The infrared spectrum indicated the presence of water of crystallization.

Conversion of sodium 1-hydroxy-1,3-propanedisulfonate to 1,3-propanesultone. A solution of 50.0 g. of crude sodium 1-hydroxy-1,3-propanedisulfonate (prepared from 8.9 g. of 95% acrolein and 29.8 g. of sodium metabisulfite) in 200 ml. of water was treated with 20.0 g. of 36% hydrochloric acid. The solution was boiled until the odor of sulfur dioxide was gone from the vapors (30 min). The solution was cooled, neutralized to *p*H 7.05 with aqueous sodium hydroxide, and hydrogenated over Raney nickel at 32–80° and 1300–770 p.s.i.g. Hydrogen adsorption amounted to 0.16 mole. The catalyst was removed by filtration. The filtrate was passed over Dowex 50 (H^+) ion exchange resin to remove sodium ion. The solution was concentrated under vacuum and the bottoms were distilled, yielding 14.6 g. of propanesultone b.p. 96° (1 mm.), ester value, 0.819 eq./100 g., calcd. ester value 0.820 eq./100 g. (79% conversion on acrolein).

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EMERYVILLE, CALIF.

Reactions of Hindered Phenols. III.[1] Reaction of Nitrous Acid with Hindered Phenols

M. S. KHARASCH[2] AND B. S. JOSHI[3]

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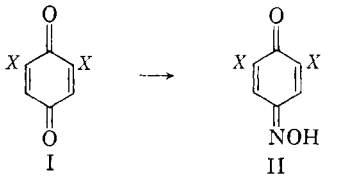
The tautomeric behavior of nitrosophenols (quinone oximes) is well known and on the basis of electronic spectra, Havinga and co-workers[4] have shown that *p*-nitrosophenol exists in solution as the phenol along with the quinone monoxime, whereas in the solid state it occurs as the oxime. Hadzi has recently shown on the basis of infrared studies that in the solid state it could be represented as the monoxime and in chloroform solution, the oxime structure predominates.[5] X-ray determination of 3-chloroquinone-4-oxime and 3-methyl-6-chloroquinone-4-oxime has indicated that the molecules exist in the quinone oxime form.[6]

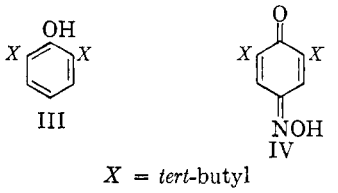
If the quinone is sterically hindered by substituents in the *ortho* position as in I, then the product obtained by the action of hydroxylamine has the structure II.[7] Hodgson and co-workers have carried



I II

X = Cl, Br, CH_3, i-C_3H_7

out a large amount of work on the nitrosation of substituted phenols.[8] We were interested in studying the reaction of nitrous acid on sterically hindered phenols. 2,6-Di-*tert*-butylphenol (III) gave on treatment with nitrous acid, an excellent yield of a compound melting at 221–222°. The ultraviolet spectrum showed λ_{max} 302,418 mμ, ϵ_{max} 15,300 and 3700, respectively, which indicates predominantly a monoxime structure.[4] The infrared spectrum (Nujol mull), 3330 cm.$^{-1}$ (OH), 1613 cm.$^{-1}$ (C=O), 1560 cm.$^{-1}$ (C=N), and 1042 cm.$^{-1}$ (N–OH stretching), supports an

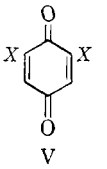


III IV

X = *tert*-butyl

oxime structure (IV).[5] Metro[9] obtained a compound melting at 219–220° by treating 2,6-di-*tert*-butylbenzoquinone with hydroxylamine hydrochloride. This obviously has the identical structure (IV).

A number of methods are known for the preparation of 2,6-di-*tert*-butylbenzoquinone (V).[10–14] Since the oxime (IV) was obtained in almost quantitative yield, the hydrolysis of the same appeared to be



V

X = *tert*-butyl

a simple route for the preparation of V. Thus by the hydrolysis of the oxime (IV) with 20% hydrochloric acid in the presence of cuprous oxide, a 75% yield of V was obtained.

Hart and Cassis[15] found that the action of nitric acid and acetic acid on 2,6-di-*tert*-butylphenol

(1) Part II, Ref. 17.
(2) Deceased.
(3) Present address: National Chemical Laboratory, Poona 8, India.
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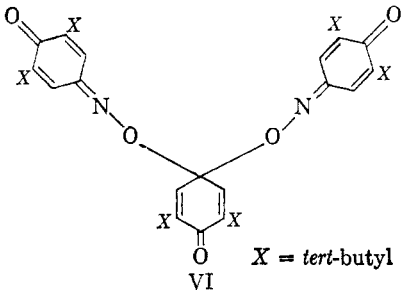
(III) gave 2,4-dinitro-6-*tert*-butylphenol or 3,5,3′,5′-tetra-*tert*-butyl-4,4′-diphenoquinone, depending upon the condition of the reaction.

The nitrosophenols or the quinone oximes on oxidation with alkaline potassium ferricyanide are known to give the corresponding nitrophenols.[16] However, when a benzene solution of the quinone oxime (IV) was treated with alkaline potassium ferricyanide with a view to prepare 4-nitro-2,6-di-*tert*-butylphenol, an excellent yield of a crystalline product, m.p. 141–142° dec., was obtained. The compound had an analysis corresponding to the molecular formula $C_{42}H_{60}O_5N_2$ and had a molecular weight of 662 (depression of freezing point; Rast method could not be used because of the highly colored melt). The ultra-violet spectrum showed $\lambda_{max}^{isooctane}$ 225, 293, and 310 mμ; ϵ_{max} 12,400, 32,000, and 33,600 respectively. This indicates the presence of a dienone grouping and also the chromophoric group of the quinone oxime. The infra-red spectrum indicated the absence of hydroxyl and nitro groups but exhibited the characteristic twin band at 1665 cm.$^{-1}$ and 1640 cm.$^{-1}$ due to the dienone grouping.[17] When one part of the compound was heated with 50% sulfuric acid, two parts of the quinone oxime (IV), and approximately 0.5 parts of the benzoquinone (V) (calculated on the theoretical yields) were obtained. From this evidence, the structure VI has been proposed for the oxidation product.

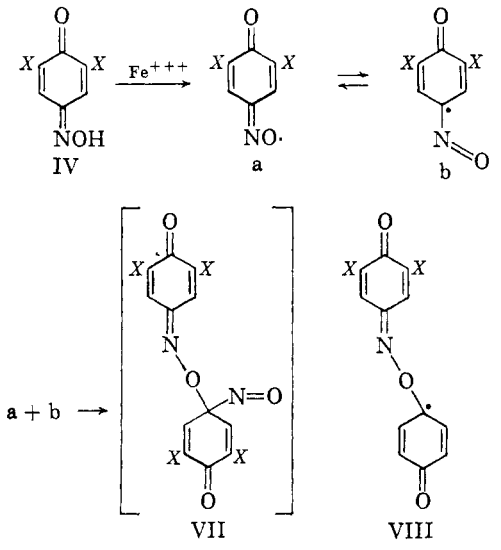


VI

X = *tert*-butyl

Although it is not possible to propose a definite mechanism, compound VI appears to be formed from IV by the following sequence of reactions. The attack of base on the tertiary nitroso compound (VII) possibly removes nitrous acid to give the phenol which forms the radical (VIII), and coupling with (a) gives the compound VI.

Attempts to condense two moles of the oxime (IV) with one mole of the benzoquinone (V) using *p*-toluenesulfonic acid as the dehydrating agent, were not successful. It was also not possible to obtain VI by carrying out the reaction in alkali only without potassium ferricyanide. Compound VI could not also be obtained by oxidation of IV



IV a b

VII VIII

with lead dioxide in an ether solution. This showed the necessity of both base and an oxidizing agent for the reaction.

EXPERIMENTAL

Preparation of 2,6-di-tert-butylbenzoquinone oxime-4 (IV). To a solution of 2,6-di-*tert*-butylphenol (3 g.) in ethanol (25 ml.), concentrated hydrochloric acid (2 ml.) was added and the solution cooled to −5°. To the cooled mixture, a solution of sodium nitrite (1.1 g. in 5 ml. of water) was gradually added under vigorous agitation, maintaining the temperature at 0 to −5°. After complete addition (15 min.), the yellow product was agitated 30 min. longer and poured into ice water. The yellow precipitate (3.4 g.) gave on crystallization from benzene, shining yellow plates which melted at 221–222°.

Anal. Calcd. for $C_{14}H_{21}O_2N$: C, 71.4; H, 9.0. Found: C, 71.3; H, 9.2.

The light absorption spectrum showed $\lambda_{max}^{ethanol}$ 302 and 418 mμ; ϵ_{max} 15,300 and 3700 respectively.

Acetyl derivative of the quinone oxime (IV). The quinone oxime (1.2 g.) was heated under reflux with acetic acid (5 ml.) and acetic anhydride (1 ml.) for about 10 min. The solution after cooling, was poured into water, collected on a filter and dried (1.1 g.). The acetyl derivative crystallized from petroleum ether (b.p. 60–80°) as pale yellow rhombic plates, m.p. 102°.

Anal. Calcd. for $C_{16}H_{23}O_3N$: C, 69 3; H, 8.3. Found: C, 69.7; H, 8.4.

Preparation of 2,6-di-tert-butylbenzoquinone (V). The quinone oxime (0.45 g.) was dissolved in Methyl Cellosolve (10 ml.), acetone (1 ml.) and hydrochloric acid (34%, 5 ml. in 1.5 ml. of water), and cuprous oxide (1 g.) was added to it. The mixture was refluxed for 1 hr. The solution was carefully steam distilled and from the distillate a yellow crystalline product (0.33 g.) m.p. 68°, identified as 2,6-di-*tert*-butylbenzoquinone (75%), was obtained.

Reaction of the quinone oxime with alkaline potassium ferricyanide. To a vigorously stirred mixture of benzene (60 ml.), water (30 ml.), potassium ferricyanide (10 g.) and potassium hydroxide (2 g.), a solution of the oxime (3.2 g.) in benzene (200 ml.) was added during 1 hr. The reaction was carried out under nitrogen atmosphere. After stirring the solution for 4 more hr., the aqueous layer was separated, washed with water, dried, and the benzene removed under reduced pressure (nitrogen atmosphere). This gave a colorless product (2.7 g.). From the filtrate which was colored dark purple, 50 mg. more of the colorless crystalline solid was obtained. It was soluble in ether, petroleum ether, and benzene. These

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solutions decomposed to a dark red solution in a few hours after contact with air. The solid (0.7 g.) on quick crystallization from acetone (200 ml.) under nitrogen atmosphere gave colorless long needles which melted at 141–142°.

Anal. Calcd. for $C_{42}H_{60}O_5N_2$: C, 74.9; H, 9.0; N, 4.2. Found: C, 75.0, 75.2, 74.3; H, 9.1, 9.3, 9.0; N, 4.3, 4.0.

Hydrolysis of compound VI. The crystalline compound (0.2 g.) was dissolved in acetone (25 ml.) by warming, and 50% sulfuric acid (5 ml.) was added to it. This was gently heated under reflux for about 5 min. The acetone was removed under reduced pressure, the resulting solid dissolved in benzene and extracted with 5% sodium hydroxide. The benzene layer on drying and concentration gave (0.077 g.) of the impure quinone. Steam distillation gave 34 mg. of pure 2,6-di-*tert*-butylbenzoquinone.

The alkaline layer was acidified and the precipitate collected (0.12 g.). Crystallization from benzene gave shining yellow flakes, m.p. 220°, which were identical with the quinone oxime (IV), in their melting point, ultraviolet, and infrared spectra.

POONA, INDIA

A Study with C^{14} of the Hydrolysis of Unsymmetrical 2,5-Piperazinedione into Dipeptides

PATRICE TAILLEUR AND LOUIS BERLINGUET

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The hydrolysis of 2,5-piperazinedione has been extensively studied.[1–4] With unsymmetrical 2,5-piperazinediones it should in theory give a mixture of two dipeptides. Previous work was done at that time when the modern techniques of chromatography and electrophoresis were unknown. The analytical methods then used were based on the titration of free carboxyl or amino group liberated during the hydrolysis. The emphasis was therefore more on the study of the ideal conditions and of the rate of the hydrolysis rather than on the relative proportions and identities of the products formed.

As no definite rules have been laid out for the opening of unsymmetrical 2,5-piperazinediones, this method of synthesis of dipeptides, first proposed by Fischer and Shrauth,[5] has been neglected.

In a recent publication[6] it has been shown that the partial hydrolysis of 1,4-diazaspiro[4.5]decane-2,5-dione (V) by 1*N* hydrochloric acid gives two dipeptides: glycylamino-1 cyclopentanecarboxylic acid (IV) and amino-1-cyclopentanecarboxylglycine (VI), these two peptides having been identified by paper chromatography. Connors and Ross[7] in a recent work have obtained by the opening of the same piperazinedione only one peptide, VI.

Theoretically it became interesting to study quantitatively the yield of the two peptides expected after the hydrolysis. One could expect that assymetry of the molecule will favor the opening of one peptide bond over the other. However, there are practical difficulties in this study because of the similarity in the chemical properties of the two peptides and their abnormal reaction with ninhydrin.[6] To overcome this, we incorporated in this substituted 2,5-piperazinedione a radioactive carbon. Starting from glycine-1-C^{14} we have prepared IV by the carbodiimide method. This peptide was then cyclized into the corresponding piperazinedione (V), which after hydrolysis gave the two radioactive peptides. These were separated by paper chromatography and the radioactivity of each was determined. The relative proportion of the two peptides was 58% for IV and 42% for VI. In this case, the difference in the respective yields is not sufficient to allow for theoretical considerations. However, this new method using C^{14} incorporated into the piperazinedione appears the ideal one for similar studies with other unsymmetrical piperazinediones.

EXPERIMENTAL

N-Carbobenzoxyglycine-1-C^{14} (I). A solution containing 5.05 mg. of glycine-1-C^{14} (total activity, 0.1 mc.) in 10 ml. of water was made. An aliquot of 4 ml. was taken and 2 g. of glycine were dissolved in it. Then sodium hydroxide and benzyl chloroformate were added and I was isolated as usual. Yield: 4.4 g. (79%) m.p. 119–120°.[8] Specific activity: 3.3×10^3 c.p.m./mg.

Anal. Calcd. for $C_{10}H_{11}NO_4$: N, 6.70. Found: N, 6.75.

Benzylamino-1-cyclopentanecarboxylate (II). This compound was prepared by a method recently described.[6]

Benzyl N-carbobenzoxyglycyl-1-C^{14}-amino-1-cyclopentanecarboxylate (III). To a solution of 4.0 g. of I, and 4.4 g. of II in 40 ml. of tetrahydrofuran was added 4.2 g. of *N,N'*-dicyclohexylcarbodiimide, and III was isolated according to Sheehan and Hess[8] by recrystallizing with ethyl acetate and petroleum ether. This yielded 6.8 g. (86%) of III, m.p. 107–108°. Specific activity: 1.6×10^3 c.p.m./mg.

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: N, 6.83. Found: N, 6.94.

Glycyl-1-C^{14}-amino-1-cyclopentanecarboxylic acid (IV). A solution of 4.1 g. of III in 30 ml. of ethanol containing a little acetic acid was hydrogenated for 6 hr. over 0.1 g. of palladium 10% on carbon. The catalyst was filtered, and the solution evaporated to dryness, washed with acetone, and filtered. The insoluble peptide was recrystallized from water and acetone. Yield: 1.3 g. (70%), m.p. 277°.[6] Specific activity: 2.8×10^3 c.p.m./mg.

Anal. Calcd. for $C_8H_{14}N_2O_3$: N, 15.05. Found: N, 15.08.

1,4-Diazospiro[4.5]decane-2,5-dione-5-C^{14} (V). A mixture of 1 g. of IV and 6 g. of β-naphthol[9] was heated for 3 hr. at 145° in an oil bath, with occasional stirring. After cooling, the yellowish residue was thoroughly extracted two or three times with ether to remove the β-naphthol. After dissolving

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