Alicyclic Syntheses. III. The Diels–Alder Reaction with Alkylmercaptotoluquinones. A Synthesis of *trans*-9-Methyl-Δ^6-octalin-1,4-dione[1]

V. GEORGIAN[2a] AND L. L. SKALETZKY[2b]

Department of Chemistry, Tufts University, Medford, Massachusetts, and The Department of Chemistry, Northwestern University, Evanston, Illinois

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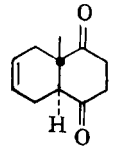
The structures of the mercaptotoluquinols arising from toluquinone by the action of sodium thiosulfate have been established as the 5-mercapto and (principally) the 6-mercapto isomer, contrary to previous reports that this reaction was unidirectional and that the latter substance (m.p. 111–112°) was the 3-mercapto isomer. A corresponding change has been made in the methylmercaptotoluquinone structures and the latter have been utilized in the Diels–Alder reaction with butadiene to synthesize *trans*-9-methyl-Δ^6-octalin-1,4-dione, an intermediate of potential utility in steroid total synthesis. The course of the desulfuration–reduction of the alkylmercaptoquinone–diene adducts by means of zinc–acetic acid has been elucidated and found to proceed *via* the reduction initially of the dioxoethylenic function to a dihydro stage XV.

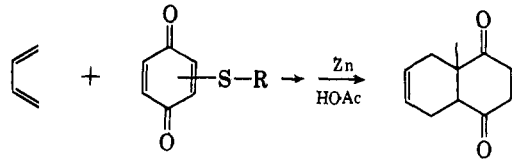
The potential utility of *trans*-9-methyl-Δ^6-octalin-1,4-dione (I) as the A/B ring moiety in projected total synthesis of steroids may be demonstrated. Apart



I

from the obvious gross relationship of this structure to that of the lower portion of the steroid molecule, this fragment bears the following features: (1) carbonyls at C-1 and C-4 which may be differentially masked or altered to permit attachment of rings C/D or C/D-homo by adaptation of methods already recorded in the now substantial lore of alicyclic synthesis[3]; (2) the C-4 carbonyl which, having served the function of controlling the stereochemistry of the ring fusion, also affords a means of introducing unsaturation at some appropriate juncture in a synthesis in the lower portion of the steroid molecule (either at 5,6 or 4,5, steroid numbering system), a matter of some concern in A/B-*trans* steroidal systems,[4] or alternatively of introducing alkyl or other groups at position 6 in the steroid molecule, a substitution which has yielded currently some of the most active progestational and antiphlogistic compounds[5]; (3) the Δ^6 olefinic function, which by virtue of its transformability into isomeric halohydrins either by hypohalous acids or chromyl chloride[6] or epoxidation, etc., is tantamount to having a C-2 or C-3 oxygen function in the steroid molecule. Thus, a facile route to I was desired.

Our previous experience with diene additions to *p*-tolylthiotoluquinone followed by zinc–acetic acid desulfuration, yielding what appeared to be most likely angularly methylated polycarbocyclic systems,[7] suggested as the most efficient way of obtaining I the Diels–Alder reaction of butadiene with a 5- or 6-alkylmercaptotoluquinone.



Whereas in the previous work[7] a *p*-thiocresyl moiety had been affixed to the quinone in a convenient one-step operation and without regard for its exact position thereon either at C-5 or C-6, it was felt a more deliberate synthesis of the simpler 5- or 6-methylmercaptotoluquinone would better serve the problem at hand and secure more firmly the structures postulated formerly for the diene adducts with thio-substituted quinones. Moreover, although the course of Diels–Alder reaction with this class of dienophiles leading to the angularly methylated structures[7] had been inferred from the parallel reactions with the electronically closely related alkoxytoluquinone system,[8] more corroborative evidence on this point was deemed necessary. To this end a synthesis of 5- and/or 6-methylmercaptotoluquinone was sought, and the butadiene addition to this system and the subsequent zinc–acetic acid desulfuration–reduction were studied.

Of the three possible methylmercaptotoluquinones only two isomers had been described. Alcalay[9] had reported the preparation of 5-methylmercaptotoluquinone (IV) from the corresponding mercaptan III

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(2)(a) Department of Chemistry, Tufts University, Medford 55, Mass.; (b) U. S. Rubber Fellow, 1956–1957. Union Carbide Fellow, 1957–1958.

(3) In particular, see L. D. Bergelson, *Tetrahedron* **6**, 161 (1959), on the elaboration by I. N. Nazarov and co-workers of some interesting synthetic substances which resemble steroids.

(4) See R. N. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956), for a discussion of the problem and for references to earlier work in this area principally by Djerassi and co-workers.

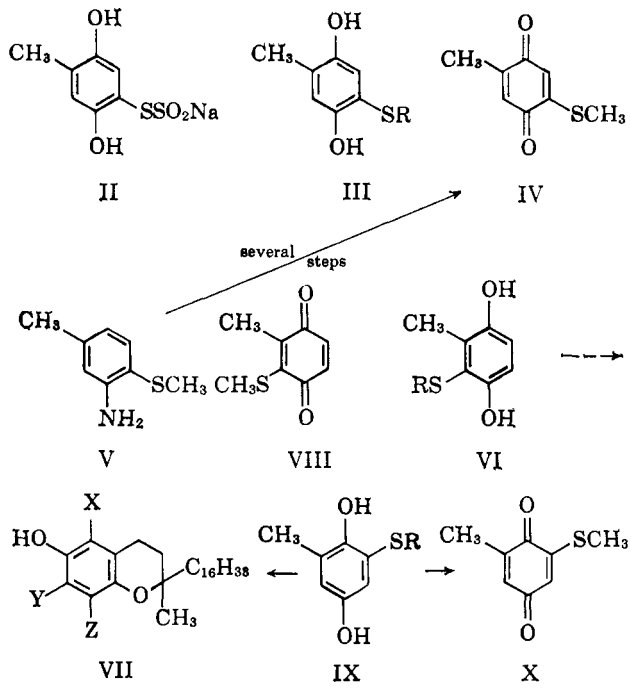
(5) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956); J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *ibid.*, **80**, 2904 (1958); H. J. Ringold, E. Batres, and G. Rosenkrantz, *J. Org. Chem.*, **22**, 99 (1957); J. A. Hogg, C. B. Spero, J. L. Thompson, B. J. Magerlein, W. B. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. Ind.* (London), 1002 (1958); A. Bowers, and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 4423 (1958); J. A. Edwards, A. Zaffaroni, H. J. Ringold, and C. Djerassi, *Proc. Chem. Soc.*, 87 (1959).

(6) S. L. Cristol and K. R. Eilar, *J. Am. Chem. Soc.*, **72**, 4353 (1950); H. L. Slates and N. L. Wendler, *ibid*, **78**, 3749 (1956). See also L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., N. Y., 1959, Chap. 7, for a general treatment of steroid ring A olefins and oxidation products derived therefrom.

(7) V. Georgian and J. Lepe M., papers I and II in this series, *J. Org. Chem.*, **29**, 40, 45 (1964).

(8) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952); M. Orchin and L. W. Butz, *J. Org. Chem.*, **8**, 509 (1943).

(9) W. Alcalay, *Helv. Chim. Acta*, **30**, 578 (1947).

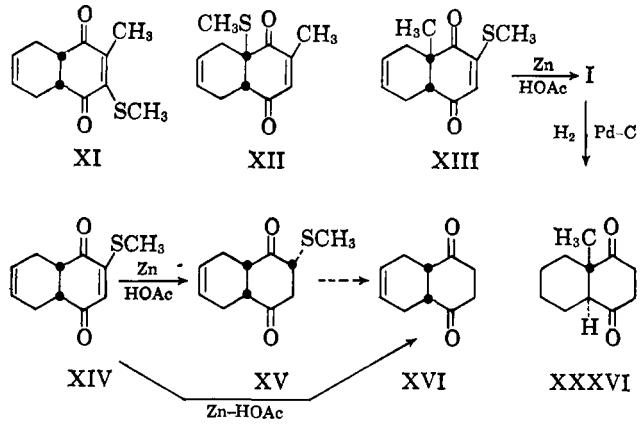


(R = H) by S-alkylation and oxidation with ferric chloride. Mercaptan III (R = H) was claimed to have been prepared in quantitative yield by the reaction of *p*-toluquinone with sodium thiosulfate and subsequent reduction of the resulting sodium aryl thiosulfate II with zinc and hydrochloric acid. Alcalay reported melting points for III (R = H) and IV, as 136° and 113°, respectively, but supplied no details as to a proof for the constitution of these substances.

Repetition of this work, however, paralleled the experiences of Karrer and Dutta[10] who, like us, found that this reaction led to more than a single product. Karrer and Dutta obtained by the Alcalay procedure a mixture of two mercaptans, separable into a minor fraction, m.p., 176–179°, and a major one, m.p., 111–112°. The minor product was converted into a methylmercaptotoluquinone, m.p. 139–140°, established unequivocally as the 5-isomer IV by means of an independent synthesis from methylmercapto-*m*-toluidine (V). The mercaptan of m.p. 176–179° is thus authentic III (R = H).

The corresponding methylmercaptotoluquinone from the preponderant lower melting mercaptan (111–112°) melted at 140–142°, depressed the melting point of the 5-isomer IV, and was assigned the structure of 3-methylmercaptotoluquinone (VIII). This assignment was based primarily on observation that the corresponding methylmercaptotoluquinol of m.p. 83–84° yielded on reaction with phytol (in a typical acid-catalyzed coumaran synthesis) a methylmercaptomethyltocol, which generated, after desulfuration, a substance which was taken to be 8-methyltocol (VII, X = Y = H, Z = CH_3; in the precursor, X = H, Y = SCH_3, Z = CH_3). The identification of the methyltocol was made solely on the basis of mixture melting point comparison of a derivative of the synthetic product with the corresponding one from δ-tocopherol, despite a small difference in their melting points. Structure VI (R = CH_3) was thereby deduced for the methylmercaptotoluquinol of m.p. 83–84°. Because of the possibility of isomorphism of these derivatives and the lack of additional more compelling structure proofs[11] for the intermediates involved in these transformations, this assignment of structure for the isomeric methylmercaptotoluquinone of m.p. 140–142° appeared rather tenuous. Thus, it was desired to approach the problem more directly, since its solution would in turn comprise an essential step in the structural elucidation of the Diels–Alder adducts from this class of quinones.

The position of the methylmercapto group in the quinone (m.p. 140–142°) was established by a study of the ultraviolet absorption spectrum of the Diels–Alder adduct of the quinone with butadiene. Under the conditions used in the diene addition of 5-methoxy-*p*-toluquinone with butadiene[8] (*ca.* 4 days at 100°), the quinone (m.p. 140–142°) gave an 80% yield of a light yellow adduct, which absorbed in the infrared at 5.89 and 6.00 mμ indicative of conjugated carbonyl function and gave an elemental analysis which was in agreement with the possible isomeric structures XI, XII, and XIII:



The ultraviolet spectrum of this adduct possessed a λ_{max}^{EtOH} 322 mμ (log ε 3.95). Structure XII may thus be dismissed as a possibility for this substance, since the chromophoric system of XII is known to absorb maximally at 237 mμ.[12] The bathochromic shifts upon substitution in the chromophoric system X–C=C–C=O have been recorded[13a] for the following auxochromic groups X: CH_3 (10), OCH_3 (50), SR (85 mμ), the shifts referring to systems where X = H. In the dioxoethylenic parent chromophore at hand, —COCX=CHCO—, the corresponding bathochromic shifts were found to be 15 and 47 mμ for X = CH_3 and OCH_3, respectively.[12] The butadiene–methylmercaptotoluquinone adduct shows a bathochromic shift of 100 mμ which is indicative of the presence of the SR auxochrome[13b] but does not distinguish between the two possible structures XI and XIII. As a comparison substance with a corresponding chromophoric system the adduct XIV from butadiene and methylmercapto-*p*-benzoquinone was prepared and found to possess maximum absorption at 332 mμ (log ε 3.83), coincident with that of the adduct in question. Therefore, the latter must be the angularly methylated structure XIII, and the toluquinone of m.p. 140–142° necessarily pos-

(10) P. Karrer and P. C. Dutta, *Helv. Chim. Acta.*, **31**, 2080 (1948).

(11) One further piece of information taken[10] in favor of structure VIII was that it could be converted to a bismethylmercapto derivative (assumed to be the 3,5 isomer) on direct reaction with methyl mercaptan, whereas the 5-mercaptoquinone IV did not yield a recognizable product; see also ref. 15.

(12) H. Bastron, R. Davis, and L. W. Butz, *J. Org. Chem.*, **8**, 515 (1943).

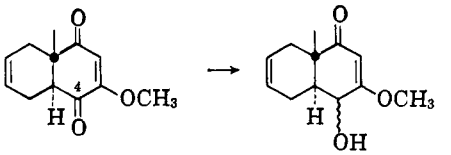
(13)(a) K. Bowden, E. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946); (b) see also H. P. Koch, *ibid.*, 387 (1949), on absorption spectra of unsaturated sulfides.

sesses the 6-methylmercapto structure X. The corresponding hydroquinone of 83–84° accordingly must be IX (R = CH_3) which forces the conclusion that Karrer and Dutta's methyltocol derived from IX possesses the structure of a 5- or 7-methyltocol. Subsequent to the termination of this phase of our work, these conclusions were confirmed by unequivocal syntheses[14] of 5-, 7- and 8-methyltocols (VII, X = CH_3, Y,Z = H; VII, Y = CH_3, X, Z = H; VII, Z = CH_3, X,Y = H, respectively) which served to settle the ambiguities with respect to these structures discussed previously. Karrer and Dutta's methyltocol was proved in fact to have been 7-methyltocol corroborating our conclusions concerning 6-methylmercaptotoluquinone (X).[15]

The proof of the course of the Diels–Alder reaction of dienes with 6-alkylmercaptotoluqinones resulting in addition to the methylated side of the quinone justifies with complete assurance the angularly methylated structures adduced previously in the analogous reactions with 5(or 6)-*p*-tolylthiotoluquinone.[7]

Since the Alcalay procedure did not avail a very convenient method of obtaining one particular mercaptotoluhydroquinone which would serve as a precursor to a conveniently blocked toluquinone useful in producing angularly methylated decalin or polycarbocyclic systems in general, the direct interaction of methyl mercaptan with toluquinone was investigated.[10,16] This reaction was carried out in the presence of excess methyl mercaptan and was followed by subsequent oxidation with ferric chloride. A good total yield (84%) of isomeric methylmercaptotoluquinones was obtained which could be separated only after chromatography on silica gel. There were isolated here also both the 5- (IV) and 6- (X) methylmercaptotoluquinones in 17% and 57% yields, respectively. Crystallization of the crude reaction mixture afforded only the 6 isomer (X) and a sharply melting (104°) mixture of isomers. This direct one-step method is accordingly preferred to that of Alcalay for the production of the 6 isomer (X).

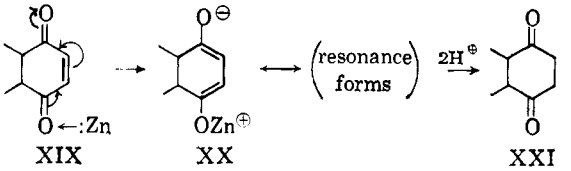
Attention was next directed to a study of the mechanism of the zinc–acetic acid desulfuration reaction discovered earlier in similar systems.[7] The simpler adduct XIV from methylmercaptobenzoquinone was studied first. When a solution of XIV, light yellow in color, in aqueous acetic acid was treated with zinc dust for 5 min. at 50°, a white solid was obtained which was found to contain sulfur, possessed infrared absorption characteristic of nonconjugated carbonyl groups, and gave an elemental analysis in accord with the dihydro derivative XV. The facile reduction of the conjugated ethylenic bond in simple diene–quinone adducts with zinc–acetic acid is well known and widely used,[17] but this result contrasts with the finding of Speziale, Stephens, and Thompson,[18] who showed that the analogous reaction of the *trans* isomeride of the 5-methoxytoluquinone–butadiene adduct (XVII) resulted in reduction of the C-4 carbonyl to an excellent yield of XVIII.



XVII XVIII

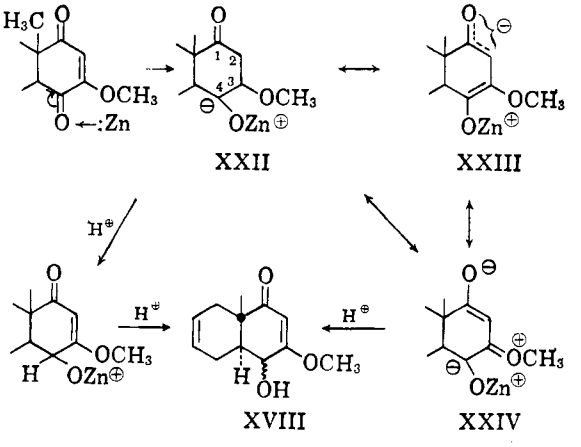
This difference is not without intrinsic interest and may well be accounted for on the basis of the changes symbolized in the following mechanistic schemes, A, B, and C. Zinc, as a source of electrons, may supply these electrons to the parent unsubstituted system XIX through one of the termini of the conjugation as depicted in XIX (arrows), Scheme A, to yield the enolate

Scheme A



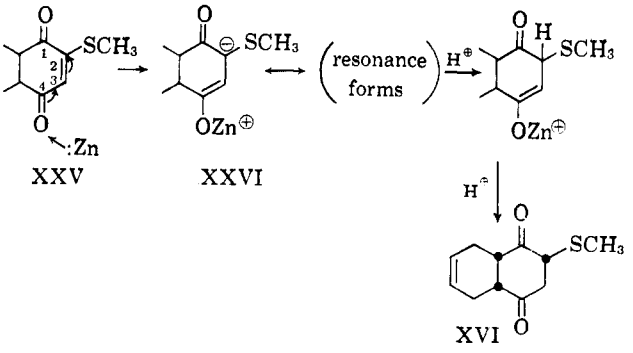
XIX XX XXI

Scheme B



XXII XXIII XVIII XXIV

Scheme C



XXV XXVI XVI

of lowest energy XX (plus usual resonance structures). Protonation of XX on oxygen will, of course, be reversible, ultimately leading to protonation on carbon with

(14) D. McHale, P. Mamalis, J. Green, and S. Marcinkiewicz, *J. Chem. Soc.*, 1600 (1958); D. McHale, P. Mamalis, S. Marcinkiewicz, and J. Green, *ibid.*, 3358 (1959); J. Green, D. McHale, P. Mamalis, and S. Marcinkiewicz, *ibid.*, 3374 (1959).

(15) The bismethylmercapto derivatives of toluquinone and of toluhydroquinone derived from X are thus very probably the 3,6-bis substitution products, since these substances were not derivable from IV.[10]

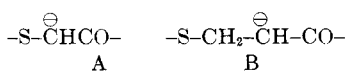
(16) A. Schöberl and A. Wagner "Methoden der Organischen Chemie," Vol. 9, Houben-Weyl, Ed., 4th Ed. Georg Thieme Verlag, Stuttgart, 1955, p. 130. See also A. Blackhall and R. H. Thomson, *J. Chem. Soc.*, 1138 (1953), for a related reaction of toluquinone and thioglycolic acid, as well as J. M. Snell and A. Weissberger, *J. Am. Chem. Soc.*, **61**, 450 (1939).

(17) K. Alder and G. Stein, *Ann.*, **501**, 247 (1933); C. Chuang and C. Han, *Ber.*, **68**, 876 (1935); P. A. Robins and J. Walker, *J. Chem. Soc.*, 3960 (1954); 177 (1957); 409 (1958).

(18) A. J. Speziale, J. A. Stephens, and Q. E. Thompson, *J. Am. Chem. Soc.*, **76**, 5011 (1954).

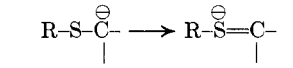
production of the usually encountered dihydro product XXI. The methoxyl- and methylthio-substituted cases may now be expected to differ from or resemble this main reductive scheme by the course most likely to be taken in the protonation steps of the enolates in the respective cases. The most electronically attractive route for the approach of zinc to the methoxytoluquinone adduct is that *via* the C-4 carbonyl indicated in XXII, Scheme B, because of lower electron density on this oxygen than on the alternate one, which was supplied electrons by resonance with the conjugated methoxyl (vinylogous ester system). Although the resulting enolate XXII will have contributing structures involving the distribution of the negative charge on the C-1 oxygen and C-2, (XXIII), it may be expected reasonably that higher electron density will be located obtain on C-4 than on C-2. The electron delocalization demanded by the C-1 carbonyl will be satisfied by a flow from C-4 as well as from the methoxy group, XXIV. Thus, while protonation at the site of highest electron density (C-1 oxygen) will be reversible, C-4 protonation will compete favorably with C-2 protonation, because of the relatively higher electron density on the former, and lead to the observed product XVIII.

The methylmercapto-substituted case, Scheme C, is analogous to the basic Scheme A with the added qualification that, notwithstanding an apparently "wrong" initial approach by the zinc to the carbonyl oxygen conjugated with the methylthio group XXV, the resulting enolate XXVI will have considerable weight in the delocalization of the electron pair among the various contributing forms and may very reasonably be expected to influence protonation in the direction indicated to yield the observed product XV. In point of fact, the approach of zinc with its electrons to the oxygen atom indicated in XXV, Scheme C, is not at all "wrong" as it would have been in the corresponding methoxyl case (Scheme B), since the electron pair donor-type conjugative effect of a divalent sulfur function is much less than that of an oxide as demonstrated by Bordwell.[19] Moreover, the lack of shortening of the C–S bond in thioacetic acid[20] indicates a lower resonance effect of covalent sulfide than of covalent oxide, a point quite germane to the vinylogous thiol ester moiety present in XXV. Hence, no extraordinary electron density may be anticipated on the C-4 oxygen in XXV to ward off approach by zinc. Of especial significance to this scheme is the fact that there is generated thereby an enolate of lower energy than attack on the C-1 carbonyl would have produced, since in XXVI a sulfur atom is juxtaposed with the carbanionic center. Such carbanions as A were recognized by Woodward[21] as being of particular importance in determining the rate-controlled course of a Dieckmann reaction in competition with carbanions of the type B, and subsequent investigations[22] on similar systems have shown that sulfur has a decided acidifying influence on α hydrogens,



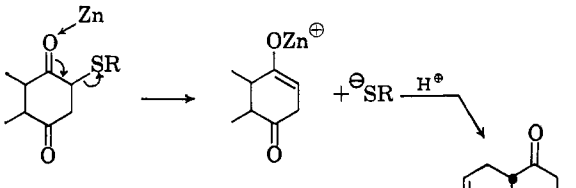
A B

possibly due more to valence shell expansion of sulfur than to simple inductive stabilization of the resulting carbanion by the relatively low electronegativity of sulfur. Bordwell[19b] concluded on this point that the "presence of a powerful electron donor such as a carbanion is necessary to evoke a clearly recognizable electron pair acceptor-type conjugation in divalent sulfur groups," *i.e.*, precisely the situation obtaining in XXVI.

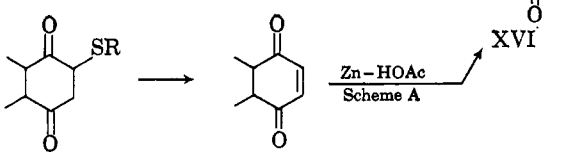


When a solution of XIV in aqueous acetic acid was treated with zinc dust at room temperature for longer periods (*ca.* 2 hr.) methyl mercaptan was evolved and the product *cis*-Δ^6-octalin-1,4-dione (XVI) was isolated in 61% yield. The structure of XVI was established by comparison (infrared and mixture melting point) with an authentic sample of XVI.[17] The exact sequence of events in this desulfuration reaction cannot be definitely particularized beyond the stage of a 2,3-dihydro intermediate XV. At this point an option is available of either direct reduction of the β-oxo sulfide structure, Scheme D, or acid-catalyzed β-elimination in the γ-oxo sulfide grouping, Scheme E, followed by reduction of the resulting ene–dione. Precedent exists for both views. Wahl[23] observed the liberation of benzyl mercaptan in the zinc–acetic acid treatment of

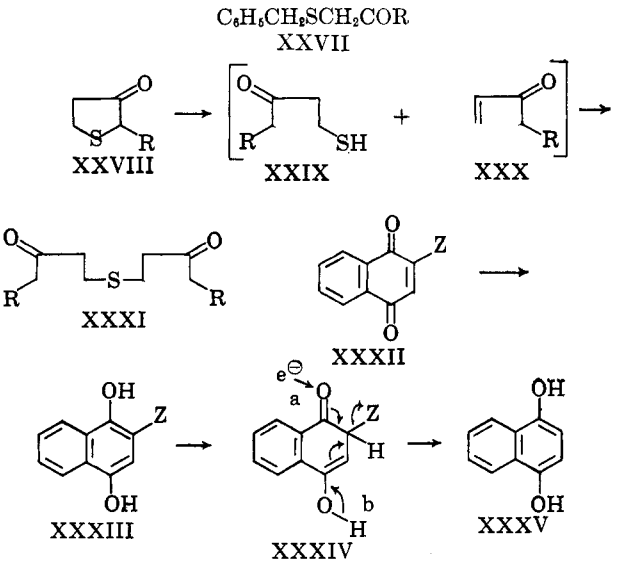
Scheme D



Scheme E



Scheme F



(19)(a) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952); (b) F. G. Bordwell and P. J. Boutan, *ibid.*, **78**, 854 (1956).

(20) W. Gordy, *J. Chem. Phys.*, **14**, 560 (1946), finds an interaction between —S— and C=O in thioacetic acid no greater than *ca.* 6%.

(21) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946).

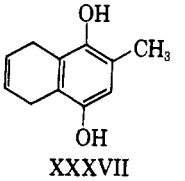
(22) W. J. Brehm and T. Levenson, *ibid.*, **76**, 5839 (1954); See also earlier work by E. Rothstein, *J. Chem. Soc.*, 155 (1940). and former papers.

(23) C. Wahl, *Ber.*, **55**, 1449 (1922).

β-oxo sulfides XXVII, and Schmid and Schnetzler[24] reported that 3-oxothiophanes of the type XXVIII under Clemmensen reduction yield bimolecularly produced sulfides, type XXXI. To explain their generation it is necessary to invoke the intercession of intermediates XXIX and XXX arising both by reduction of the sulfide bond α to the carbonyl (Scheme D) and acid-catalyzed β-elimination of a mercaptide (XXX would correspond to an intermediate in Scheme E). Additional analogies in this area may be found in the reductive elimination of certain electronegative groups, including alkylmercapto and arylmercapto, from 2-substituted naphthoquinones XXXII by means of stannous chloride yielding naphthohydroquinone XXXV.[25a] The course of this reduction may be viewed as proceeding through the hydroquinone form XXXIII which may then suffer further reduction through the intermediacy of a tautomer either directly (Scheme F), XXXIV (arrow a), or by acid-catalyzed β-elimination, XXXIV (arrow b), succeeded by reduction of the resulting quinone (not shown). Evidence suggesting the former direct reduction scheme was found[25a] in the reductive cleavage by stannous chloride of 1-*p*-tolylthio-2-naphthol to toluene-*p*-thiol and β-naphthol, in which case clearly only an intermediate of the type XXXIV (arrows a, functional group positions reversed, 4-OH lacking) can be envisaged. Thus, perhaps the balance of evidence weighs more in favor of Scheme D as the one applicable to our situation. This probability is further heightened by our observation (*vide infra*) that the over-all desulfuration–reduction reaction proceeded at a qualitatively slower rate in the case of the adduct XIII, which would necessitate approach by zinc to a more hindered carbonyl function, in this case, at the time of reductive cleavage of the mercapto moiety in a dihydro intermediate corresponding to XV[25b] with an angular methyl group.

The desulfuration–reduction of the 6-methylmercaptotoluquinone–butadiene adduct (XIII) required more strenuous conditions than those needed for the unmethylated model XIV. Slow evolution of methyl mercaptan (trapped as the yellow lead salt) was noted upon refluxing with zinc in aqueous acetic acid for a few hours. Isomerization of the *cis* ring junction was undoubtedly caused by this more vigorous treatment, and the product of m.p. 87°,[26a] 9-methyl-Δ⁶-octalin-1,4-dione (I), is thus assigned the *trans* configuration. The *trans* ring juncture is postulated on the basis of findings by Robins and Walker[26b] and our own investigations on zinc–acetic acid reductions of Diels–Alder products from quinone and 3,20-diacetoxypregna-5,16,20-triene.[26c] Short treatment of a few minutes' duration without heat of a *cis*-1,4-dioxo-Δ²-octalin with zinc–acetic acid usually permits the reduction of the ethylenic bond with survival of the *cis* ring juncture. Prolonged treatment supplemented by heating results in reduction concomitant with isomerization to a *trans* ring fusion. Moreover, whereas *cis*-α-decalone isomerizes only extremely slowly to *trans*-α-decalone at room temperature,[27a] *cis*-1,4-dioxodecalins have been found to be considerably less stable with respect to their *trans* isomerides.[27b] The *trans* ring assignment in structure I appeared to be confirmed by the infrared absorption of this compound showing a single strong band in the 1450–1475-cm.$^{-1}$ region characteristic of a *trans* angularly methylated decalin system.[27c] An identity was established also between this material and that of the same melting point obtained previously[27d] from an analogous set of reactions commencing with 5(or 6)-*p*-tolylthiotoluquinone and butadiene followed by zinc–acetic acid. Substance I could be hydrogenated over palladium–charcoal with the uptake of one mole of hydrogen to yield what is undoubtedly *trans*-9-methyldecalin-1,4-dione (XXXVI).

It was hoped to simplify the preparation of I by omitting the mercapto–quinone isomer separation, employing the total crude reaction mixture of predominantly 5- and 6-methylmercaptotoluquinones, and resorting to subsequent isomer elimination in the desulfuration–reduction step. A direct Diels–Alder reaction with butadiene on such a mixture of quinones, obtained from methyl mercaptan and toluquinone followed by oxidation with ferric chloride and crystallization to m.p. 104–135° (thus eliminating any unchanged toluquinone), resulted in a good yield of a distilled adduct whose ultraviolet absorption indicated *ca.* 60% of the angularly methylated material. However, zinc–acetic acid reduction of this mixture did not afford any overall better yield of I than had been obtained before. There was isolated in addition, in small yield, however, a substance melting at 166–168°, identified as 2-methyl-5,8-dihydro-1,4-naphthohydroquinone (XXXVII) by comparing it with an authentic sample of this



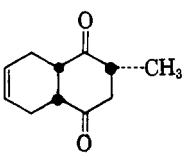
XXXVII

compound. The generation of this hydroquinone XXXVII may be due to the presence of the unknown 3-methylmercaptotoluquinone (VIII) in the original crude mercaptotoluquinone mixture employed in this Diels–Alder reaction. The precursor to compound XXXVII would then have been the adduct XI. This is indirect proof that all three available positions of tolu-

(24) H. Schmid and E. Schnetzler, *Helv. Chim. Acta*, **34**, 894 (1951).

(25)(a) D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 1428 (1954). (b) The zinc–acetic acid desulfuration–reduction is particularly advantageous in securing dehydrodecalin systems such as I since Raney nickel has been found to over-reduce systems constructed similarly to those treated herein (ref. 7); see also R. K. Hill and J. G. Martin, *Proc. Chem. Soc.*, 391 (1959), and G. Stork, E. E. van Tamelen, L. J. Friedman, and A. B. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953), for instances of over-reduction of ethylenic systems in attempted Raney nickel desulfurations.

(26)(a) Our product melted very close to the melting point, 85–86°, reported by Chuang and Han[17] for the substance obtained by mild zinc–acetic acid reduction of the following butadiene–tolquinone adduct.



A depression in melting point resulted on admixture, and the infrared spectra of the two substances differed. (b) P. A. Robins and J. Walker, *J. Chem. Soc.*, 642, 1612 (1952); 3960 (1954); 177 (1957). (c) V. Georgian and Lupe T. Georgian, paper IV in this series, *J. Org. Chem.*, **29**, 58 (1964).

(27)(a) W. Hückel, *Ann.*, **441**, 1 (1925); (b) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952); (c) R. H. Baker, L. S. Minckler, and A. S. Hussey, *ibid.*, **81**, 2379 (1959); (d) V. Georgian, J. Lepe M., and L. L. Skaletzky, unpublished results, manuscript in preparation.

quinone are attacked by methyl mercaptan in the order C-6 > C-5 ≫ C-3.

Recently there appeared what is undoubtedly the method of choice in preparing a monothiolated toluhydroquinone. It was found[28] that 5-bromotoluhydroquinone on being refluxed a short while with alcoholic sodium sulfide gave an excellent yield of 5-mercaptotoluhydroquinone (III, R = H). Methylation on sulfur may be readily effected, and oxidation by the usual means to 5-methylmercaptotoluquinone (IV) would make the latter most plentifully available for employment in the general synthetic scheme developed in this paper.

Experimental[29a]

Benzoquinone.—Benzoquinone was prepared according to a literature method.[29b] The yellow quinone, which was dried in a desiccator over calcium chloride, melted at 110–112° and was used without further purification.

Potassium S-(1,4-dihydroxy-2-phenyl)thiosulfate (II).—The thiosulfate was prepared according to a literature procedure.[29c] To a solution of 99 g. (0.62 mole) of anhydrous sodium thiosulfate in 200 ml. of water, cooled in an ice–salt bath, was added with stirring a warm (40–50°) solution of 43.2 g. (0.4 mole) of quinone in 150 ml. of glacial acetic acid. The addition time was 0.75 hr., and the reaction mixture was maintained at 0–10°. The red reaction mixture, after a few minutes additional stirring, became almost colorless and was saturated with potassium chloride. After 2 hr. in the cold room, the white precipitate was filtered and washed with cold saturated potassium chloride solution. The white solid was dried in air and used directly in the reduction with zinc and hydrochloric acid.

2-Mercaptohydroquinone.—To the crude potassium S-(1,4-dihydroxy-2-phenyl)thiosulfate dissolved in 8 *N* hydrochloric acid was added slowly zinc dust (2 g. of zinc dust for 1 g. of potassium salt in 30 ml. of 8 *N* hydrochloric acid.) Hydrogen and hydrogen sulfide were immediately evolved and the solution was maintained at 40–50° by cooling in a cold water bath when necessary. After being cooled, the acid solution was extracted several times with ether. The ether extracts were dried (sodium sulfate) and evaporated to dryness in a desiccator in the presence of potassium hydroxide. Several recrystallizations from benzene gave 2-mercaptohydroquinone, 15 g. (27% based on quinone), as colorless needles, m.p. 118° (lit.[9] m.p. 118°).

2-Methylmercaptoquinone.—To a cold solution of 15 g. (0.105 mole) of 2-mercaptohydroquinone in 270 ml. of 2% sodium hydroxide solution containing a little sodium hydrosulfite was added with stirring 14.5 ml. (0.105 mole) of methyl sulfate in three portions. After each addition the solution was stirred for 15 min. and finally until the complete disappearance of the methyl sulfate. The solution was acidified and the hydroquinone was oxidized at 20° with 105 ml. of 2 *N* ferric chloride. The orange solid was filtered, washed well with water, and dried in a vacuum desiccator over potassium hydroxide. The orange quinone was purified by crystallization from methanol. The yield was 9.1 g. (56%) of 2-methylmercaptoquinone, m.p. 146–146.5° (lit.[9] m.p. 148°).

***cis*-2-Methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIV).**—A mixture of 10 ml. of 1,3-butadiene, 5.7 g. of 2-methylmercaptoquinone, and 10 ml. of anhydrous benzene containing a trace of hydroquinone was heated in a sealed Carius tube at 110 ± 5° for 4 hr. The tube was cooled in acetone–Dry Ice and opened. Evaporation of the benzene gave 5.3 g. (69%) of yellow Diels–Alder adduct, m.p. 81–84°. The product on recrystallization from ether–hexane gave XIV as yellow needles, m.p. 85–86°. The ultraviolet spectrum showed an absorption maximum, λ_{max}^{EtOH} 332 mμ (log ε 3.83). Infrared spectrum showed carbonyl bands at 5.89 and 6.0, and double bond band at 6.4 μ (C=C–S–R).

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81. Found: C, 63.62; H, 5.73.

Zinc–Acetic Acid Reduction of *cis*-2-Methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone. A. Five-Minute Reduction. *cis*-2-Methylmercapto-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (XV) (*cis*-2-Methylmercapto-Δ⁶-octalin-1,4-dione).—To 1 g. of zinc dust suspension in 3 ml. of water at 50° was added dropwise with vigorous stirring glacial acetic acid (3 ml.) containing 0.5 g. of 2-methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIV). After the addition was complete (5 min.), the yellowish solution was decanted from the zinc, diluted with water, and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, and then with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the ether and addition of alcohol precipitated some white solid, which was filtered and recrystallized several times from aqueous alcohol to give XV as needles, m.p. 111–112°. The solid gave a positive sulfur test.

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71. Found: C, 63.21; H, 6.44.

B. Two-Hour Reduction. *cis*-2,3,5,8,9,10-Hexahydro-1,4-naphthoquinone (XVI) (*cis*-Δ⁶-Octalin-1,4-dione).—To a stirred solution of 0.5 g. of *cis*-methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIV) in 95% acetic acid there was added 5 g. of zinc dust in five portions over 1 hr. The suspension was stirred for an additional hour during which time traces of methyl mercaptan were detected by lead acetate paper. The solution was decanted from the zinc which was washed thoroughly with acetone. The acetic acid–acetone solution was concentrated *in vacuo* and the residue extracted with benzene. The benzene solution was washed with water, sodium bicarbonate solution, and again with water. The dried (sodium sulfate) benzene was concentrated to 0.24 g. (61%) white solid, m.p. 101–103°. Crystallization from ether–hexane gave the *cis*-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (XVI) as colorless needles, m.p. 103–104°. No sulfur could be detected on sodium fusion. Alder and Stein reported the melting point of *cis*-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone as 108°.[30] However, preparation of the diketone according to their directions gave colorless needles, m.p. 103–104°. A mixture melting point of the desulfuration product and authentic *cis*-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone of Alder and Stein did not depress. The infrared spectra of these two materials were superimposable.

Addition of Methyl Mercaptan to Toluquinone. 5-Methylmercaptotoluquinone (IV) and 6-Methylmercaptotoluquinone (X).—To a solution of methyl mercaptan (15–25 g.) in 250 ml. of methanol, cooled in an ice–salt bath at 0–5°, was added with vigorous stirring a solution of 30 g. (0.25 mole) of toluquinone in 150 ml. of methanol. During the half hour addition period, each drop of the quinone solution gave a fleeting red coloration. After the addition was complete, the yellow solution was concentrated *in vacuo* to 250 ml. The mixture of methylmercaptotoluquinones was oxidized with 250 ml. of 2 *N* ferric chloride solution at 20°. The orange precipitate was filtered, washed well with water, and dried in a vacuum desiccator over potassium hydroxide. The crude methylmercaptotoluquinone mixture, 35.1 g. (84%), melted at 104–135°. A 15-g. sample of the methylmercaptotoluquinone mixture was crystallized several times from methanol to give 5 g. of 6-methylmercaptotoluquinone (X), m.p. 140–142°. From the mother liquors, was isolated material of sharp m.p. 104° which could be purified by sublimation, but which was not encountered later after chromatography over silica gel, and must have been a sharply melting mixture of isomers.

A separation of the crude methylmercaptotoluquinone mixture could be obtained by chromatography over silica gel using ether–hexane as the eluting agent. The orange 6-methylmercaptotoluquinone (X) (57%), m.p. 140–142°, and 5-methylmercaptotoluquinone (IV) (17%), m.p. 136–137°, were isolated. These two quinones were shown to be different, since a mixture melting point showed a depression (m.p. 105–125°) and their infrared spectra were quite different in the fingerprint region. The infrared spectra showed bands at 6.03, 6.07, 6.15, and 6.4 μ. The

(28) J. Green, D. McHale, P. Mamalis, and S. Marcinkiewicz, *J. Chem. Soc.*, 3374 (1959).

(29)(a) All melting points and boiling points are uncorrected. Microanalyses were performed by Miss H. Beck, Microanalytical Laboratory, Northwestern University. Infrared spectra were measured on a Baird *Model AB-2 double-beam spectrophotometer or on a Perkin-Elmer Infracord.* Ultraviolet spectra were measured in 95% ethanol on a Beckman Model DU spectrophotometer. (b) H. W. Underwood, Jr. and W. L. Walsh, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 553. (c) German Patent 175,070 (1905); *Frdl.*, **8**, 140 (1905).

(30) K. Alder and G. Stein, *Ann.*, **501**, 277 (1933). P. Robins and J. Walker, *J. Chem. Soc.*, 409 (1958), reported m.p. 103–105° for this compound in agreement with our value.

substance, m.p. 104°, was probably a mixture of the two monomethylmercaptotoluquinones described previously, since its infrared spectrum had only those bands which appeared in the spectra of the 140–142° and 136–137° isomers. The monomethyl mercaptotoluquinone of Alcalay,[9] m.p. 113°, was not encountered. Analytical samples of each were prepared by recrystallization from methanol.

Anal. Calcd. for $C_8H_8O_2S$: C, 57.14; H, 4.79. Found for IV, m.p. 136–137°: C, 57.22; H, 4.72. Found for X, m.p. 140–142°: C, 57.42; H, 4.79. Found for isomer mixture, 104°: C, 57.23; H, 4.61.

Samples of IV and X prepared by the combined Alcalay[9]–Karrer[10] procedure were found to be identical with those prepared previously by infrared and melting point comparisons.

Diels–Alder Reaction of 1,3-Butadiene and 6-Methylmercaptotoluquinone (X, 140–142° Monomethylmercaptotoluquinone Isomer). 2-Methylmercapto-9-methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIII).—Butadiene (15–20 ml.), 3 g. of 6-methylmercaptotoluquinone (isomer, m.p. 140–142°), and 30 ml. of anhydrous benzene containing a trace of hydroquinone were heated in a sealed Carius tube at 100° for 4 days (96 hr.). The color of the reaction mixture changed during this period from red to light yellow.

The Carius tube was opened, and the benzene solution was filtered to remove some traces of butadiene polymer. The reaction tube was washed out with several portions of benzene. The combined benzene solution was concentrated to 5.1 g. of yellow oil. The oil was taken up in ether and was washed several times with sodium hydroxide–sodium hydrosulfite solution in order to remove traces of quinone still present. (These washings resulted in a loss of product since it was later shown that the diketone was somewhat soluble in dilute base.) The ether solution was washed with water and dried over sodium sulfate. Evaporation of the ether gave 4.6 g. of yellow oil which solidified on standing several days at room temperature. Crystallization from ether–ligroin (35–60°) gave 3.1 g. (80%) of Diels–Alder adduct as yellow needles, m.p. 79–80°. The 2-methylmercapto-9-methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone shows a band λ_{max}^{EtOH} 332 mμ (log ε 3.95), and the infrared spectrum shows carbonyl bands at 5.89 and 6.0 μ.

Anal. Calcd. for $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35. Found: C, 64.83; H, 6.10.

Zinc–Acetic Acid Reduction of 6-Methylmercaptotoluquinone–Butadiene Adduct XIII. *trans*-9-Methyl-Δ⁵-octalin-1,4-dione (I).—The adduct XIII (0.68 g.) dissolved in 100 ml. of 95% acetic acid was refluxed with 3 g. of zinc dust for 2.5 hr. During this period a stream of nitrogen swept the methyl mercaptan evolved into a lead acetate trap, where it precipitated a yellow lead salt. Then 3 g. more of zinc was added and the reaction mixture was refluxed an additional 2.5 hr.

The acetic acid solution was decanted from the zinc–zinc acetate solids which were washed thoroughly with glacial acetic acid. The acetic acid was concentrated *in vacuo* and the residue was extracted with ether. The ether layer was washed with water, sodium bicarbonate solution, and water and was dried over sodium sulfate. Evaporation of the ether gave 0.44 g. (81%) white solid, m.p. 60–65° which gave a negative sulfur test. Recrystallization of this material from hexane afforded *trans*-9-methyl-Δ⁵-octalin-1,4-dione (I), m.p. 86.5–87.0°. Infrared showed nonconjugated carbonyl absorption at 5.80 μ. A mixture melting point with *cis*-2-methyl-2,3,5,7,9,10-hexahydro-1,4-naphthoquinone (m.p. 85–86°[17]) showed a large depression, and the infrared spectra of the two compounds differed.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 8.02.

***trans*-9-Methyldecalin-1,4-dione (XXXVI). Hydrogenation of I.**—The diketone I, of m.p. 87°, was hydrogenated in a microvolumetric hydrogenation apparatus in 10 ml. of ethanol over 5% palladium–charcoal at room temperature and at near atmospheric pressure. Hydrogen, 23.5 ml. (93%), was absorbed in *ca.* 0.5 hr. The catalyst was filtered, and the alcohol was stripped to yield *trans*-9-methyldecalin-1,4-dione (XXXVI), m.p. 95.5–97°. Recrystallization from hexane afforded the analytical sample, m.p. 97.0–97.4°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.65.

Diels–Alder Reaction of the Crude Methylmercaptotoluquinone Mixture and Butadiene.—In a sealed Carius tube, 10 g. of methylmercaptotoluquinone mixture (m.p. 104–135°, containing essentially 5- and 6-methylmercaptotoluquinones), 30 ml. of butadiene, 40 ml. of anhydrous benzene, and 0.1 g. of hydroquinone were heated at 100° for 4 days. The contents were combined with a run using 6 g. of the crude quinone mixture and corresponding amounts of the other reagents.

The benzene solution was concentrated and the yellow oil distilled in vacuum to give 11.9 g. of yellow oil which showed a strong band in the ultraviolet at λ_{max}^{EtOH} 332–333 mμ (log ε 3.73). Since the crude quinone mixture shows no absorption at this wave length, from the relative intensities of absorption of this reaction mixture and of pure XIII it was estimated that there was approximately 55–60% of angular methylated adduct in the reaction mixture. This reaction product was submitted to zinc–acetic acid reduction–desulfuration as in the following experiment.

Zinc–Acetic Acid Reduction of the Isomeric Mixture of Methylmercaptotoluquinone–Butadiene Adducts. *trans*-9-Methyl-Δ⁶-octalin-1,4-dione (I) and 2-Methyl-5,8-dihydro-1,4-naphthohydroquinone (XXXVII).—To 4.0 g. of Diels–Alder adduct of the isomeric methylmercaptotoluquinones and butadiene obtained from the previous procedure, dissolved in 200 ml. of 95% acetic acid there was added 12 g. of zinc dust, and the reaction mixture was refluxed 2 hr. A nitrogen stream swept the methyl mercaptan produced into a lead acetate trap where it was precipitated as the yellow lead salt.

The reaction mixture was permitted to cool, the supernatant liquid was decanted, and the zinc sludge was washed thoroughly with acetone. The acetic acid–acetone solution was concentrated *in vacuo* and the residue extracted with ether. The ether extract was washed with water, sodium carbonate solution, and again with water. The dried ether solution (sodium sulfate) was evaporated to a small volume which was put on silica gel chromatographic column. Elution with ether–ligroin (35–60°) gave 0.4 g. of solid, m.p. 166–168°, and 0.7 g. of solid, m.p. 52–65°.

The substance, m.p. 166–168°, was shown to be identical with 2-methyl-5,8-dihydro-1,4-naphthohydroquinone (XXXVII), m.p. 166–168°, prepared according to the directions of Chuang.[17] These two materials did not depress on mixture melting point and had superimposable infrared spectra.

The low melting material after many recrystallizations from hexane gave 0.2 g. of a white solid, m.p. 85–86°, which gave a negative sulfur test. Further recrystallization from hexane gave the diketone I as colorless needles, m.p. 87°. A mixture melting point with *cis*-2-methyl-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (m.p. 85–86°[17]) showed a large depression, and the infrared spectra of the two compounds differed.

***cis*-2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone.**—A solution of 2.4 g. of toluquinone, 4.4 g. (7 ml.) of butadiene and 10 ml. of benzene was heated in a sealed tube at 105° for 5 hr. The yellow solution was concentrated *in vacuo* and the residue was crystallized from ether–ligroin (35–60°) to give 2.0 g. (58%) of colorless needles, m.p. 79.5–80.5° (lit.[17] m.p. 79–81°).

***cis–syn*-2-Methyl-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (*cis–syn*-2-Methyl-Δ⁶-octalin-1,4-dione).**—A solution of the preceding butadiene–toluquinone adduct (0.7 g.) in 3 ml. of glacial acetic acid was added dropwise to a well stirred suspension of 1 g. zinc dust in 3 ml. of water at 50°. After the addition was complete, the colorless solution was quickly decanted. The acetic acid solution was cooled and the reduction product was filtered and washed with cold water. One crystallization from ligroin (35–60°) gave the diketone, 0.5 g. (72%), m.p. 85.5–86° (lit.[17] m.p. 85–86°).

2-Methyl-5,8-dihydro-1,4-naphthohydroquinone (XXXVII).—2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone dissolved in glacial acetic acid was isomerized with a trace of hydrogen bromide in glacial acetic acid. The precipitated hydroquinone was filtered and washed with cold water. The product, after drying in air, melted at 165.5–168°.

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