seemed to be no great difference in the results obtained with two different nitrobenzene samples with any of the nitroanilines.

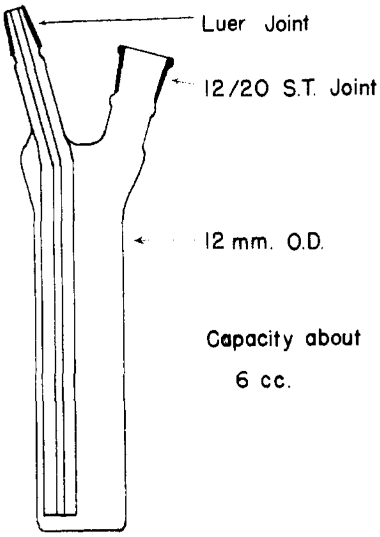

Fig. 2.—Sampling tube for quantitative infrared analyses. The sample is weighed into the tube directly or on a small aluminum foil boat; the volatile solvent, CS_2, acetone, etc., then is added and the tube weighed. Loss of solvent is prevented by a 12/20 plug and by a Luer cap, the latter being one of the standard Luer fittings obtainable from Becton, Dickinson and Co., Rutherford, N. J. The Luer joint fits the Perkin–Elmer cells and the sample transfer is effected by warming the upper part of the sampling tube with the hand. Designed by D. F. DeTar and V. Gold.

The isolation of the dinitrobiphenyl fraction was accomplished as follows: the nitrobenzene layer was separated, washed twice with water, dried over calcium chloride, and distilled under reduced pressure to remove most of the nitrobenzene. The tarry residue was transferred to a 300-ml. Kjeldahl flask using methylene chloride as a solvent, the solvent removed, and the residue subjected to distillation with superheated steam, the temperature of the steam just before entering the condenser was 175–185° (bath temperature about 220°). About 7 l. of distillate was collected, the last liter of which was clear and colorless. The first few hundred ml. containing a little nitrobenzene was discarded, the rest of the distillate was combined in a 12-l. flask and stirred several hours with 700 ml. of methylene chloride. The above steam-distillation procedure was then repeated, but only 5 l. of distillate needed to be collected. The residue in the Kjeldahl flask was negligible. It consisted of a slight film of tarry material which had carried over in the first distillation. The analysis was carried out on this dinitrobiphenyl mixture.

The last run reported in Table I was carried out somewhat differently. Crystalline 4-nitrobenzenediazonium chloride was prepared. Recrystallized 4-nitroaniline (6.90 g.) was dissolved in 25 cc. of glacial acetic acid (refluxing); dry hydrogen chloride was passed in, the mixture cooled at below 20° and 7 ml. of *n*-butyl nitrite added to the amine hydrochloride suspension. Addition of ether gave two layers. The upper ether layer was decanted and crystals obtained from the lower layer by successive additions of dimethylformamide and of ether. The resulting 5.2 g. of pale yellow hygroscopic diazonium salt was dissolved in water, treated with Norit, filtered, and diluted to 25 cc. Analysis of aliquots by precipitation of the azo compound with β-naphthol showed that 10 cc. contained 9.1 ± 0.2 mmoles of the diazonium salt. A 10-cc. aliquot was stirred with 50 cc. of purified nitrobenzene and a solution of 13.6 g. of sodium acetate trihydrate added at room temperature while the solution was vigorously stirred. After one hour it was no longer possible to obtain a color test for diazonium salt with β-naphthol. The *p*H of the solution was 5.7. The dinitrobiphenyl fraction was isolated by the general procedure described above except that phenolic material was extracted with sodium hydroxide. There was obtained 0.85 g. (38%) of dinitrobiphenyl fraction, 0.23 g. of alkali-soluble material, and 1.36 g. of material not volatile with superheated steam at 238° (temperature of vapors leaving steam-distillation flask).

COLUMBIA, SOUTH CAROLINA

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Synthesis of 5,6-Dimethoxyindoles and 5,6-Dimethoxyoxindoles. A New Synthesis of Indoles

BY GORDON N. WALKER

RECEIVED NOVEMBER 20, 1954

5,6-Dimethoxyoxindole and 5,6-dimethoxyindoles have been synthesized by a new process involving low-pressure hydrogenation of 4,5-dimethoxy-2-nitrophenylacetic acid and 4,5-dimethoxy-2-nitrophenylacetonitriles, respectively, in the presence of palladium–charcoal. Evidence was found for formation of 2-aminoindoles as intermediates in hydrogenation of nitronitriles of this type. 3-Substituted oxindoles were prepared by condensation of 5,6-dimethoxyoxindole with aldehydes and subsequent hydrogenation. Hydrochlorides of 6-methoxybufotenine methyl ether and the corresponding 2-amino derivative, prepared by this method, produced a lowering of blood pressure in dogs.

The few reports of synthesis of dimethoxyindoles which have appeared have indicated that such compounds are not stable. Huebner and co-workers[1] very recently synthesized 5,6-dimethoxyindole by hydrogenation of 3,4-dimethoxy-6,β-dinitrostyrene and confirmed an earlier observation[2] that this indole is unstable. Similar lack of stability was noticed in other compounds[1] which were prepared by 3-substitution of the indole.

Since dimethoxyindoles are especially unstable in oxidizing environments, it was felt that a synthetic process involving reductive conditions would be favorable in preserving the indoles, once they were formed. The purpose of this report is to describe the successful development of a new synthesis of methoxyindoles and related oxindoles, based on palladium-catalyzed reduction of appropriate nitro-compounds.

Hydrogenation of nitro-ester I in ethyl acetate at room temperature in the presence of palladium–charcoal gave amino-ester II, but when acetic acid was used as solvent and the reaction carried out at 80°, ring closure to the oxindole III occurred. It

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[1] C. F. Huebner, H. A. Troxell and D. C. Schroeder, THIS JOURNAL, **75**, 5887 (1953).

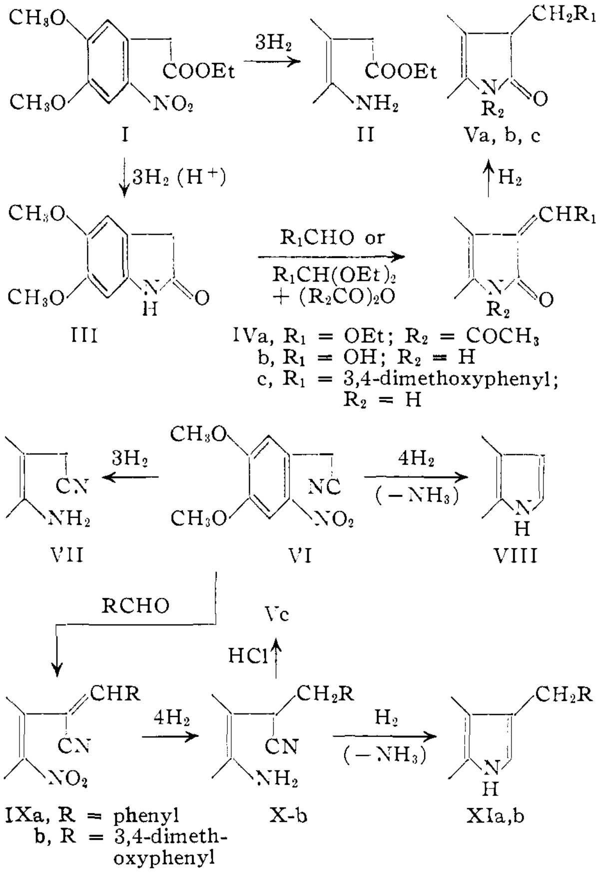
[2] A. E. Oxford and H. S. Raper, *J. Chem. Soc.*, 417 (1927).

was found that either the nitroester or the nitroacid (I) could be used in preparing III, the acid requiring a longer period of heating at 80° for complete lactam formation, after hydrogen consumption was complete. Evidently the carboxyl group in these compounds is sufficiently reactive so that lactamization occurs under rather mild conditions. Hahn[3,4] has reported parallel results with similarly constituted *o*-nitrophenylacetamides.

Several 3-substituted 5,6-dimethoxyoxindoles (V) were prepared from III as indicated in the chart. Condensation of III with ethyl orthoformate after acetylation, as described for oxindole,[5] gave the N-acetyl-3-ethoxymethylene derivative (IVa). Hydrogenation of IVa in acetic acid in the presence of palladium–charcoal involved β-elimination of the ethoxy group and absorption of two moles of hydrogen, and gave the 1-acetyl-3-methyloxindole (Va). The corresponding 3-hydroxymethyleneoxindole IVb was obtained by mild alkaline hydrolysis of IVa. Catalytic reduction (palladium) of IVb in acetic acid also involved absorption of two moles of hydrogen with elimination of water and led to the 3-methyloxindole Vb which gave Va upon acetylation. These hydrogenolyses are similar to some reactions described by Julian and his students[6-8] in the N-methyloxindole series and for derivatives of oxindole itself, and also bear some resemblance to hydrogenolysis of 2-hydroxymethylenetetralones, a reaction which leads to formation of 2-methyltetralins. The oxindole III was found to react smoothly with aldehydes in the presence of piperidine or piperidine acetate. Thus with veratraldehyde III was converted to IVc. This compound readily consumed a mole of hydrogen (palladium) and the product was Vc.

Attention was directed next to the more interesting problem of reduction of *o*-nitrophenylacetonitriles. It was anticipated that cyclization might accompany reduction in such compounds in view of the results experienced with I and also for the reason that reductive cyclizations involving nitrile groups are known, a recent and pertinent example being furnished by Boekelheide.[9] This expectation was confirmed in hydrogenation experiments with VI. Like the nitroester I, the nitronitrile VI absorbed three moles of hydrogen in the presence of palladium–charcoal catalyst at room temperature in ethyl acetate solvent, the product being the aminonitrile VII. When the reaction was conducted at 80°, however, *four* moles of hydrogen were absorbed. Ammonia was formed, and the crystalline product was 5,6-dimethoxyindole, identical in all respects with material prepared by other methods.[1,2] For this transformation there is little precedent other than the Pschorr–Hoppe[10] and Stephen[11] syntheses of indole, both of which rely on chemical, rather than catalytic, means, and which have found little use.

CHART 1



It was obviously of interest to examine the course and the usefulness of this new reaction, and in particular to determine whether or not it could be applied to nitronitriles substituted at the carbon atom adjacent to the cyano group, for these should lead to 3-substituted indoles. Reduction of substituted nitriles proved to be possible. Compounds IXa and IXb, the benzylidene and veratrylidene derivatives, respectively, of VI, upon exhaustive hydrogenation in the presence of 10% palladium–charcoal in ethyl acetate at 80°, absorbed five moles of hydrogen and gave indoles XIa and XIb, respectively, ammonia being formed in the process. Evidence that XIa and XIb were indoles was had from analysis, which showed that only one nitrogen atom was present, from the infrared spectra (absorption at 2.86 and 6.11 μ, as with VIII), the ultraviolet spectra, which were in each case very similar to the ultraviolet spectrum of VIII, and from the fact that XIa and XIb gave positive Ehrlich and ferric chloride tests.[1,2]

It was noted that the final absorption of one mole of hydrogen was very slow in the reduction of IXb. A hydrogenation of IXb was carried out using less concentrated (7%) catalyst, and the reaction was stopped when four moles of hydrogen had been taken up. Ammonia was not formed, and the crystalline product proved to be Xb, as evidenced by analysis and infrared spectrum (nitrile band at 4.45 μ), and also by the fact that the com-

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(3) G. Hahn and H. J. Schulz, *Ber.*, **72**, 1308 (1939).

(4) G. Hahn and H. R. Tulus, *ibid.*, **74**, 500 (1941).

(5) H. Beringer and H. Weissauer, *Chem. Ber.*, **85**, 774 (1952).

(6) P. L. Julian, J. Pikl and F. E. Wantz, THIS JOURNAL, **57**, 2026 (1935).

(7) P. L. Julian and H. C. Printy, *ibid.*, **75**, 5301 (1953).

(8) P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, *ibid.*, **75**, 5305 (1953).

(9) V. Boekelheide, W. J. Linn, P. O'Grady and M. Lamborg, *ibid.*, **75**, 3243 (1953).

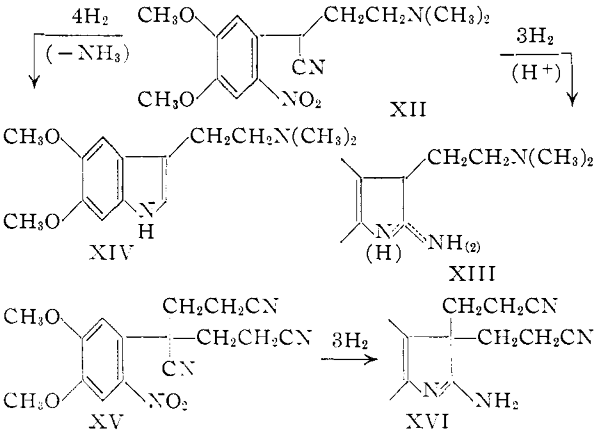
(10) R. Pschorr and G. Hoppe, *Ber.*, **43**, 2543 (1910).

(11) H. Stephen, *J. Chem. Soc.*, 1876 (1925).

pound cyclized to the oxindole Vc in the presence of acid. Thus it was apparent that aminonitriles X were formed as intermediates in reduction of compounds IX to indoles.

Further information on the course of the cyclization was obtained in experiments with the β-dimethylaminoethyl-substituted nitronitrile XII. Hydrogenation of XII in ethyl acetate (10% palladium–charcoal catalyst) at 80° afforded ammonia and the indole XIV. Compound XIV was an unstable oil and was characterized as the methiodide and the picrate. Further evidence for the indole structure XIV was obtained, as before, from spectra and color tests. However, hydrogenation of XII in the presence of 7% palladium–charcoal in acetic acid at 80° did not result in formation of an appreciable amount of ammonia. The product in this case, also, was an unstable oil but did not yield a crystalline methiodide or picrate, and did not have an ultraviolet spectrum characteristic of indoles. However, it was possible to prepare a crystalline hydrochloride from this material, and analytical figures for this substance were in agreement with a dihydrochloride corresponding to structure XIII. The infrared spectrum (no nitrile band) and ultraviolet absorption (λ_{max} 293 mμ) showed that cyclization had taken place and that the product was indeed XIII.

CHART 2



Finally, the bis-substituted nitronitrile XV was subjected to exhaustive hydrogenation under the same conditions which had been found favorable for conversion of the aforementioned compounds to indoles. Ammonia was not formed, and analysis and spectra confirmed structure XVI for the crystalline product. The ultraviolet spectra of XIII and XVI (see Experimental part) were very similar, and the infrared spectrum in each case exhibited absorption close to 6.0 μ (C=N). Thus XIII and XVI may be represented most accurately as 2-aminoindolenines. Substances XIII and XVI are representative of a class of compounds which has received little attention inasmuch as efficient preparative methods have not been devised heretofore. Certain calabash curare alkaloids have been said to feature a 2-aminoindole structural moiety.

The course of the reductive cyclization of the nitronitriles is made fairly clear by these data. The first products, *o*-aminophenylacetonitriles, undergo what may be regarded as internal amidine formation. In the case of reduction of XII in acetic acid, the reaction stops at this stage, presumably because of resonance stabilization of an amidinium salt or because of inability of the catalyst to adsorb a protonated form of XIII. In a neutral solvent (ethyl acetate), however, the amidines (2-aminoindolenines) probably change tautomerically (except in the case of XVI where this is impossible) to 2-aminoindoles, which, under sufficiently strong hydrogenation conditions, undergo removal of the amino group as ammonia and become indoles. This final step cannot take place in the absence of a hydrogen atom at position 3 (as in XVI), and thus the elimination of ammonia must be due to either hydrogenolysis of the amino group of the 2-aminoindole form or saturation of the double bond followed by β-elimination involving a 3-hydrogen atom. It is felt that true hydrogenolysis is responsible for removal of the nitrogen atom at position 2 under the conditions used here, since the double bond of indoles and of amidines is not ordinarily susceptible to hydrogenation in the presence of palladium. However, it is not possible at present to make a final decision on this point.

In the course of his very informative work on synthesis of hydroxyindoles, Harley-Mason[12] hydrogenated XII to a triamine, O-demethylated that compound, and oxidized the resulting dihydroxytriamine with potassium ferricyanide in an effort to obtain 6-hydroxybufotenine. An appreciable amount of this product could not be isolated, although there was evidence for indole formation. The present author finds that a hydrochloride can be prepared from XIV under strictly anhydrous and anaerobic conditions, but that the salt deteriorates rapidly in the presence of air and moisture. Possibly 6-hydroxybufotenine salts, which were formed in the reaction described by Harley-Mason and Jackson, are even less stable than salts of the corresponding O,O-dimethyl derivative (XIV·HCl), and thus may be extremely difficult to isolate. Similar considerations apply to compounds VIII, XIa, XIb and XIII, and compounds prepared by Huebner,[1] all of which decompose in air, especially in the presence of acids.

Aqueous solutions of hydrochlorides of XIII and XIV were administered to normal dogs. Both salts produced a marked, transient fall of blood pressure with accompanying tachycardia at dose levels of 8 to 16 mg. per kg. There were no antagonistic effects to histamine, epinephrine, acetylcholine or tetramethylammonium salts, and the hypotensive action may well have been due to peripheral vasodilatation. These results are in marked contrast to the pharmacology of bufotenine and serotonin, both of which are primarily strong vasoconstrictors. Remarkably enough, the actions of XIII and XIV hydrochlorides in dogs were very similar. Unfortunately it was not possible to prepare an oxindole corresponding to these compounds either by hydrolysis of XIII or by other methods, and thus a true comparison of indole and oxindole pharmacology in this series is not available at this time. Ap-

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(12) J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.*, 1165 (1954).

parently XIII dihydrochloride is stable in water solution, since there is no appreciable shift in the position of the maximum absorption in the ultraviolet spectrum of the salt in the presence of water, as compared with the spectrum in ethanol. Water solutions of XIV are also fairly stable if air is excluded.

The synthetic method described here may be useful in obtaining indoles, oxindoles and 2-aminoindolenines related to various natural products, which are not readily available through other routes. Further applications of the method are being studied at present.

Acknowledgments.—I am indebted to Mrs. Iris Siewers and Miss Fleur Bateman of the Instrument Laboratory for the spectra reported in this paper, and to Dr. William C. Alford and his staff for microanalytical data. I also wish to thank Dr. Neil C. Moran of the Laboratory of Chemical Pharmacology for the pharmacological data mentioned.

Experimental[13]

2-Nitro-4,5-dimethoxyphenylacetic Acid.—A solution of 50 g. of homoveratric acid in 200 ml. of acetic acid was treated with 75 ml. of concd. nitric acid in five portions, while the mixture was swirled in an ice-bath to prevent the temperature from rising above 65°. The mixture was allowed to stand 15 minutes at room temperature, and was poured into cold water. Recrystallization from methanol gave 55 g. (90%) of pure product, m.p. 206–208° (lit.[14] m.p. 206–207°). The infrared spectrum (Nujol) had peaks at 5.85–5.92 and 6.60 μ.

Attempts to condense this acid with formaldehyde and dimethylamine hydrochloride gave the dimethylammonium salt of the acid, m.p. 152.5–154.5° dec., from methanol–ethyl acetate.

Anal. Calcd. for $C_{12}H_{18}O_6N_2$: C, 50.34; H, 6.34. Found: C, 50.14; H, 5.69.

Ethyl Ester (I).—Esterification of 10.1 g. of the nitro-acid in 475 ml. of ethanol containing 24 ml. of concd. sulfuric acid (3-hour reflux) gave 10.2 g. (90%) of neutral product as lemon-yellow needles, m.p. 113–114° from methanol. The infrared spectrum (chf) of this nitro-ester is anomalous, having peaks at 5.97, 6.24, 6.30 and 6.90 μ; apparently interaction of the ortho-groups is responsible for a marked shift to longer wave lengths.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.53; H, 5.62. Found: C, 53.58; H, 5.65.

Ethyl 2-Acetylamino-4,5-dimethoxyphenylacetate (II acetate).—A solution of 1.6 g. of nitro-ester I in 150 ml. of ethyl acetate containing 1.0 g. of 7% palladium–charcoal catalyst was shaken under hydrogen (40 lb.) at room temperature for 1.5 hours. The catalyst was filtered. The solution was treated with 30 ml. of acetic anhydride and was allowed to stand (stoppered) for 4 days. Evaporation of the solvents and recrystallization of the residue from ethyl acetate afforded colorless crystals, m.p. 122.5–123.5°. The infrared spectrum (chf) had peaks at 3.00 and 5.86–5.97 μ.

Anal. Calcd. for $C_{14}H_{19}O_5N$: C, 59.77; H, 6.81. Found: C, 59.79; H, 6.70.

Attempts to isolate the free amine by evaporation of the solution from hydrogenation led to partial formation of oxindole III and partial decomposition.

5,6-Dimethoxyoxindole (III).—A mixture of 45 g. of 2-nitro-4,5-dimethoxyphenylacetic acid, 250 ml. of glacial acetic acid and 7 g. of 8% palladium–charcoal catalyst was shaken under hydrogen (40 lb.) at 80° for 3 hours. The theoretical amount (3 moles) of hydrogen was absorbed in 0.7 hour. Filtration of the hot mixture gave a colorless solution which immediately began to deposit crystals. The mixture was diluted with 100 ml. of ethyl acetate and 100 ml. of ether, was stoppered tightly, and was kept at ice temperature overnight. The crystals were collected, washed with ethyl acetate, and air-dried. The yield of colorless oxindole, m.p. 208–210°, was 27 g. (75%). Recrystallization from methanol did not raise the m.p. (lit.[3] m.p. 204–205°). The infrared spectrum (chf) was very characteristic, having peaks at 2.84, 3.08, 5.69–5.81 (twin) and 6.09 μ.

Anal. Calcd. for $C_{10}H_{11}O_3N$: C, 62.14; H, 5.74. Found: C, 62.21; H, 5.60.

The oxindole was also obtained in 78% yield by hydrogenation of nitro-ester I under the same conditions for 2 hours.

1-Acetyl-3-ethoxymethylene-5,6-dimethoxyoxindole (IVa).—A mixture of 14.5 g. of III and 200 ml. of acetic anhydride was refluxed for 5 hours. When the cooled solution was allowed to stand overnight, crystals were deposited. A sample of this material, **1-acetyl-5,6-dimethoxyoxindole,** was found to have m.p. 163–165° after recrystallization from ethyl acetate. The infrared spectrum (chf) had peaks at 5.69 and 5.88 μ.

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57. Found: C, 61.00; H, 5.41.

The mixture was treated with 20 ml. of ethyl orthoformate and was refluxed for an additional 9 hours. The resulting deep green solution was chilled 4 days, and the crystals were collected and air-dried. The yield of green crystals, m.p. 175–179°, was 14.6 g. (67%). Recrystallization from ethyl acetate (Norit) gave pale green-yellow needles, m.p. 180–181°. The infrared spectrum (chf) had peaks at 5.73–5.85 (doublet), 6.00 and 6.16 μ.

Anal. Calcd. for $C_{15}H_{17}O_5N$: C, 61.84; H, 5.88. Found: C, 61.70; H, 5.77.

3-Hydroxymethylene-5,6-dimethoxyoxindole (IVb).—A mixture of 11.4 g. of the ethoxymethyleneoxindole IVa, 90 ml. of 5% sodium hydroxide solution and 10 ml. of methanol was heated on a steam-cone for 15 minutes with swirling. The solution was filtered, chilled in ice, and acidified with cold, concd. hydrochloric acid. After standing 2 hours at ice temperature, the thick suspension was filtered. The crystals were washed with 10 ml. of water and were dried *in vacuo* over potassium hydroxide. There was obtained 8.5 g. (98%) of orange crystalline solid, m.p. 207–209° dec. Recrystallization from methanol did not raise this m.p. The compound was moderately soluble in water and gave a green color with ferric chloride solution. It decomposed slowly in air, especially in the presence of solvents. The infrared spectrum (chf) had peaks at 2.90, 3.16, 5.70, 5.88 and 6.07 μ.

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.72; H, 5.01. Found: C, 59.94; H, 5.29.

Acetylation of IVb in hot acetic anhydride for 2 hours gave **1-acetyl-3-hydroxymethylene-5,6-dimethoxyoxindole** in a quantitative yield; yellow needles, m.p. 229–231° dec., from ethyl acetate.

Anal. Calcd. for $C_{13}H_{13}O_5N$: C, 59.31; H, 4.98. Found: C, 59.49; H, 5.19.

3-Veratrylidene-5,6-dimethoxyoxindole (IVc).—A mixture of 0.9 g. of III, 1.0 g. of veratraldehyde, 3 drops of piperidine, 8 drops of acetic acid and 40 ml. of dry toluene was refluxed under a constant water-separator for 2.5 hours. The cooled solution was diluted with ethyl acetate and was washed with two portions of water. Evaporation of the solvents gave 1.3 g. of red crystals, m.p. 187–191°, raised to 199–200° by recrystallization from methanol. The infrared spectrum (chf) had peaks at 2.83, 3.09, 5.84 and 6.12 μ.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61. Found: C, 66.66; H, 5.69.

1-Acetyl-3-methyl-5,6-dimethoxyoxindole (Va).—Hydrogenation of 3.4 g. of IVa in 120 ml. of glacial acetic acid in the presence of 2.5 g. of thoroughly dried 8% palladium–charcoal catalyst at 40 lb. pressure and 80° gave, after filtration of the catalyst, evaporation of the solvent and trituration with ethyl acetate, 2.3 g. of pale yellow crystals, m.p. 151–153°. Recrystallization from ethyl acetate raised the m.p. to 153–155°. The infrared spectrum (chf) had peaks at 5.69, 5.87 and 6.18 μ.

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07. Found: C, 62.56; H, 6.09.

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[13] Melting points are corrected.

[14] R. K. Callow, J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 658 (1929).

3-Methyl-5,6-dimethoxyoxindole (Vb).—Hydrogenolysis of 1.5 g. of IVb under the conditions described in the preceding experiment afforded 0.9 g. of crystals, m.p. 126–128°, after trituration with ethyl acetate. The compound was moderately soluble in water. Two crystalline forms of the material were obtained, as follows. Recrystallization from water gave pale yellow needles, m.p. 155–156.5° with crystalline transformation at 128–130°. Recrystallization from dry ethyl acetate gave material, m.p. 132–134°. The infrared spectra of the two samples (chf) were identical, having bands at 2.90, 3.15, 5.85 and 6.12 μ. The mixed m.p. of the two forms was 155–156° with crystalline transformation at 128–130°. The low-melting form was transformed into the one of higher m.p. by recrystallization from water.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32. Found: C, 63.59; H, 6.39.

Acetylation of the compound in hot acetic anhydride (1.5 hours) gave crystals, m.p. 151–153°, after recrystallization from ethyl acetate. The mixed m.p. with Va, obtained as described in the preceding experiment, was 152–154° (undepressed), and the infrared spectra (chf) were identical.

3-(3',4'-Dimethoxybenzyl)-5,6-dimethoxyoxindole (Vc).—A mixture of 1.0 g. of IVc, 1.0 g. of 7% palladium-charcoal catalyst and 50 ml. of acetic acid was hydrogenated (40 lb.) at 80° for 1.5 hours. Isolation of the product in the usual way gave a glass which crystallized very slowly in the presence of a trace of methanol. Recrystallization from ethyl acetate afforded pale yellow crystals, m.p. 128–130°. The infrared spectrum (chf) had peaks at 2.85, 3.07, 5.82 and 6.10 μ.

Anal. Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.17. Found: C, 66.67; H, 6.01.

2-Nitro-4,5-dimethoxyphenylacetonitrile (VI).—A solution of 30.5 g. of homoveratronitrile in 100 ml. of glacial acetic acid was treated with 45 ml. of concd. nitric acid in four portions while swirling the solution in an ice-bath to prevent the temperature from rising above 65°. The mixture was allowed to stand at 10° for 15 minutes and was poured into cold water. After crystallization was complete (a half-hour at ice temperature), the product was collected, washed with four small portions of cold water, pressed dry, and recrystallized from methanol. The yield of crystals, m.p. 109–111°, was 27 g. (71%). Further recrystallization from methanol gave yellow needles, m.p. 111–113°. The infrared spectrum (chf) had peaks at 4.42 and 6.52–6.56 μ.

Anal. Calcd. for $C_{10}H_{10}O_4N_2$: C, 54.05; H, 4.54. Found: C, 54.09; H, 4.65.

2-Amino-4,5-dimethoxyphenylacetonitrile (VII).—A solution of 3.5 g. of VI in 200 ml. of ethyl acetate containing 1.5 g. of 8% catalyst was shaken under hydrogen (40 lb.) at room temperature for an hour. The theoretical quantity of hydrogen (3 moles) was absorbed. Filtration of the catalyst and evaporation of half of the solution gave crystals which, after recrystallization from ethyl acetate, had m.p. 95–98°. The infrared spectrum (chf) had peaks at 2.90–2.95 and 4.45 μ. The compound was unstable, and a satisfactory analysis could not be obtained. The remaining half of the solution from the hydrogenation was treated immediately with 20 ml. of acetic anhydride and the solution was allowed to stand (stoppered) at room temperature for 24 hours. Evaporation of the solvents and trituration of the residue with ethyl acetate gave 1.5 g. of the **N-acetyl** derivative as colorless needles, m.p. 179–180°, which was not improved on further recrystallization. The infrared spectrum (chf) had peaks at 2.93, 3.04, 4.45 and 5.95 μ.

Anal. Calcd. for $C_{12}H_{14}O_3N_2$: C, 61.52; H, 6.02. Found: C, 61.71; H, 6.17.

5,6-Dimethoxyindole (VIII).—A solution of 5.0 g. of VI in 150 ml. of ethyl acetate containing 2.5 g. of 10% palladium-charcoal catalyst[15] was shaken under hydrogen (40 lb.) at 80° for 1.5 hours. Three moles of hydrogen was absorbed in 12 minutes and an additional mole was taken up subsequently during a period of 15 minutes. An ammoniacal odor was noticed when the gas pressure was released after the reaction was complete, and ammonium chloride was formed when this gas was brought into contact with hydrogen chloride. The hot solution was filtered quickly and the solvent was removed as speedily as possible by distillation *in vacuo*. The residue crystallized upon cooling. Trituration with methanol gave 2.4 g. (60%) of gray crystals, m.p. 154–156°. Recrystallization from methanol afforded colorless, gleaming crystals having the same m.p. (lit. m.p. 152–153°,[1] 154–155°[2]).

Anal. Calcd. for $C_{10}H_{11}O_2N$: N, 7.91. Found: N, 7.81.

The infrared spectrum (chf) had peaks at 2.87 (mod.), 2.95 (weak) and 6.12 μ. The ultraviolet spectrum (ethanol) had λ_{max} 218 mμ (log ϵ 4.41), 273 mμ (log ϵ 3.69), 294 mμ (log ϵ 3.88), 300 mμ (log ϵ 3.88) and 306 mμ (log ϵ 3.81), in good agreement with reported[1] values. The compound gave a green color with ferric chloride[1,2] and a positive test with Ehrlich reagent, and exhibited blue fluorescence in ethanol solution.[1] Acetylation with acetic anhydride and potassium acetate gave the **1-acetyl** derivative, m.p. 151–153° (lit.[2] m.p. 150–152°).

Anal. Calcd. for $C_{14}H_{15}O_4N$: C, 64.35; H, 5.79. Found: C, 64.31; H, 6.27.

Compound VIII was also obtained by hydrogenation of VI in the presence of 8% palladium-charcoal in glacial acetic acid at 80°. In this case, however, isolation of the indole (as above) was more difficult, since it deteriorated rapidly in the acid medium, and the yield of product, m.p. 147–150°, was only 24%.

α-(2'-Nitro-4',5'-dimethoxyphenyl)-β-phenylacrylonitrile (IXa).—A solution of 10.5 g. (0.0473 mole) of VI and 6.5 g. (0.061 mole) of benzaldehyde in 250 ml. of boiling absolute ethanol was treated with 5 ml. of piperidine. The solution was boiled for a half-hour and was allowed to stand at room temperature for two days. The crystals were collected and were triturated with hot methanol (100 ml.). The yield of product, m.p. 194–196°, was 13.2 g. (90%). Recrystallization from ethyl acetate gave yellow crystals, m.p. 196–197.5°. The infrared spectrum (chf) had peaks at 4.51 and 6.57–6.60 μ.

Anal. Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55. Found: C, 65.50; H, 4.63.

α-(2'-Nitro-4',5'-dimethoxyphenyl)-β-(3',4'-dimethoxyphenyl)-acrylonitrile (IXb).—Condensation of 12.6 g. of VI and 10.2 g. of veratraldehyde in the presence of 7 ml. of piperidine, as described in the preceding experiment, and trituration of the product with hot methanol gave 18.0 g. (86%) of yellow crystals, m.p. 196–198°, raised by recrystallization (ethyl acetate) to 199–200°. The infrared spectrum (chf) had peaks at 4.50 and 6.55–6.60 μ.

Anal. Calcd. for $C_{19}H_{18}O_6N_2$: C, 61.62; H, 4.90. Found: C, 61.36; H, 4.98.

α-(2'-Amino-4',5'-dimethoxyphenyl)-β-(3',4'-dimethoxyphenyl)-propionitrile (Xb).—A mixture of 2.7 g. of IXb, 1.2 g. of 7% palladium-charcoal catalyst and 120 ml. of ethyl acetate was hydrogenated (40 lb.) at 70°. The reaction was stopped when 4 moles of hydrogen had been taken up (1.5 hours) and the catalyst was filtered. Evaporation of the solvent and trituration of the residue with methanol gave 1.1 g. of crystals, m.p. 145–149° dec. Recrystallization from methanol afforded colorless crystals, m.p. 150–152° dec. The infrared spectrum (chf) had peaks at 2.90–2.97 and 4.45 μ.

Anal. Calcd. for $C_{19}H_{22}O_4N_2$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.65; H, 6.66; N, 7.93.

Acetylation with acetic anhydride at room temperature gave a monoacetate, m.p. 189–191° dec., from methanol-ethyl acetate.

Anal. Calcd. for $C_{21}H_{24}O_5N_2$: N, 7.29. Found: N, 7.00.

When Xb was treated with 10% hydrochloric acid, a clear solution was obtained in 2 minutes. The solution became cloudy after 4 minutes, and deposited pale yellow crystals upon standing overnight. These crystals were collected, washed with water and air-dried. The m.p. was 129–131°, undepressed on admixture with Vc. The infrared spectra (chf) of the two samples were identical.

3-Benzyl-5,6-dimethoxyindole (XIa).—A mixture of 7.6 g. of IXa, 3 g. of 10% palladium-charcoal catalyst[15] and 120 ml. of ethyl acetate was hydrogenated (40 lb.) at 80° for 1.3 hours. Five moles of hydrogen was absorbed in 25 minutes. The gas released after the reaction contained ammonia. Filtration of the catalyst, evaporation of the solvent and trituration of the residue with methanol gave 3.2 g. (49%) of colorless crystals, m.p. 140–142°, not raised by further recrystallization. The infrared spectrum (chf) had sharp

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[15] Obtained from Matheson, Coleman and Bell Division of the Matheson Co., Inc.

peaks at 2.85 and 6.10 μ. The ultraviolet spectrum (ethanol) had λ_{max} 217 mμ (log ϵ 4.52), 297 mμ (log ϵ 3.94), 302 mμ (log ϵ 3.93) and 308 mμ (log ϵ 3.86). The compound gave a blue Ehrlich test, and a red color with ferric chloride solution. Analysis indicated that the crystals were a hemihydrate. The water of crystallization could not be removed without undue decomposition.

Anal. Calcd. for $C_{17}H_{17}O_2N\cdot{}^1/_2H_2O$: C, 73.89; H, 6.57; N, 5.07. Found: C, 74.13; H, 6.68; N, 5.05.

It was not possible to limit hydrogen absorption to 3 moles in this case, and thus Xa could not be isolated.

3-(3′,4′-Dimethoxybenzyl)-5,6-dimethoxyindole (XIb).—Complete hydrogenation of 5.0 g. of IXb was effected in the presence of 5.5 g. of 10% catalyst[15] and 150 ml. of ethyl acetate at 80° and 40 lb. for 4 hours. Four moles of hydrogen was absorbed rapidly (11 minutes) and an additional mole was taken up slowly. Ammonia was present in the exit gases. The product was isolated in the usual way. Trituration with methanol gave 2.8 g. (58%) of crystals, m.p. 136–139°. Recrystallization from methanol gave colorless crystals, m.p. 143–145°. The infrared spectrum (chf) had sharp peaks at 2.85 and 6.11 μ. The ultraviolet spectrum (ethanol) had λ_{max} 224 mμ (log ϵ 4.53), 284 mμ (log ϵ 3.93), 297 mμ (log ϵ 3.92), 302 mμ (log ϵ 3.91) and 308 mμ (log ϵ 3.83). The compound gave a blue Ehrlich test and a red-orange color with ferric chloride solution.

Anal. Calcd. for $C_{19}H_{21}O_4N$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.97; H, 6.73; N, 4.15.

α-(2′-Nitro-4′,5′-dimethoxyphenyl)-γ-dimethylaminobutyronitrile (XII).—Homoveratronitrile (52 g.) was alkylated with β-dimethylaminoethyl chloride (from 50 g. of the hydrochloride) in the presence of 12 g. of sodium amide in refluxing xylene, according to a procedure described earlier.[12] Distillation of the crude, neutral product afforded 46 g. of yellow oil, b.p. 151–175° (2.0 mm.). This material, impure α-(3′,4′-dimethoxyphenyl)-γ-dimethylaminobutyronitrile, was dissolved in 300 ml. of dry ether, and the solution was saturated with hydrogen chloride at ice temperature. The crude, gummy, white hydrochloride which separated was dissolved in 90 ml. of water, and the solution was washed with ether. The solution of hydrochloride was added slowly to 220 ml. of concd. nitric acid while swirling the mixture in an ice-bath to prevent the temperature from rising above 20°. The solution was kept at 0° overnight, and the nitro-amino nitrile was isolated according to previous directions.[12] The crude product crystallized after standing several weeks. Recrystallization from methanol afforded 19 g. (22% from homoveratronitrile) of yellow crystals, m.p. 78–80°. The infrared spectrum (chf) had peaks at 4.46 and 6.55 μ. This compound was described[12] earlier as non-crystalline.

Anal. Calcd. for $C_{14}H_{19}O_4N_3$: C, 57.32; H, 6.53; N, 14.33. Found: C, 56.81; H, 6.65; N, 13.88.

Hydrolysis of XII with 5% sodium hydroxide solution led to formation of dimethylamine as well as ammonia, and no nitro-acid could be isolated after acidification.

The hydrochloride was recrystallized from ethanol; pale yellow crystals, m.p. 193–195° dec. (lit.[12] m.p. 189–190°).

2-Amino-3-(β-dimethylaminoethyl)-5,6-dimethoxyindolenine Dihydrochloride (XIII·2 HCl).—A solution of 5.3 g. of XII in 150 ml. of glacial acetic acid containing 3.5 g. of 8% palladium-charcoal catalyst was shaken under hydrogen (40 lb.) at 80° for 2.5 hours. Absorption of three moles of hydrogen occurred in 20 minutes. The catalyst was filtered, and the solution was distilled *in vacuo* at 100° as rapidly as possible to remove the solvent. The residue was a brown oil which did not crystallize. It was dissolved in 20 ml. of ethanol and 10 ml. of ether, and the solution was saturated with hydrogen chloride at ice temperature. The gummy, green solid which separated was collected and was recrystallized immediately from ethanol. There was obtained 3.2 g. (50%) of greenish crystals, m.p. 190–194° dec. Further recrystallization from ethanol gave slightly discolored crystals, m.p. 194–196° dec. This material was a hydrate.

Anal. Calcd. for $C_{14}H_{25}O_3N_3Cl_2$: C, 47.46; H, 7.12; N, 11.87; Cl, 20.02. Found: C, 47.57; H, 7.66; N, 11.79; Cl, 19.67.

Prolonged drying at 80° *in vacuo* resulted in a 4.3% weight loss and gave nearly pure anhydrous salt, m.p. 191–194° dec.

Anal. Calcd. for $C_{14}H_{23}O_2N_3Cl_2$: C, 49.99; H, 6.89; N, 12.50; Cl, 21.09. Found: C, 49.50; H, 6.80; N, 11.75; Cl, 21.18.

The infrared spectrum (Nujol mull) had peaks at 2.85, 2.92, 5.95 and 6.12 μ. The nitrile band was absent. The ultraviolet spectrum (ethanol) had λ_{max} 230 mμ (log ϵ 4.32) and 293 mμ (log ϵ 3.90). The compound gave a weak Ehrlich test on prolonged standing, and a red color with ferric chloride solution. It was readily soluble in water, the solution gradually becoming dark upon exposure to air.

Attempts to acetylate the crude base gave dark, unstable, material which was not crystalline. The picrate was also unstable, and the ethiodide and methiodide were glassy. Ammonia was evolved when the material was warmed with dilute alkali or treated with lithium aluminum hydride in ether, but no pure products could be isolated either from these reactions or from acidic hydrolysis.

3-(β-Dimethylaminoethyl)-5,6-dimethoxyindole (XIV).—Complete hydrogenation of XII was effected by shaking 1.2 g. of it in 100 ml. of ethyl acetate in the presence of 1.5 g. of 10% catalyst[15] under hydrogen (40 lb.) at 80° for 1.5 hours. Ammonia was formed. The catalyst was filtered, and the solvent was distilled *in vacuo* on a steam-cone as rapidly as possible. The residual oil showed moderately strong infrared absorption at 2.85 μ, and no nitrile or nitro bands. The ultraviolet spectrum (ethanol) bore a strong resemblance to other indole spectra, having λ_{max} 224, 297, 302 and 308 mμ. Attempts to prepare the acetate were unsuccessful, owing to the unstable nature of the product. **The methiodide** was fairly stable, and had m.p. 213–216° dec., after numerous recrystallizations from ethanol. The infrared spectrum of this salt (Nujol) had peaks at 2.97 and 6.11 μ. The ultraviolet spectrum (ethanol) had λ_{max} 220 mμ (log ϵ 4.63), 279 mμ (log ϵ 3.72), 297 mμ (log ϵ 3.91), 302 mμ (log ϵ 3.90) and 307 mμ (log ϵ 3.83).

Anal. Calcd. for $C_{15}H_{23}O_2N_2I$: C, 46.16; H, 5.94; N, 7.18; I, 32.5. Found: C, 45.9; H, 6.16; N, 7.13; I, 31.4.

The picrate was prepared in ethyl acetate and was recrystallized from methanol as red needles, m.p. 182–184° dec.

Anal. Calcd. for $C_{20}H_{23}O_9N_5$: C, 50.31; H, 4.86; N, 14.67. Found: C, 50.46; H, 4.75; N, 14.36.

The hydrochloride was prepared as follows: a filtered solution from reduction of 1.7 g. of XII, as described above, was immediately chilled in ice, and was saturated with dry hydrogen chloride. The mixture was allowed to stand at ice temperature (stoppered) for an hour until coagulation of the gummy material was complete. The solvent was decanted. The material was washed with dry ether by decantation and was dried *in vacuo* over potassium hydroxide immediately. White powder was obtained. The salt could be preserved at ice temperature in a tightly closed vessel, but upon exposure to the atmosphere it became dark and gummy rapidly. The ultraviolet spectrum (ethanol) had λ_{max} 222 mμ (log ϵ 4.32), 278 mμ (log ϵ 3.59), 297 mμ (log ϵ 3.97), 302 mμ (log ϵ 3.78) and 307 mμ (log ϵ 3.71).

γ-Cyano-γ-(2′-nitro-4′,5′-dimethoxyphenyl)-pimelonitrile (XV).—Homoveratronitrile was treated with acrylonitrile, according to a procedure described earlier.[16] A solution of 6.0 g. of the bis-cyanoethyl compound in 19 ml. of glacial acetic acid was treated with 11 ml. of concd. nitric acid at ice temperature. The solution was kept at ice temperature for 3 days, and was poured into cold water. Recrystallization of the product from methanol gave 5.7 g. (67%) of crystals, m.p. 125–128°, sharpened on further recrystallization to 126–128°. The infrared spectrum (chf) had peaks at 4.46 and 6.55 μ.

Anal. Calcd. for $C_{16}H_{16}O_4N_4$: C, 58.53; H, 4.91. Found: C, 58.22; H, 4.85.

2-Amino-3,3-bis-(β-cyanoethyl)-5,6-dimethoxyindolenine (XVI).—A solution of 2.3 g. of XV in 130 ml. of ethyl acetate containing 2.0 g. of 10% catalyst[15] was shaken under hydrogen (40 lb.) at 80° for 4 hours. Three moles of hydrogen were absorbed. The catalyst was filtered. Evaporation of the solvent and trituration of the residue (methanol) gave 1.6 g. of product, m.p. 173–177°. Recrystallization from ethyl acetate gave colorless crystals, m.p. 176–177°. The infrared spectrum (Nujol) had peaks at 2.92–2.98, 4.45

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(16) E. C. Horning, M. G. Horning, M. S. Fish and M. W. Rutenberg, THIS JOURNAL, **74**, 773 (1952).

and 6.01–6.07 μ. The ultraviolet spectrum (ethanol) had λ_{max} 228 mμ (log ε 4.45) and 292 mμ (log ε 4.02). The compound was soluble in dilute acid and did not give ferric chloride or Ehrlich tests.

Anal. Calcd. for $C_{16}H_{18}O_2N_4$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.25; H, 6.04; N, 18.72.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY, AND EIN SHAMS UNIVERSITY]

Photochemical Reactions in Sunlight. XVII.[1] Experiments with 4-Cyano-1,2-naphthoquinone

BY ALEXANDER SCHÖNBERG, WILLIAM IBRAHIM AWAD AND GAMAL AHMED MOUSA

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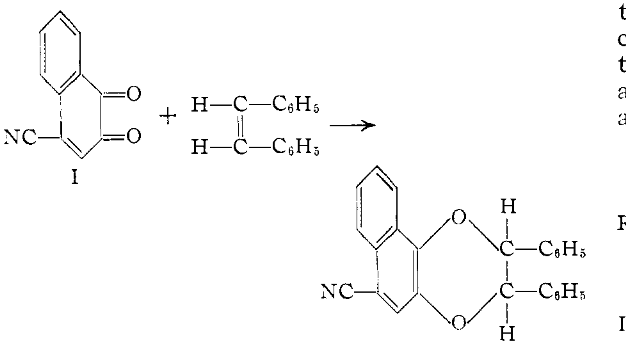
Photochemical reactions (sunlight) of 4-cyano-1,2-naphthoquinone are investigated. The addition of stilbene yields II; the addition of some derivatives of benzaldehyde and of cinnamaldehyde proceeds according to scheme B. The photoreaction with acetaldehyde leads to the formation of 1,2-dihydroxy-3-aceto-4-cyanonaphthalene (V) and with propionaldehyde, 1,2-dihydroxy-3-propiono-4-cyanonaphthalene is obtained. Blank, dark experiments in all cases proved to be negative.

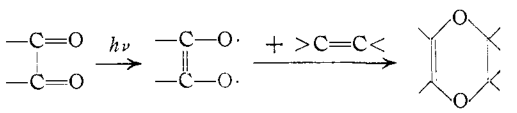
(a) We have investigated the action of stilbene on 4-cyano-1,2-naphthoquinone and found that whereas no action takes place in the dark, in sunlight 6-cyano-2,3-diphenyl-2,3-dihydronaphtho-(1,2)-*p*-dioxin (II) is formed. The reaction takes place as in the case of phenanthrenequinone[2] and similar quinones[3]; 4-cynano-1,2-naphthoquinone is therefore less reactive than certain derivatives of *o*-benzoquinone, *e.g.*, tetrachlorobenzoquinone which adds stilbene even in the dark.[4]



I

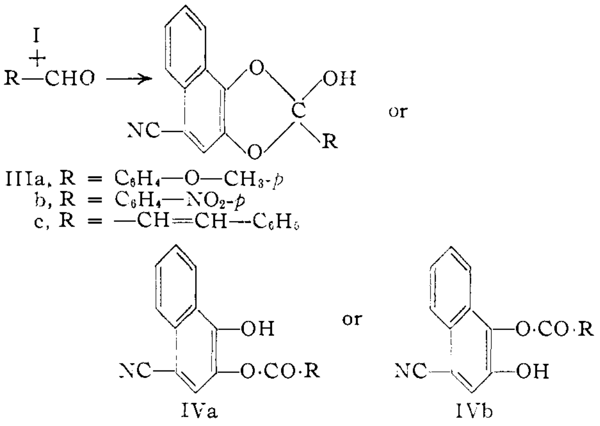
II Scheme A

On the Mechanism of the Photoaddition of Olefins to *o*-Quinones.—Though we have described a great number of such photoadditions,[3] (compare scheme A) we have not yet offered a mechanism. Recently Schenck[5a] and Schenck and Schmidt-Thomée[5b] have advanced the theory that the quinones are changed photochemically into diradicals followed by the addition of the olefins.



Some of these olefins polymerize in sunlight, *e.g.*, stilbene forms a photo dimer.[6] The monomer therefore can be activated by the action of sunlight, and the possibility that the photoaddition of *o*-quinones to the olefins may be due to the action of the photoactivated olefins on the non-activated quinones should not be overlooked. It also is possible that both mechanisms are operative.

(b) **Photochemical Action of 4-Cyano-1,2-naphthoquinone on Aldehydes.**—We have found that in the case of anisaldehyde, cinnamaldehyde, colorless addition products were obtained and in the case of *p*-nitrobenzaldehyde the reaction product was yellow. The products have either the constitution III, IVa or IVb. The possibility of ring chain tautomerism should be taken into consideration.[7,8] None of these photoaddition products in alcoholic solution gives a color reaction with aqueous ferric chloride.



IIIa, R = C_6H_4—O—CH_3-*p*
b, R = C_6H_4—NO_2-*p*
c, R = —CH=CH—C_6H_5

IVa or keto form

IVb or keto form

Scheme B

In contrast to anisaldehyde, cinnamaldehyde and *p*-nitrobenzaldehyde the addition of acetaldehyde and propionaldehyde leads to orange colored products giving in alcohol a green ferric chloride reaction.[9] It is believed that in these cases the reaction proceeds according to scheme C (acetaldehyde is taken as an example).

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[1] Part XVI, *J. Chem. Soc.*, 1346 (1951).

[2] A. Schönberg and A. Mustafa, *ibid.*, 387 (1944); 2126 (1948).

[3] A. Schönberg and A. Mustafa, *Chem. Revs.*, **40**, 190 (1948).

[4] A. Schönberg and N. Latif, THIS JOURNAL, **72**, 4828 (1950).

[5] (a) G. O. Schenck, *Naturwissenschaften*, **40**, 229 (1953); (b) G. O. Schenck and G. A. Schmidt-Thomée, *Ann.*, **584**, 199 (1953).

[6] G. Ciamician and P. Silber, *Ber.*, **35**, 4129 (1902).

[7] A. Schönberg and R. Moubasher, *J. Chem. Soc.*, 1430 (1939); A. Schönberg and co-workers, *J. Chem. Soc.*, 1364 (1951).

[8] R. F. Moore and W. A. Waters, *ibid.*, 238 (1953).

[9] M. S. Kharasch, W. H. Urry and B. M. Kuderna, *J. Org. Chem.*, **14**, 239 (1949), observed differences in the free radical reactions of aryl or α,β-unsaturated aldehydes and aliphatic aldehydes with olefins.