A possible alternative step for initiating the metal catalyzed chain is the reaction

$$HOOR_2COH + Cu^{+2} \xrightarrow{k_{8b}} Cu^{+} + H^{+} + \cdot OOR_2COH$$

which would replace k_8. While our data do not completely eliminate this as a possibility, it has the disadvantage that it would indicate a slight dependence of the metal-catalyzed rate on concentration and nature of alcohol (because of the k_6 step.) It is encouraging to note that all the types of steps and of intermediates are known types.

Acknowledgment. We wish to thank Miss Irma S. Silva for the product identification and Dr. D. V. Wells for careful perusal of the manuscript. A research grant from the BECCO Division of Food Machinery and Chemical Corp. aided in the purchase of the spectrophotometer. Fellowships from the Union Carbide and Carbon Corp. (DLB) and from the Monsanto Chemical Co. (MMC) are gratefully acknowledged.

PROVIDENCE, R. I.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, VETERANS ADMINISTRATION CENTER, WICHITA, KANSAS, AND THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF WICHITA]

The Reaction of Cholesteryl *p*-Toluenesulfonate with Dimethyl Sulfide and Methanethiol[1]

N. F. BLAU AND C. G. STUCKWISCH

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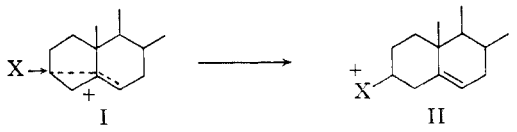
Dimethyl sulfide reacts with cholesteryl *p*-toluenesulfonate to give 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate. Cholesteryl *p*-toluenesulfonate and methanethiol yield chiefly 3β-methylthio-5-cholestene together with small amounts of 3α-methylthio-5-cholestene and 3,5-cyclo-6-methylthiocholestene. Reasons for the structural and stereochemical assignments are given and some reactions of the compounds are described.

During recent years a number of investigations have been directed toward introducing sulfur-containing groups into natural steroids in order to study the effect of such substitution on physiological activity. Cholesterol has been converted to 5-cholestene-3β-thiol by reaction of cholesteryl *p*-toluenesulfonate with thiourea[2] or potassium thiocyanate[3,4] followed by hydrolysis. The conversion of steroidal ketones to thioketones has been accomplished recently[5,6] and alkanethiolic acids and mercaptans have been added to appropriately unsaturated steroidal ketones.[7,8]

Our interest in sulfur-containing steroids stems from a broad investigation being carried out in these laboratories into the chemical[9] and physiological properties of sulfur compounds, the sulfonium compounds in particular. Dodson and Riegel[10] have shown that the reaction product of thiourea with cholesteryl *p*-toluenesulfonate[2] is a 3β-thiouronium derivative. The reaction is very probably a nucleophilic attack by thiourea on a hybrid carbonium ion as depicted in formulas Ia→IIa.



I II

I, II. a, X = $H_2NC(=S)NH_2$
I, II. b, X = CH_3SCH_3

The 3β-configuration (equatorial) for the introduced isothiouronium group is in accord with current views on the stereochemistry of reactions[11] involving nucleophilic displacements in homoallylic systems of the type found in 5-cholestenes.

Thus it seemed to us, that mechanistically it was possible to achieve a direct synthesis of 3β-dialkylsulfonio-5-cholestenes by the reaction of dialkyl sulfides with cholesteryl *p*-toluenesulfonate (Ib→IIb). Indeed, this proved to be the case. In nitromethane as a solvent, dimethyl sulfide reacted with cholesteryl *p*-toluenesulfonate to yield 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate (IIb) in 90% yield.

(1) Presented in part before the Fourth International Congress of Biochemistry, Vienna, Austria, September 1958.

(2) L. C. King, R. M. Dodson, and L. A. Subluskey, *J. Am. Chem. Soc.*, **70**, 1176 (1948). For the reaction of saturated steroidal tosylates with thiourea, see V. H. Turnbull, *Chem. & Ind. (London)*, 515 (1959).

(3) T. Wagner-Jauregg and T. Lennartz, *Ber.*, **74B**, 27 (1941).

(4) R. Bourbon, *Bull. Soc. Chim.*, 1117 (1958).

(5) R. M. Dodson and P. B. Sollman, U. S. Patent **2,840,577**, June 24, 1958.

(6) R. Bourbon, *Bull. Soc. Chim.*, 722 (1958).

(7) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959).

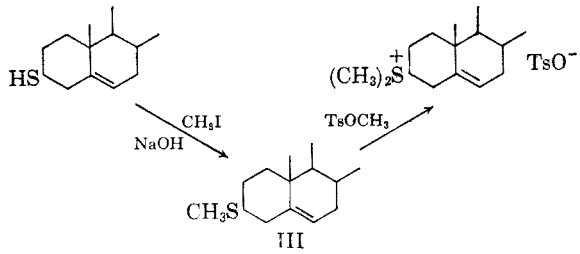
(8) J. W. Ralls, R. M. Dodson, and B. Reigel, *J. Am. Chem. Soc.*, **71**, 3320 (1949).

(9) N. F. Blau and C. G. Stuckwisch, *J. Org. Chem.*, **22**, 82 (1957).

(10) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).

(11) S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948).

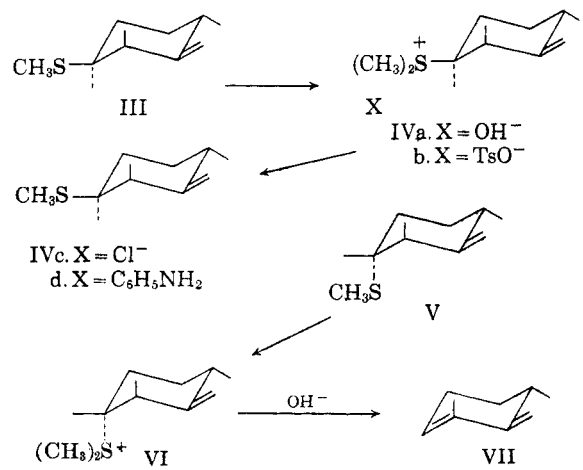
The structure and stereochemistry assigned to IIb followed from its mode of preparation, elemental analysis, desulfurization to 5-cholestene, and an independent synthesis from 5-cholestene-3β-thiol.



III

3β-Methylthio-5-cholestene (III) has been prepared by the alkylation of 5-cholestene-3β-thiol.[12] A more facile, one-step method of preparation is afforded by the reaction of methanethiol with cholesteryl *p*-toluenesulfonate. When the reaction is carried out in glacial acetic acid the product separates from the reaction mixture. Crystallization from ether-methanol and then acetone yields 3β-methylthio-5-cholestene (III), m.p. 125–126° in 80% yield.[13] From the mother liquors a small amount of the isomeric 3α-methylthio-5-cholestene (V), m.p. 110°, was isolated.

The configurational assignment for III is based on an independent synthesis from 5-cholestene-3β-thiol and on the reaction of its sulfonium derivative with various nucleophilic reagents, particularly hydroxide ion. Nucleophilic attack occurred exclusively on an *S*-methyl group giving the steroid sulfide with displacement of the methyl group. This was the case with hydroxide ion (IV)a, *p*-toluenesulfonate ion (IVb), chloride ion (IVc), and aniline (IVd).[14]



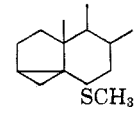
(12) A. S. Jones, F. Smith, and M. Webb, *Nature*, **162**, 857 (1948).

(13) Previous attempts to prepare alkylthiocholesterol derivatives by solvolysis of cholesteryl *p*-toluenesulfonate with boiling propane-1-thiol [H. McKennis, *J. Am. Chem. Soc.*, **70**, 675 (1948)] or with ethanethiol in acetone or dioxane [J. C. Colbert, Ph.D. thesis, Northwestern University, 1946, p. 51] have been unsuccessful.

(14) F. Challenger, R. Bywood, P. Thomas, and B. Hayward, *Arch. Biochem. Biophys.*, **69**, 514 (1957).

On the other hand, the sulfonium derivative (VI) of the axial isomer (V) reacts with hydroxide ion to give dimethyl sulfide and 3,5-cholestadiene (VII). These results are in agreement with earlier observations concerning quaternary ammonium hydroxides.[15,16] Hofmann elimination is favored by a *trans* coplanar arrangement in the transition state of the hydrogen atom, dimethylsulfide group and two carbon atoms going from sp^3 to sp^2 bonding. In such a transition state, the leaving hydrogen atom and the dimethyl sulfide group are axial. The equatorial 3β-sulfonium derivative lacks the steric requirements for facile Hofmann elimination, hence displacement at the *S*-methyl group is favored.[17] Attack at C_3 to give cholesterol would not be anticipated since, in addition to the statistical factor of two in favor of *S*-methyl attack, steric factors make S_N2 displacements at cyclohexyl-carbon atoms much slower.[18] A further consequence of the axial conformation in V is its much slower reaction with methyl iodide as compared to the rate of reaction of the equatorial isomer (III).[19]

When cholesteryl *p*-toluenesulfonate was treated with methanethiol in nitromethane the major product again was 3β-methylthio-5-cholestene. In addition to the major product a very small amount of a compound melting at 90–92° was isolated. We have tentatively assigned the *i*-cholestane structure, 3,5-cyclo-6β-methylthiocholestane (VIII) to this isomer.



VIII

This assignment is based on the following data: elemental analyses, reaction with methyl iodide to form a sulfonium derivative, rearrangement to cholesteryl acetate in acetic acid containing a few drops of sulfuric acid, and rearrangement to 3β-methylthio-5-cholestene in the presence of methanethiol and *p*-toluenesulfonic acid.[20] The β-conformation at C_6 is assigned on the basis of facile Hofmann elimination of dimethyl sulfide with alkali. This conformation is also in agreement with the orientation of 3,5-cyclo-6β-methoxycholestane obtained by

(15) D. Y. Curtin, R. D. Stolow, and W. Maya, *J. Am. Chem. Soc.*, **81**, 3330 (1959).

(16) R. D. Haworth, J. McKenna, and R. G. Powell, *J. Chem. Soc.*, 1110 (1953).

(17) For an excellent paper and leading references on the decomposition of sulfonium hydroxides see C. K. Ingold and K. C. Kurijan, *J. Chem. Soc.*, **136**, 991 (1933).

(18) A. Streitwieser, *Chem. Revs.*, **56**, 668 (1956).

(19) B. Gent and J. McKenna, *J. Chem. Soc.*, 573 (1956), have made a similar observation with tertiary amines.

(20) The conclusions drawn from the recorded observations are based on the assumption that the 3,5-cyclo-6-methylthiocholestene undergoes reactions similar to its oxygen analog. See L. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, N. Y., 1959, pp. 314–320.

methanolysis of cholesterol *p*-toluenesulfonate.[21]

At this point it is of interest to note tht the reaction of thiophenol with cholesteryl *p*-toluenesulfonate leads to 3,5-diphenylthiocholestane.[22] On the other hand extended treatment of cholesteryl *p*-toluenesulfonate with sodium thiophenoxide yields 3,5-cyclo-6-cholestene (8%), 6β-phenylthio-3,5-cyclocholestane (32%), and 3α-phenylthio-5-cholestene (13%). No detectable amount of 3β-phenylthio-5-cholestene is formed. Shoppee and co-workers have attributed these results to the abnormally great reactivity of the thiophenoxide ion in processes involving attack on covalently bound hydrogen and to the high nucleophilic power of this ion. In contrast, methanethiol and dimethyl sulfide, weak nucleophilic reagents, react chiefly by a unimolecular heterolysis leading to retention of configuration.

EXPERIMENTAL

3β-Dimethylsulfonio-5-cholestene p-toluenesulfonate (IV). (*a*) *From cholesteryl p-toluenesulfonate and dimethylsulfide.* Cholesteryl *p*-toluenesulfonate, 2.71 g. (0.005 mole), was suspended in 75 ml. of nitromethane contained in a pressure bottle (Fisher Scientific Co., Catalog No. 3-100), a large excess (10–15 ml.) of dimethyl sulfide was added, and the stoppered flask placed in an oven at 40°. The fine sterol particles gradually disappeared and were replaced by flat platelike crystals adhering to the wall of the flask. This transformation was usually complete at the end of the fourth day. The mixture was cooled at 0° and the crystals were washed with cold nitromethane, then with ether. The mother liquor and washings were evaporated *in vacuo*. The residue was dissolved in methanol and the small ether-insoluble component was added to the main crop of crystals. Recrystallized from methanol-ether, they weighed 2.78 g. (90%), m.p. 195–200°, $[\alpha]_D^{25}$ −15° in alcohol, $\lambda_{max}^{CH_3OH}$ 217 mμ, ε 13,000.

Anal. Calcd. for $C_{36}H_{58}O_3S_2$: C, 71.5; H, 9.62. Found: C, 71.34; H, 9.59.

When the reaction was run at 80° for 24 hr. two products were obtained: one melting at 200°, the other at 124–125°. The latter showed no depression in melting point when mixed with 3β-methylthio-5-cholestene.

(*b*) *From 3β-methylthio-5-cholestene and methyl p-toluenesulfonate.* A mixture of 2.1 g. (0.005 mole) of 3β-methylthio-5-cholestene, 2 ml. of methyl *p*-toluenesulfonate, and 25 ml. of nitromethane was heated at 40° for 10 days. The mixture was diluted with ether and filtered. The residue was crystallized from ethanol. The melting point of the product (204°) was undepressed when mixed with the product obtained from cholesteryl *p*-toluenesulfonate and dimethylsulfide.

3β-Methylthio-5-cholestene (III). (*a*) *From cholesteryl p-toluenesulfonate and methanethiol.* Cholesteryl *p*-toluenesulfonate, 2.71 g. (0.005 mole), was mixed in a pressure bottle with 25 ml. of glacial acetic acid and 5 ml. of methanethiol. After 4 or 5 days at 40° the long, needle-shaped, reddish colored crystals were separated from the cooled liquid and were washed with cold methanol until nearly white. Crystallization from ether-methanol and then from acetone gave 1.64 g. (79%) of needle-shaped crystals, m.p. 125–126°, $[\alpha]_D^{25}$ = −19° in chloroform, $\lambda_{max}^{Cyclohexane}$ 207 mμ, ε 6,270.

Anal. Calcd. for $C_{28}H_{48}S$: C, 80.79; H, 11.54. Found: C, 80.44; H, 11.48.

The mother liquor and washings from the above were concentrated and the sticky residue was dissolved in methanol. A small amount of crystals was obtained which melted at 110°. They were shown to be 3α-methylthio-5-cholestene, (VI). $[\alpha]_D^{25}$ = −24° in chloroform.

Anal. Calcd. for $C_{28}H_{48}S$: C, 80.79; H, 11.54. Found: C, 80.52; H, 11.44.

The reaction was carried out in a similar manner with 75 ml. of nitromethane as the reaction medium instead of glacial acetic acid. After the main product was removed from the mixture a small crop of crystals (70–100 mg.) melting at 90–92° precipitated from the concentrated mother liquor on standing at 0°. The *i*-cholestane structure (VIII) is tentatively assigned to this product. $[\alpha]_D^{25}$ = +15° in chloroform.

Anal. Calcd. for $C_{28}H_{48}S$: C, 80.79; H, 11.54. Found: C, 81.01; H, 11.67.

(*b*) *From 5-cholestene-3β-thiol and methyl iodide.* Two grams (0.005 mole) of 5-cholestene-3β-thiol[2] and 5 ml. of methyl iodide in 50 ml. of 2% alcoholic potassium hydroxide were placed in a pressure bottle and allowed to stand at 40° for 24 hr. with occasional shaking. The mixture was diluted with water, the solid product filtered and crystallized from acetone. The yield of 3β-methylthio-5-cholestene, melting at 126°, was 0.7 g. (85%).[23]

3β-Dimethylsulfonio-5-cholestene iodide.[12] A solution containing 700 mg. (1.7 mmoles) of 3β-methylthio-5-cholestene and 1 ml. of methyl iodide in 5 ml. of ether was allowed to stand at room temperature. After 4 hr. the crystalline mass which had separated was filtered and crystallized from methanol, m.p. 165°, yield, 95%.

3α-Dimethylsulfonio-5-cholestene iodide. The 3α-isomer was prepared from 3α-methylthio-5-cholestene by a procedure similar to that used for the 3β-isomer. The reaction time was 24 hr. The compound melted at 162°.

Anal. Calcd. for $C_{29}H_{51}SI$: I, 22.9 Found: I, 23.2.

Reaction of 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate with potassium hydroxide (IVa). A mixture containing 50 ml. of water, 50 ml. of ethanol, 10 g. of potassium hydroxide, and 1.5 g. (0.0025 mole) of 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate was refluxed for 2 hr. The cooled mixture was diluted with water and filtered. The residue, after crystallization from acetone, melted at 126°. No depression was observed in a mixed melting point with 3β-methylthio-5-cholestene.

When 3β-dimethylsulfonio-5-cholestene iodide[13] was treated with aqueous-alcoholic potassium hydroxide the resulting product again was 3β-methylthio-5-cholestene. On the other hand, treatment of 3α-dimethylsulfonio-5-cholestene iodide with aqueous-alcoholic potassium hydroxide yielded 3,5-cholestadiene (VIII), melting at 79–80° after crystallization from methanol. $[\alpha]_D^{25}$ = −91.5°.

Reaction of 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate with aniline. (IVd). One gram of the sulfonium compound and 1 g. of aniline were heated for 2 hr. at a bath temperature of 160°. The cooled mixture was dissolved in ether and extracted with 5% hydrochloric acid. The residue from the ether layer, crystallized from acetone, gave a product melting at 126°, which showed no depression on mixing with authentic 3β-methylthio-5-cholestene.

The hydrochloric acid extract from the above was made alkaline with 10% sodium hydroxide and treated with benzenesulfonyl chloride. The alkali-insoluble product was

(21) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(22) C. W. Shoppee, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 4817 (1956).

(23) Methylation of 5-cholestene-3β-thiol has been reported by Jones, Smith, and Webb (ref. 12) without experimental details. Their melting point, 141°, is at variance with our melting point of 126°. We prepared our compound in two different ways, each of which gave a product of correct analytical values for the substance sought. The melting point of our 3β-dimethylsulfonio-5-cholestene iodide of 165° agrees with that of Jones, Smith, and Webb.

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.

WICHITA 8, KAN.

(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 $R_2C{=}N{-}N{=}R'{=}O$. Gerhardt[2] has shown that phenanthraquinone condenses with

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

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