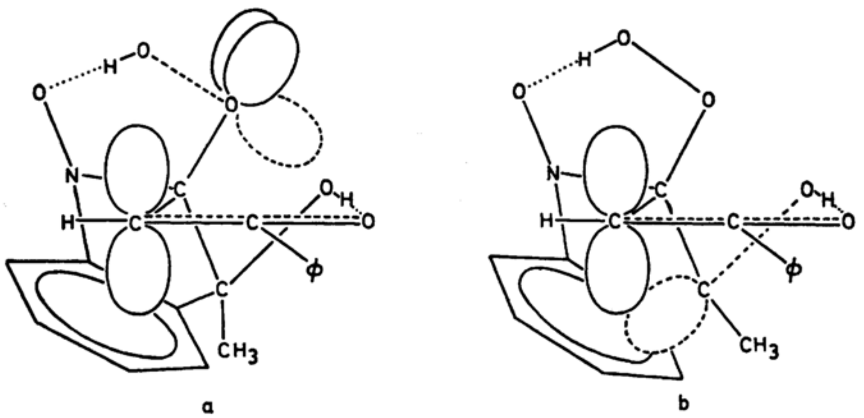


Fig. 2. Transition state for the reaction of XII. Overlapping of the orbitals is inhibited (a) or allowed (b).

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[9] E. g., H. O. House, "Modern Synthetic Reactions," Benjamin, New York (1965), p. 117.

[10] H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959).

[11] In the nucleophilic substitution of the peroxide, the nucleophile is assumed to approach the peroxides along the line formed by the two peroxide oxygens. (J. O. Edwards, "Peroxide Reaction Mechanisms," ed. by J. O. Edwards, Interscience Publishers, New York (1962), p. 69).

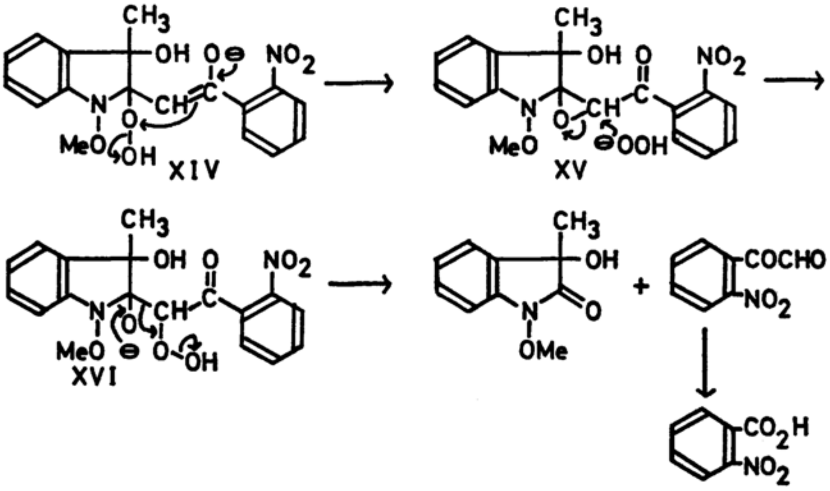

Chart 2

ether of compound A. The reaction of compound A methyl ether with alkaline hydrogen peroxide in dioxane followed quite a different course from that of compound A, leading to 1-methoxy-3-methyldioxindole, which was previously obtained by the ozonolysis of the methyl ether,[3] and *o*-nitrobenzoic acid, along with a small amount of *o*-nitroacetophenone. The difference is not due to the solvent effect since the oxidation of compound A under the same condition as the methyl ether gave dehydro-compound A as a sole product. A mechanism shown in Chart 2 may be proposed for the oxidation of the methyl ether.

In the transition state of the oxidation of the methyl ether, however, the hydrogen bond would be too weak to prevent the overlap of the p-orbital of the α-carbon atom with the vacant orbital on the oxygen atom in the peroxide group. The epoxide may be attacked by another hydroperoxide ion at the electron-defficient site to produce an open-chain alkoxide ion XVI, which will give the dioxindole and *o*-nitrophenylglyoxal, the latter being further oxidized into *o*-nitrobenzoic acid.

o-Nitroacetophenone was formed apparently by the oxidation of the dioxindole, because it was formed in some quantity even when *o*-nitrobenzoic acid was formed almost quantitatively.

Experimental

Hydrogenation of Dehydro-compound A Methyl Ether. 3-(*o*-Aminobenzoyl)-1-methoxy-4-methyl-2-quinolone (VIII). A solution of 2.8 g of dehydro-compound A methyl ether in 80 cc of ethanol was hydrogenated at atmospheric pressure using 1.4 g of 5% palladium-on-carbon to absorb 530 cc (20°C) of hydrogen. During the hydrogenation greenish yellow crystals separated. The catalyst was removed by filtration from the hot solution and washed well with hot ethanol. Evaporation of the ethanol left 2.5 g of yellow amine, which, after recrystallization from ethanol, melted at 220—222°C. $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 230 (4.68), 266—270 (4.14), 336 (3.98), 384 (4.00). $\lambda_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3425, 3310 (NH), 1645, 1613 (C=O).

Found: C, 70.15; H, 5.69; N, 9.20%. C-Methyl group (Kuhn-Roth):[12] 0.52. Calcd for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09%. C-Methyl group: 1.00.

***N*-Acetyl Derivative (IX)** was obtained by treatment of 0.7 g of the amine with 10.5 cc of boiling acetic anhydride for 5 min. Excess of the anhydride was decomposed with water and the product was recrystallized from methanol, mp 202—203°C. $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 232 (4.74), 275 (4.27), 340 (4.13). $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3290 (NH), 1698, 1650, 1634 (C=O), 1520 (amide II).

Found: C, 68.63; H, 5.26; N, 8.32%. Calcd for $C_{20}H_{18}O_4N_2$: C, 68.56; H, 5.18; N, 8.00%.

Sodium Borohydride Reduction of the *N*-Acetyl Derivative was effected in methanol at room temperature. After being allowed to stand overnight, the reduction mixture was diluted with water and evaporated to remove methanol. Extraction with benzene gave crystals, which, after recrystallization from benzene-ligroin, decomposed at 141—143°C. $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 230 (4.77), 276 (3.86), 331 (3.76). $\lambda_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3345 (OH and NH), 1695, 1637 (C=O), 1522 (amide II).

High Pressure Hydrogenation of Dehydro-compound A. 3-(*o*-Aminobenzoyl)-4-methyl-2-quinolone (V). Hydrogenation of 1.4 g of dehydro-compound A was effected in ethanol over 0.8 g of Raney nickel at a hydrogen pressure of 80 atm and at a temperature of 115°C for 16 hr. Without removal of the catalyst, the solvent was distilled off under reduced pressure. The resulting residue was heated with acetic anhydride under reflux for one hour. After removal of the catalyst, work-up in usual way gave crystals, which were recrystallized repeatedly from methanol. From the less soluble fraction, the monoacetyl derivative VI was obtained as leaflets, mp 274—276°C.

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[12] E. J. Eisenbraun, S. M. McElvain and B. F. Aycock, *J. Am. Chem. Soc.*, **76**, 607 (1954).

$\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 230 (4.68), 270 (4.28), 328—332 (4.08). $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3248 (NH), 1692, 1658, 1631 (C=O), 1520 (amide II).

Found: C, 70.56; H, 5.08; N, 8.93%. Calcd for $C_{19}H_{16}O_3N_2$: C, 71.24; H, 5.03; N, 8.75%.

The monoacetyl derivative was identified with the independently synthesized amide VI (see below) by a mixed melting point determination.

The more soluble fraction gave the diacetyl derivative VII as leaflets melting at 218—220°C. $\lambda_{\max}^{\mathrm{EtOH}}$: 328 m$\mu$ (log ε 3.82). $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1706, 1672, 1637 (C=O).

Found: C, 69.84; H, 5.16; N, 8.02%. Calcd for $C_{21}H_{18}O_4N_2$: C, 69.60; H, 5.00; N, 7.73%.

A mixture of 35 mg of the monoacetyl derivative and 1 cc of concentrated hydrochloric acid was heated on a water bath for 3 hr. Evaporation of the hydrochloric acid *in vacuo* followed by recrystallization from 90% acetic acid gave bright yellow prisms decomposing at 272—275°C. Hydrolysis of the diacetyl derivative in a similar way afforded a base decomposing at 277—279°C, which showed no depression by a mixed melting point determination with the product from the monoacetyl derivative. $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 229—230 (4.62), 270 (4.08), 335 (3.87), 350 (3.88), 378—382 (3.89). $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3400, 3290 (NH), 1647, 1626 (C=O).

Found: C, 73.10; H, 5.26; N, 9.97%. Calcd for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.07%.

The amine was identified with the authentic specimen (see below) by ultraviolet and infrared spectroscopy.

4-Methyl-3-(*o*-nitrobenzoyl)-2-quinolone (IV). A mixture of 0.55 g of *o*-aminoacetophenone and 0.95 g of ethyl *o*-nitrobenzoylacetate was heated in a sealed tube at 170—200°C for 4 hr. The mixture was treated with benzene and the resulting precipitate was recrystallized from methanol to give leaflets, mp 238—240°C. $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 231 (4.51), 284 (3.95), 351 (3.75). $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1681, 1621 (C=O), 1531, 1351, 860 (NO_2).

Found: C, 66.42; H, 4.13; N, 9.20%. Calcd for $C_{17}H_{12}O_4N_2$: C, 66.23; H, 3.92; N, 9.09%.

3-(*o*-Aminobenzoyl)-4-methyl-2-quinolone (V). A solution of 48 mg of the nitro compound IV in 1 cc of ethanol was hydrogenated in the presence of 40 mg of 5% palladium-on-carbon to give amine V decomposing at 275—277°C.

3-(*o*-Acetamidobenzoyl)-4-methyl-2-quinolone (VI). Acetylation was accomplished by heating 36 mg of the amine IV in 3 cc of acetic anhydride under reflux. Work-up in the usual way and recrystallization from methanol gave 31 mg of crystals melting at 282—284°C.

Alkaline Hydrogen Peroxide Oxidation of Compound A Methyl Ether. To a solution of 690 mg of compound A methyl ether in 5 cc of dioxane was added 2 cc of 10% methanolic potassium hydroxide, followed by the addition of 5 cc of 30% hydrogen peroxide with cooling. After removal of half of the solvent under reduced pressure, the residue was made acidic with 20% hydrochloric acid. The resulting mixture was extracted with a mixture of benzene and ether, and the extract was washed with aqueous sodium hydrogencarbonate solution. Acidification of the aqueous solution gave 329 mg (96.5%) of *o*-nitrobenzoic acid. The neutral fraction (190 mg) was chromatographed on active alumina "Wako" as a benzene solution. The first band was eluted with benzene to give 48 mg of an oil; it was characterized as a 2,4-dinitrophenylhydrazone, mp 170—174°C, which was identified with that of *o*-nitroacetophenone by infrared spectroscopy. The second band, eluted with a mixture of 300 cc of benzene and 5 drops of ethanol gave 130 mg of crystals, which, after recrystallization from benzene-ligroin, melted at 134—135°C, and which was identified with 1-methoxy-3-methyldioxindole[3] by infrared spectroscopy.

Alkaline Hydrogen Peroxide Oxidation of Compound A in Dioxane. A solution of 347 mg of compound A in 3 cc of dioxane was treated with 1.5 cc of 10% methanolic potassium hydroxide and 1.5 cc of 30% hydrogen peroxide. After being stirred overnight, the mixture was acidified with saturated sulfur dioxide solution. Concentration of the mixture, followed by filtration of the resulting precipitate gave 258 mg of crude dehydro-compound A, which, after recrystallization from methanol, was identified with the authentic sample[2] by infrared spectroscopy.