extracted with ether, the ether evaporated, and the residual *N*-methylbenzenesulfonanilide crystallized from aqueous methanol, (m.p. 79°).[24]

Desulfurization of 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate and of 3β-methylthio-5-cholestene. Recently activated Raney nickel was filtered and rapidly washed with cold dioxane to remove water. Ten grams of the metal were added to an ice-cold solution of 1.0 g. of the sulfur-containing sterol in dioxane. The mixture was warmed cautiously, then refluxed gently for 7 hr. The residue on the filter was washed with ether and the ether dioxane filtrate distilled *in vacuo*. The solution of the residue in ether, treated with methanol, yielded a crystalline product. After several recrystallizations, this melted at 90–91° and showed a specific rotation of −56, values which agree with those given in the literature for 5-cholestene. The qualitative test for sulfur was negative. The sulfur-free products from both sulfur derivatives were identical as shown by mixed melting point determinations.

In both instances large losses of product occurred and no attempt was made at precise quantitative recovery.

Preparation of 3β-dimethylsulfonio-5-cholestene chloride from 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate by ion exchange. Amberlite IRA-410 (Rohm & Haas), chloride form, was washed well with methanol and drained on a filter. To 90 g. of wet resin a methanolic solution of 6.5 g. of 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate was added and allowed to stand at room temperature for 48 hr. with occasional shaking.

After further mechanical shaking for 3 hr., 800 ml. of methanol were percolated through the resin bed supported on a filter. The concentrated percolate (*ca.* 25 ml.), treated with acetone, gave, on standing overnight in the refrigerator, 5.0 g. (theory 5.04 g.) of glistening plates melting at 185°. Recrystallization from methanol-ether raised the melting point to 187°.

Anal. Calcd. for $C_{29}H_{51}ClS$: Cl, 7.58. Found: Cl, 7.45.

On standing at room temperature the sulfonium chloride slowly decomposes as evidenced by a drop in melting point. The decomposition results probably from the attack of the chloride ion on the *S*-methyl group of the sulfonium ion (Xc). Recrystallization of the partially decomposed product from methanol-ether gave pure 3β-dimethylsulfonio-5-cholestene chloride and 3β-methylthio-5-cholestene, melting at 126°.

3,5-Cyclo-6β-dimethylsulfoniocholestane iodide. To 416 mg. (1.0 mmole) of 3,5-cyclo-6-methylthiocholestane in ether was added 1.0 ml. of methyl iodide. After 6 hr. the precipitate was collected, washed with ether, and dried, m.p. 148°.

Anal. Calcd. for $C_{29}H_{51}IS$: C, 62.6; H, 8.63; I, 22.8. Found: C, 62.41; H, 8.82; I, 22.5.

When the sulfonium compound was heated with potassium hydroxide in aqueous alcohol, dimethyl sulfide was eliminated and a hydrocarbon, m.p. 71–72°, was recovered. A mixed melting point with 3,5-cyclo-6-cholestene[25] was 72°.

Reaction of 3,5-cyclo-6β-methylthiocholestane with acetic acid. A mixture of 200 mg. (0.5 mmole) of 3,5-cyclo-6β-methylthiocholestane, 5 ml. of glacial acetic acid, and one drop of sulfuric acid was refluxed for 30 min. The mixture was diluted with water and extracted with ether. Evaporation of the ether and crystallization of the residue from acetone gave 50 mg. of cholesteryl acetate, m.p. 112°.

Rearrangement of 3,5-cyclo-6β-methylthiocholestane to 3β-methylthio-5-cholestene. A solution of 200 mg. (0.5 mmole) of 3,5-cyclo-6β-methylthiocholestane, 5 ml. of benzene, 5 ml. of methanethiol, and 0.1 g. of *p*-toluenesulfonic acid was allowed to stand at 50° for 48 hr. The solution was washed several times with 5% sodium bicarbonate, then evaporated to dryness. The residue, on crystallization from acetone, gave 50 mg. of 3β-methylthio-5-cholestene, melting point 126°, unchanged when mixed with an authentic preparation.

Acknowledgment. The authors are grateful to Mrs. Dorothy Churchwell for assistance with the analyses.

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[24] R. L. Shriner, R. C. Fuson, and D. Y. Curtin. *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley & Sons, New York, N. Y., 1956, p. 289.

[25] B. Riegel, G. P. Hager, and B. L. Zenity, *J. Am. Chem. Soc.*, **68**, 2562 (1946).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, NATIONAL RESEARCH CENTRE, CAIRO]

Carbonyl and Thiocarbonyl Compounds. III.[1] Synthesis of Azines by the Reaction of Quinones with Hydrazones and Their Molluscacidal Activity

NAZIH LATIF AND IBRAHIM FATHY

Received December 3, 1959

In contrast to other hydrazones previously investigated, benzophenone hydrazone reacts with tetrachloro- and tetrabromo-*o*-benzoquinone giving benzophenone azine in both cases. The nature of the products obtained by the action of *p*-benzoquinone on hydrazones in benzene depends on the molecular ratios of the reactants used. When using equimolecular amounts, the *p*-benzoquinoazines II, III, and IV are obtained from fluorenone, xanthone, and benzophenone hydrazones, respectively. Fluorenone and xanthone azines are produced when using two moles of the corresponding hydrazones, while with benzophenone hydrazone the condensation product V is obtained. The action of hydrazine hydrate on the quinoazines II, III, and IV is investigated and a reaction mechanism is suggested. *p*-Benzoquinone reacts with hydrazones in alcohol giving mainly the corresponding ketazines independent of the molecular ratios of the reactants used. Hydroquinone is obtained almost quantitatively by the action of hydrazine hydrate on *p*-benzoquinone. The molluscacidal activity of the quinone and derivatives is tested.

During our studies on the chemical constitution and biological activity of benzoquinones, it has been found necessary to prepare benzoquinoazines of the type $R_2—C{=}N—N{=}R'{=}O$. Gerhardt[2] has shown that phenanthraquinone condenses with

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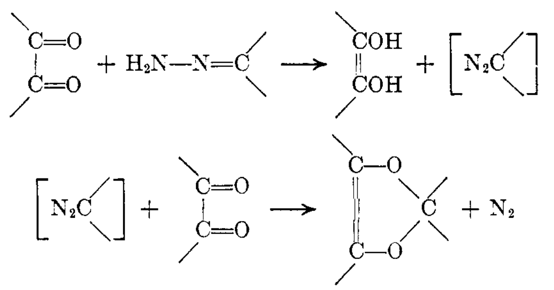
[1] Part II of this series, *J. Org. Chem.* **24**, 1883 (1959).

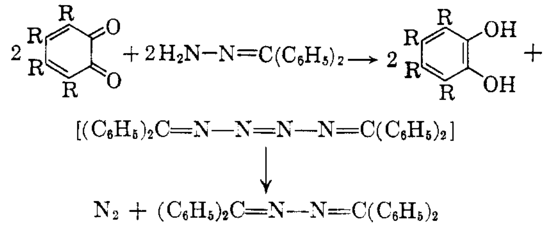
[2] O. Gerhardt, *Monatsh.*, **42**, 70 (1921); *Chem. Abstr.*, **15**, 3834 (1921).

aromatic hydrazones giving phenanthraquinoazines of the general formula I. In a previous article,[1] the authors have shown that tetrachloro- and tetrabromo-*o*-benzoquinone react with fluorenone and xanthone hydrazones giving the corresponding cyclic ethers according to Scheme A and no azines are produced.



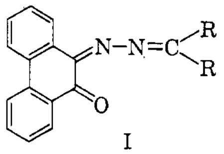
Scheme A

In trying to apply this reaction to benzophenone hydrazone, the corresponding cyclic ether is not obtained as would be expected, but instead, benzophenone azine is formed whether using tetrachloro- or tetrabromo-*o*-benzoquinone. The reaction takes place readily at room temperature and is greatly accelerated by heat, giving an almost quantitative yield of the azine. The reaction provides an easy and quantitative method for the preparation of benzophenone azine, the preparation of which has been found rather difficult by some authors.[3] It is thought that the reaction takes place through the intermediate formation of bisdiphenylmethylene tetrazone which is unstable in the presence of the high potential quinone. The formation of tetrazones by the oxidation of hydrazines is well known.[4]

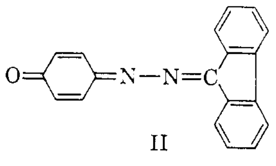


Scheme B

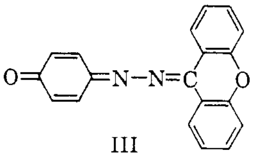
In an attempt to obtain *p*-benzoquinoazines of the type R_2—C=N—N=R′=O, the action of *p*-benzoquinone on hydrazones was investigated. Wieland and Roseeu[5] found that the quinone reacts with fluorenone hydrazone in alcohol giving fluorenone azine. In contrast, it has been found that when the reaction is carried out in *dry benzene,* the nature of the reaction products depends mainly on the molecular ratios of the reactants. Thus, when equimolecular amounts are used, the *p*-benzoquinoazines II, III, and IV are obtained by the action of *p*-benzoquinone on fluorenone, xanthone, and benzophenone hydrazones, respectively, in boiling dry benzene. The azines are highly colored, insoluble in alkali, and exhibit the usual halochromism when added to concentrated sulfuric acid.[2] On the other hand, when two moles of fluorenone or xanthone hydrazones are used in this reaction, fluorenone and xanthone azines are mainly obtained while with benzophenone hydrazone the condensation product V is formed. This difference in the nature of the products of the reaction with different hydrazones when two moles are used might be explained by assuming that the resonance structure (VI) contributes significantly to the actual state of the quinoazine molecule. In the case of II and III, the reactivity of the carbonyl group towards condensation with another molecule of the hydrazone is decreased and the carbonium ion stabilized by the strong resonance with the xanthylene and fluorenylidene residues. The formation of the azines is believed to be due mainly to the reaction between the *p*-benzoquinoazine first formed and the other molecule of the hydrazone. This is supported by the fact that when boiling a benzene solution of equimolecular amounts of III and xanthone hydrazone, the expected xanthone azine is obtained in amounts greater than would be produced from a simple oxidation of the hydrazone used. II reacts similarly with fluorenone hydrazone producing fluorenone azine. However, in the case of IV and benzophenone hydrazone, benzophenone azine together with V are obtained.



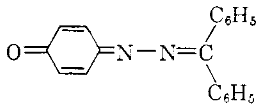
I



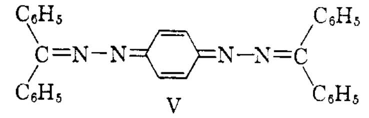
II



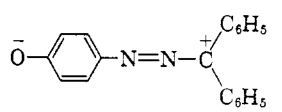
III



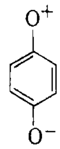
IV



V



VI



VII

When the reaction of *p*-benzoquinone and hydrazones is carried out in alcohol instead of dry benzene, the corresponding ketazines are mainly obtained regardless of the molecular ratios of the re-

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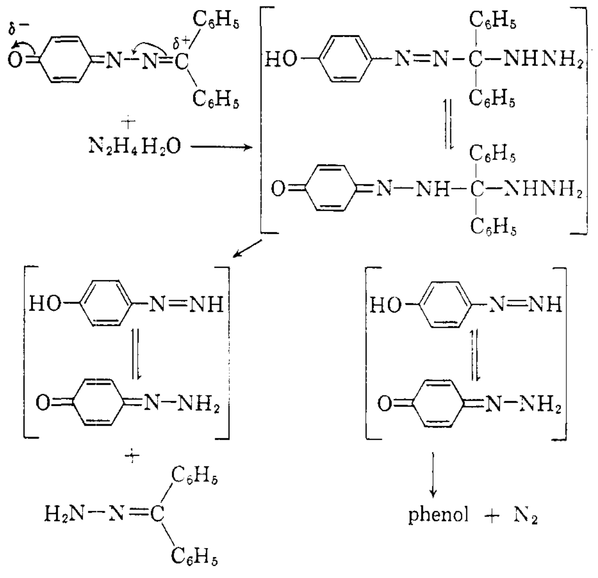
(3) *Cf.* H. Szmant and C. McGinnis, *J. Am. Chem. Soc.,* **72,** 2890 (1950).

(4) E. H. Rodd, *Chemistry of Carbon Compounds,* Elsevier Publishing Co., New York, Vol. IIIA, 379 (1954).

(5) H. Wieland and A. Roseeu, *Ann.,* **381,** 229 (1911).

actants used. It is thought that in this medium the zwitterion structure VII contributes largely to the actual state of the *p*-benzoquinone molecule.

In order to confirm the structure of the *p*-benzoquinoazines, their reaction with hydrazine hydrate was investigated. In contrast to the action of hydrazones, it has been found that hydrazine hydrate reacts with these quinoazines in alcohol giving phenol, and the corresponding hydrazones and azines in all cases. For example, when IV is allowed to react with hydrazine hydrate in boiling alcohol, phenol and benzophenone hydrazone are mainly obtained according to Scheme C, together with a small amount of benzophenone azine, and no condensation products are obtained. This might be due to the relatively high basicity of hydrazine compared with hydrazones and in turn its great nucleophilic character. Staudinger and Kupfer[6] reported the formation of hydrazones from azines by the action of hydrazine hydrate under pressure and at elevated temperature.



Scheme C

p-Benzoquinone reacts with hydrazine hydrate at room temperature giving hydroquinone in an almost pure state. This obviates the formation of by-products usually met with in the reduction of the quinone by phenyl hydrazine[7] and in turn an almost quantitative yield is obtained.

The molluscacidal activity of p-benzoquinone and derivatives. Halawani and Latif[8] found that halogenated *o*-benzoquinone and benzodioxole derivatives are toxic to *Biomphalaria boissi* snails—the intermediate host of *Schistosoma mansoni* in Egypt—in high dilutions. Latif and Fathy[9] reported similar results with certain halogenated cyclic ethers. The molluscacidal activity of *p*-benzoquinone, hydroquinone, and *p*-benzoquinoazines was investigated. It was found that *p*-benzoquinone and the quinoazine (IV) kill the snails in concentrations down to 5 p.p.m. in water during a twelve-hours exposure period while the hydroquinone is less active. II and III could not be tested since they are almost insoluble in the solvents usually used for the test. Benzophenone azine is inactive in concentrations up to 20 p.p.m. This remarkable activity of the quinone and its azine (IV) might be due to their inhibition effect on the oxygen consumption of the snails. von Brand *et al.*[10] have shown that certain phenanthra- and naphthaquinones inhibit the oxygen consumption of *Australorbis glabratus* snails in high dilutions. Details of the experiments will be published separately.

EXPERIMENTAL

p-Benzoquinone was recrystallized from petroleum ether (b.p. 40–60°) and dried. "Analar" benzene which had been dried over sodium was used. Benzophenone hydrazone was prepared by the general method described by Schönberg *et al.*;[11] the hydrazone which separated on cooling was washed well with petroleum ether (b.p. 40–60°) and dried.

Reaction of tetrachloro-o-benzoquinone with benzophenone hydrazone. A solution of benzophenone hydrazone (1 g.) in dry ether (25 ml.) was added in portions to a boiling solution of the quinone (1.3 g.) in dry ether (25 ml.). A vigorous reaction took place after each addition and the red color of the quinone disappeared. The reaction mixture was refluxed for 30 min. and left to cool. The solid was filtered, crystallized from alcohol, and shown to be benzophenone azine (melting point and mixed melting point). The mother liquor was evaporated to dryness and another crop of benzophenone azine was obtained when a few ml. of alcohol was added to the residues (total yield 0.82 g., about 90%). The alcoholic solution, after separation of the azine, was poured onto ice cold water, and acidified with a few drops of dilute hydrochloric acid. The precipitate was filtered, dried, and dissolved in acetic anhydride. The mixture was refluxed for 30 min. then left to cool. The solution was then poured onto ice, left overnight, and the solid crystallized from alcohol as colorless crystals which proved to be the diacetate of tetrachlorocatechol (melting point and mixed melting point).

When tetrabromo-*o*-benzoquinone was used in the above experiment, benzophenone azine was similarly obtained.

Reaction of p-benzoquinone with benzophenone hydrazone. (a). *Preparation of* N^1*-p-benzoquinonylidene-*N^2*-diphenylmethyleneazine* (IV). A solution of benzophenone hydrazone (0.78 g., 1 mole) and *p*-benzoquinone (0.43 g., 1 mole) in dry benzene (15 ml.) was refluxed for 3 hr. on the water bath. The reaction mixture, which became red-brown, was filtered while hot and the benzene was evaporated to dryness under reduced pressure. Then a few drops of methyl alcohol was added to the oily residue. The solid IV, which separated on standing, was recrystallized from methyl alcohol as orange crystals m.p. 109–110° (yield 0.8 g.). It is insoluble in sodium hydroxide solution (10%) and gives a brick red color with concd. sulfuric acid.

Anal. Calcd. for $C_{19}H_{14}ON_2$: C, 79.72; H, 4.89; N, 9.78. Found: C, 79.14; H, 5.13; N, 10.09.

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(6) H. Staudinger and O. Kupfer, *Ber.*, **44**, 2199, 2204 (1911).

(7) A. Giacolone, *Chem. Abstr.*, **23**, 599 (1929).

(8) A. Halawani and N. Latif, *J. Egypt. Med. Assoc.*, **37**, 957 (1954).

(9) N. Latif and I. Fathy, *Can. J. Chem.*, **37**, 863 (1959).

(10) T. von Brand, B. Mehlman, and M. O. Nolan, *Chem. Abstr.*, **43**, 9352 (1949).

(11) A. Schönberg, A. Fateen, and A. A. Samour, *J. Am. Chem. Soc.*, **79**, 6022 (1957).

(b). *Preparation of* (V). A solution of benzophenone hydrazone (1.96 g., 2 moles) and *p*-benzoquinone (0.54 g., 1 mole) in dry benzene (20 ml.) was refluxed as above, then filtered while hot. The benzene was evaporated to dryness and a few drops of methyl alcohol was added. The solid which separated was extracted with acetone. The crystalline V left was filtered and recrystallized from benzene as orange-red crystals, m.p. 210° (yield 0.85 g.). It gives a crimson red color with concd. sulfuric acid.

Anal. Calcd. for $C_{32}H_{24}N_4$: C, 82.75; H, 5.17; N, 12.06. Found: C, 82.84; H, 5.36; N, 11.49.

The acetone extract was evaporated to dryness and a few drops of methyl alcohol was added. The crystals which separated were recrystallized from alcohol and shown to be benzophenone azine (0.25 g.).

Reaction of IV *with benzophenone hydrazone.* A solution of IV (0.71 g.) and benzophenone hydrazone (0.5 g.) in dry benzene (15 ml.) was refluxed as above. The reaction mixture was filtered while hot, concentrated, and left to cool. The orange crystals which separated were recrystallized from benzene and shown to be V (melting point and mixed melting point yield 0.2 g., about 25%). The mother liquor was then evaporated to dryness and methyl alcohol added to the oily residue. The crystals which separated on standing were recrystallized from alcohol and shown to be benzophenone azine (melting point and mixed melting point, yield about 50%).

Action of hydrazine hydrate on (IV). A mixture of IV (2 g.), hydrazine hydrate (about 95%, 4 ml.), and alcohol (25 ml.) was refluxed for 1 hr. The reaction mixture was filtered while hot, concentrated, and left to cool. The crystals were filtered, crystallized from alcohol, and proved to be benzophenone azine (0.14 g.). The filtrate was concentrated and left to cool; benzophenone hydrazone (0.9 g.) was obtained. The mother liquor was then poured onto ice and a 10% solution of sodium hydroxide was added. The alkaline mixture was extracted with ether and the aqueous layer was acidified with dilute hydrochloric acid and extracted with ether several times. The ethereal extract was washed with a small amount of water and evaporated to dryness. The oily residue was extracted with boiling water and the solution was left to cool. Bromine water was then added and the crystalline solid was filtered, dried, and recrystallized from petroleum ether (b.p. 40–60°) as colorless crystals (1.3 g.) which were shown to be tribromophenol (melting point and mixed melting point).

Reaction of p-benzoquinone with xanthone hydrazone. (a) *Preparation of* N^1*-p-benzoquinonylidene-*N^2*-xanthonylidene azine* (III). A solution of xanthone hydrazone[12] (1.05 g. 1 mole) and *p*-benzoquinone (0.54 g., 1 mole) in dry benzene (15 ml.) was kept at room temperature (25°) for 1 hr. The bronze colored crystals were filtered, washed with acetone, and recrystallized from benzene giving III, m.p. 213–214° (1.2 g., about 80% yield). It gives a brown color with concd. sulfuric acid.

Anal. Calcd. for $C_{19}H_{12}O_2N_2$: C, 75.99; H, 4.03; N, 9.33. Found: C, 76.1; H, 4.05; N, 9.5.

(b). *Preparation of xanthone azine.* A solution of xanthone hydrazone (2.1 g., 2 moles) and *p*-benzoquinone (0.54 g. 1 mole) in dry benzene (20 ml.) was refluxed on the water bath. After 15 min., a crystalline solid separated and refluxing was continued for an additional 2 hr. The crystals were filtered, washed with acetone, and recrystallized from xylene as orange-yellow crystals which were shown to be xanthone azine (melting point and mixed melting point).

Reaction of III *with xanthone hydrazone.* A mixture of III (1.5 g.) and xanthone hydrazone (1 g.) in dry benzene (15 ml.) was refluxed on the water bath for 3 hr. The brown crystals which separated during the reaction were filtered and recrystallized from xylene as orange crystals which were shown to be xanthone azine (melting point and mixed melting point). The mother liquor was concentrated giving another crop of the azine (total yield 1.2 g.).

Action of hydrazine hydrate on III. To a suspension of III (2 g.) in boiling alcohol (75 ml.), hydrazine hydrate (5 ml.) was added and the mixture refluxed for 3 hr. The solid formed during the reaction was filtered and shown to be xanthone azine (identified as above). The filtrate was concentrated and left to cool, and the solid obtained was crystallized from alcohol and shown to be xanthone hydrazone (melting point and mixed point). The mother liquor was poured onto ice, and phenol was identified as in the case of IV.

Reaction of fluorenone hydrazone with p-benzoquinone. (a). *Preparation of* N^1*-p-benzoquinonylidene-*N^2*-fluorenonylidene-azine* II. A solution of equimolecular amounts of fluorenone hydrazone[5] (1.94 g.) and *p*-benzoquinone (1.08 g.) in dry benzene was refluxed for 3 hr. The reaction mixture was concentrated, left to cool, and the solid which separated was crystallized from benzene giving II as orange crystals m.p. 160–161° (1.8 g., yield about 60%). It gives a brown-red color with concd. sulfuric acid.

Anal. Calcd. for $C_{19}H_{12}ON_2$: C, 80.28; H, 4.22; N, 9.85. Found: C, 79.93; H, 4.32; N, 9.97.

(b). *Preparation of fluorenone azine.* A solution of *p*-benzoquinone (0.54 g. 1 mole) and fluorenone hydrazone (1.94 g., 2 moles) in dry benzene (25 ml.) was refluxed for 3 hr. After filtration, concentration, and cooling the solid was crystallized from benzene and shown to be fluorenone azine (melting point and mixed melting point).

Reaction of II *with fluorenone hydrazone.* The reaction was carried out as in the case of III and fluorenone azine was similarly obtained and identified.

Action of hydrazine hydrate on II. The reaction was carried out as in the case of III and fluorenone azine, fluorenone hydrazone, and phenol were formed.

Reaction of p-benzoquinone with hydrazine hydrate. p-Benzoquinone (0.5 g.) in dry benzene (10 ml.) was added in portions to a solution of hydrazine hydrate (about 95%, 0.5 ml.) in absolute alcohol (5 ml.). A vigorous reaction took place after each addition. The solid which separated during the reaction was filtered off and crystallized from benzene; hydroquinone was obtained as colorless crystals (yield almost quantitative).

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[12] A. Schönberg and Th. Stolpp, *Ber.*, **63**, 3114 (1930).