

TABLE I  
 CONDENSATION PRODUCTS FROM CINCHONINALDEHYDE AND HETEROCYCLIC REACTIVE METHYL COMPOUNDS

Compound No.	R	Heating time, hr. <sup>a</sup>	Yield, % <sup>b</sup>	M.p., °C. <sup>c</sup>	Formula	Carbon, %		Hydrogen, %	
						Calcd.	Found	Calcd.	Found
I	2-Pyridine·CH <sub>3</sub> I	2	33 (80)	249-250	C <sub>17</sub> H <sub>15</sub> N <sub>2</sub> I	54.5	54.8	4.0	4.0
		2	32 (88)						
II	2-Pyridine·C <sub>2</sub> H <sub>5</sub> I	5	65	250-251	C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> I	55.7	55.3	4.4	4.2
III	2-Pyridine· <i>n</i> -C <sub>3</sub> H <sub>7</sub> I	5	60	233-234	C <sub>19</sub> H <sub>19</sub> N <sub>2</sub> I	56.7	56.7	4.8	4.8
IV	2-Pyridine· <i>i</i> -C <sub>3</sub> H <sub>7</sub> I	2	25	220-221	C <sub>19</sub> H <sub>19</sub> N <sub>2</sub> I	56.7	56.7	4.8	4.9
		20	90						
V	4-Pyridine·CH <sub>3</sub> I	2	23 (90)	264-265	C <sub>17</sub> H <sub>15</sub> N <sub>2</sub> I	54.5	54.5	4.0	4.2
		2	20						
VI	4-Pyridine·C <sub>2</sub> H <sub>5</sub> I	7	71	225-226	C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> I	55.7	55.9	4.4	4.7
VII	4-Pyridine· <i>n</i> -C <sub>4</sub> H <sub>9</sub> I	48	70	240-241	C <sub>20</sub> H <sub>21</sub> N <sub>2</sub> I	57.7	57.7	5.1	5.0
VIII	2-Quinoline·CH <sub>3</sub> I	2	41 (75)	221-222	C <sub>21</sub> H <sub>17</sub> N <sub>2</sub> I	59.4	59.3	4.0	4.3
IX	4-Quinoline·CH <sub>3</sub> I	2	27 (50)	253-254	C <sub>21</sub> H <sub>17</sub> N <sub>2</sub> I	59.4	59.1	4.0	3.9
X	2-(4-Methylthiazole)·CH <sub>3</sub> I	1	70	226-227	C <sub>18</sub> H <sub>15</sub> N <sub>2</sub> SI·CH <sub>3</sub> OH	47.9	47.8	4.5	4.2

<sup>a</sup> The heating times and reaction conditions have no critical significance except for the two hour times in which both the reaction period and other conditions were made uniform to allow semi-quantitative comparisons of the yields (see compounds I, IV, V, VIII and IX). <sup>b</sup> Yields given correspond to the total amount of product isolated after the stated reflux time plus material recovered by working up the mother liquors and filtrates. The first yields given for compounds I, IV, V, VIII and IX refer to the product isolated on cooling the reaction mixture after the two hour interval, while the figures in parentheses represent the total yield recovered after reworking the filtrates. The reworking always involves unmeasured additional heating and standing periods. <sup>c</sup> Melting points are uncorrected. Compounds I, II, III, V, VIII, IX and X were recrystallized from methanol, while IV, VI and VII were recrystallized from methanol-ethyl acetate mixtures.

When compound I was refluxed for 70 hours with methyl iodide in methanol solution none of the bis-methiodide was obtained and unchanged I was recovered quantitatively.

### Experimental

**General Condensation Method.**—A mixture of 0.02 mole of 2-(or 4)-methylpyridine (or quinoline) alkiodide, 4 g. (0.022 mole) of cinchoninaldehyde (monohydrate), 50 cc. of methanol and 10 small drops of piperidine was refluxed for two hours on a steam-bath. The reaction mixture was chilled rapidly in cold water and allowed to stand for one hour in the cold. The crystalline product was col-

lected by filtration and was purified by recrystallization from methanol.

Evaporation of the methanol mother liquors, involving another interval of heating on a steam-bath, gave an additional yield. Some of the condensations were refluxed for longer or shorter periods, but the two-hour interval and the first crop isolated were used uniformly in those cases where comparisons were made.

Details for all compounds appear in Table I.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

## A Stereospecific Synthesis of Cantharidin

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A total synthesis of cantharidin (I) from the butadiene adduct (X) of dimethyl 3,6-epoxy-3,4,5,6-tetrahydrophthalate (IX) is described.

Cantharidin, the potent vesicant principle found in various species of cantharides beetles,<sup>2</sup> was first obtained in crystalline form by the French pharmacist Robiquet in 1810.<sup>3</sup> The remarkable properties of the substance which had acquired a certain meretricious fame as an aphrodisiac stimulated extensive structural investigations that culminated in the proposal of the correct structure (I) by Gadamer

and his school.<sup>4</sup> Although the cantharidin molecule possesses the somewhat unusual features of a 1,4-oxide bridge and two adjacent angular methyl groups, it is interesting to note that it consists of two tail-to-tail isoprene units and may thus be regarded as a bicyclic monoterpenoid.

Cantharidin is optically inactive and non-resolvable<sup>4</sup>; its anhydride ring is therefore *cis* fused. There are, nevertheless, two stereochemical arrangements which correspond to the two-dimen-

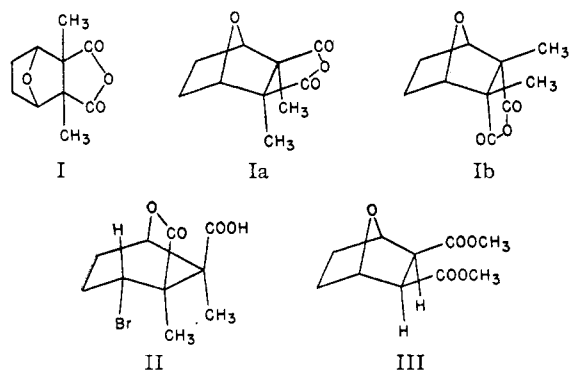
(1) National Institutes of Health Predoctoral Fellow, Harvard University, 1951-1952.

(2) Perhaps the most familiar is *cantharis vesicatoria*, more commonly known as Spanish Fly.

(3) M. Robiquet, *Ann. chim.*, [1] 76, 302 (1810).

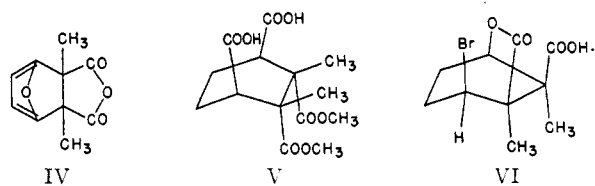
(4) J. Gadamer, *Arch. Pharm.*, 252, 609 (1914); W. Rudolph, *ibid.*, 254, 423 (1916), and later papers.

sional projection I. In one of them (Ia) the anhydride grouping is *cis* to the oxide bridge, while these two structural elements are in a *trans* relationship in the other (Ib), and it is evident that a rational synthesis of cantharidin cannot be devised without knowing which of these two possibilities represents the naturally occurring substance. Without entering into a detailed discussion it will suffice here to mention that the formation of hydrobromocantharic acid (II) by the action of hydrogen bromide in acetic acid on cantharidin<sup>5</sup> finds a satisfactory explanation only if the oxide bridge and the anhydride carbonyls are in a *cis* arrangement, as shown in Ia, which therefore represents the correct stereochemistry of cantharidin.<sup>6</sup>



A number of attempts to synthesize cantharidin have been recorded in the literature since the early experiments of von Bruchhausen and Bersch<sup>7</sup> and of Diels and Alder<sup>8</sup> who sought to build up the molecule *via* a diene synthesis between dimethylmaleic anhydride and furan. This straightforward approach, which could well have led to the correct stereochemistry,<sup>9</sup> was not successful.

The lack of success with dimethylmaleic anhydride prompted attempts to utilize the readily available dihydro adduct diester (III) derived from furan and maleic anhydride itself. Efforts to introduce the missing methyl groups by angular methylation using methyl iodide and triphenylmethylsodium were fruitless.<sup>6,10</sup>



(5) J. Gadamer, *Arch. Pharm.*, **252**, 636 (1914).

(6) K. Ziegler, G. Schenck, E. W. Krockow, A. Siebert, A. Wenz and H. Weber, *Ann.*, **551**, 1 (1942). For a further discussion of this and related points cf. R. B. Woodward and R. B. Loftfield, *This Journal*, **63**, 3167 (1941).

(7) F. von Bruchhausen and H. W. Bersch, *Arch. Pharm.*, **266**, 697 (1928).

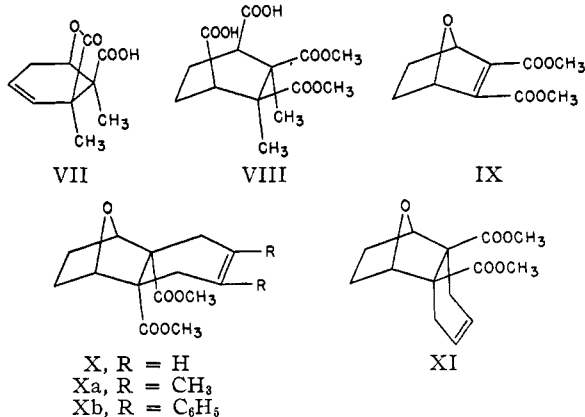
(8) O. Diels and K. Alder, *Ber.*, **62**, 554 (1929).

(9) R. B. Woodward and H. Baer, *This Journal*, **70**, 1161 (1948).

(10) This is in sharp contrast to the successful methylation of the similar compound prepared from cyclopentadiene and maleic anhydride (Ziegler, *et al.*, ref. 6). The difference is apparently the result of  $\beta$ -elimination of the oxide bridge attending the formation of the ester anion in the diester (III). It may be noted further that had the methylation been feasible, it would probably have led to the introduction of the methyl groups *cis* to the oxide bridge, and thus to IV rather than to cantharidin.

In an endeavor to obviate the lack of reaction between dimethylmaleic anhydride and furan, Diels and Olsen<sup>11</sup> attempted to condense furan with dichlorodimethylsuccinic anhydride, a reaction whose failure is to a large extent a reflection of the fact that the desired product (IV) is not capable of existence.

On the basis of Gadamer's observation<sup>5</sup> that cantharidin was reformed in good yield by the pyrolysis of hydrobromocantharic acid (II), Ziegler and his collaborators sought to solve the problem via the synthesis of the latter substance. In the course of their brilliant and extensive synthetic work they found that treatment of the silver salt of the diacid diester (V) with bromine in carbon tetrachloride produced an epimer (VI) of hydrobromocantharic acid in which the bromine atom is *cis* to the lactone bridge rather than *trans*. As would



be expected, the major product (over 90%) of the pyrolysis of that epimer was found to be the unsaturated lactonic acid, cantharic acid (VII). In spite of this unfavorable stereochemistry of VI it was found that the pyrolysis also produced a very low yield of cantharidin, thus achieving its first total synthesis.<sup>6</sup> Efforts which were later made to attain the desired stereochemistry by making use of the epimeric diester dicarboxylic acid (VIII) led unfortunately again to the same *epi*-hydrobromocantharic acid (VI).<sup>12,13</sup>

The clearly defined and relatively simple stereochemistry of cantharidin makes its synthesis an interesting goal. This paper presents an account of a stereospecific synthesis of cantharidin.<sup>16</sup>

Dimethyl 3,6-epoxy-3,4,5,6-tetrahydrophthalate (IX) was prepared by a modification of the method of Diels and Olsen<sup>11</sup> and condensed with butadiene in alcohol at 100° to give the adduct (X), m.p.

(11) O. Diels and S. Olsen, *J. prakt. Chem.*, [2] **156**, 285 (1940).

(12) K. Ziegler, W. Flaig and G. Velling, *Ann.*, **567**, 204 (1950).

(13) This brief survey of previous synthetic work is not intended to be exhaustive. Other synthetic approaches have been described *inter alia* by Guha and his collaborators.<sup>14</sup> The reported synthesis of Paranjape, Phalnikar, Bhide and Nargund<sup>15</sup> appears to be without experimental foundation.

(14) (a) K. N. Pai and P. C. Guha, *J. Indian Chem. Soc.*, **11**, 231 (1934); (b) P. C. Guha and B. H. Iyer, *J. Indian Inst. Sci.*, **21A**, 115 (1938); *C. A.*, **33**, 2134 (1939); (c) B. H. Iyer and P. C. Guha, *J. Indian Inst. Sci.*, **23A**, 159 (1941). *C. A.*, **36**, 3157 (1942).

(15) K. D. Paranjape, N. L. Phalnikar, B. V. Bhide and K. S. Nargund, *Proc. Indian Acad. Sci.*, **19A**, 385 (1944); *C. A.*, **39**, 503 (1945).

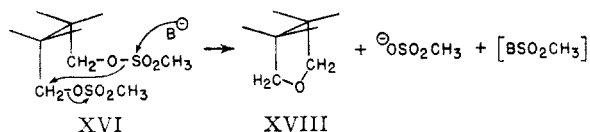
(16) A brief report of this work has already been published (G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, *This Journal*, **73**, 4501 (1951)).

78.5–79°, in almost quantitative yield.<sup>17</sup> The stereochemistry of this adduct is that indicated in X rather than in XI because the epoxide bridge in IX offers less hindrance to the approach of the butadiene molecule than does the ethylene bridge.<sup>18</sup> The relationship of the stereochemistry of the adduct (X) to that of cantharidin (Ia) makes one of the synthetic problems the conversion of the two carbomethoxy groups of X into the two methyl groups of cantharidin while the other problem is the replacement of the cyclohexene ring by the required anhydride system.

The transformation of the angular carbomethoxy functions to methyl groups was considered first. Reduction of X with lithium aluminum hydride gave the corresponding diol (XV), m.p. 154–154.5°. This was smoothly converted into the crystalline dimesylate (XVI) by treatment with excess methanesulfonyl chloride in pyridine solution. The problem of effecting the change  $R-CH_2-OSO_2R' \rightarrow R-CH_3$  has been previously solved in certain cases by conversion to the iodide, followed by hydrogenolysis with Raney nickel.<sup>19</sup> In the present case no definite product could be obtained by the application of this method, and we therefore turned to the possibility of achieving the desired change by the sequence  $R-CH_2-OSO_2CH_3 \rightarrow R-CH_2-S-R' \rightarrow R-CH_3$ . Initial experiments along these lines were directed toward the synthesis of the cyclic sulfide (XVII) by reaction of the dimesylate (XVI) with sodium sulfide in ethanolic solution. This led to

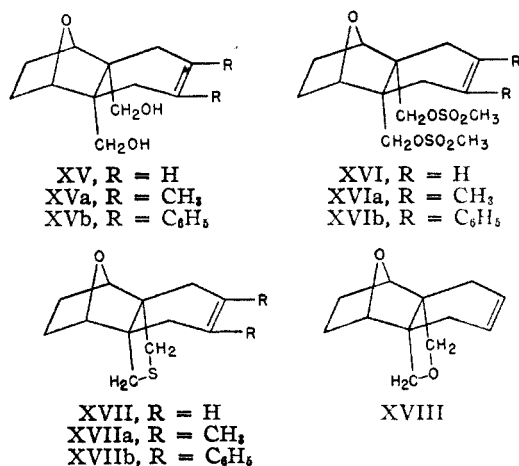
the formation of a mixture which was eventually proved to be composed of XVII and the related cyclic oxide (XVIII) although it gave analytical data close to those required by formula XVII.

The formation of this cyclic oxide (XVIII) can be rationalized by considering that the relatively large steric hindrance involved in the displacement of mesylate anion by attack on carbon in this particular case permits a certain amount of direct attack on the mesylate sulfur as depicted



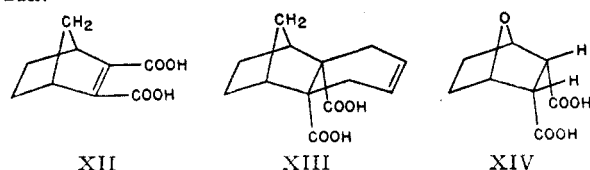
This view of the mechanism of the formation of the oxide XVIII recalls the two types of cleavage exhibited by toluenesulfonate esters of alcohols, where it has been shown that displacement either on carbon ( $R-OTs \rightarrow R-H$ ) or on sulfur ( $R-OTs \rightarrow R-O-H$ ) can be observed, depending on the particular steric situation involved.<sup>20</sup> As a corollary, it would be anticipated that lithium aluminum hydride reduction of the dimesylate (XVI) would give the same cyclic oxide (XVIII) by a mechanism similar to that shown above ( $B^- = H^-$ ). The reduction did in fact afford pure XVIII m.p. 45–46°, in excellent yield.<sup>21</sup>

The close similarity in the properties of the cyclic oxide (XVIII) and the desired cyclic sulfide (XVII) made separation of the product mixture obtained from the sodium sulfide reaction extremely difficult, and for that reason displacement with potassium ethyl mercaptide in *t*-butyl alcohol was investigated. The oxide (XVIII) was again formed together with the desired dithioethyl derivative (XIX), m.p. 45–45.5°, but in this case the considerable difference in the molecular weight of the two substances permitted their easy separation by distillation.

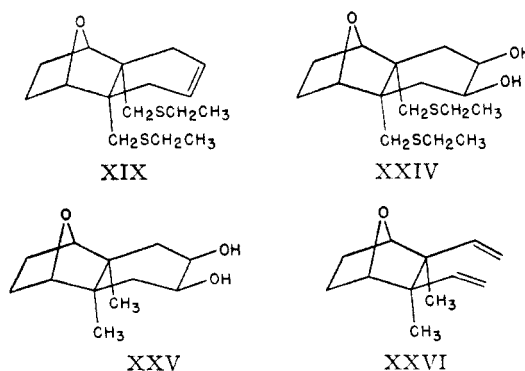


(17) Hydrolysis of this adduct gave the corresponding anhydride, m.p. 162°, prepared previously from 3,6-epoxy-3,4,5,6-tetrahydrophthalic acid and butadiene (K. Alder and K. H. Backendorf, *Ann.*, **535**, 101 (1938)).

(18) A similar situation is encountered in the addition of butadiene to the closely related dienophile XII which has been reported to lead exclusively to an adduct of the structure XIII (K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937)). Analogously, the catalytic hydrogenation of the acid corresponding to IX results in a compound for which the structure XIV has been demonstrated by Woodward and Baer.<sup>9</sup>



(19) V. Prelog, J. Norymberski and O. Jeger, *Helv. Chim. Acta*, **29**, 360 (1946).



Reductive desulfurization of the dithioethyl compound (XIX) had to be performed in such a way that some entry into the cyclohexene ring would be retained to allow later operations on that part of the molecule.<sup>22</sup> After early experiments

(20) H. Schmidt and P. Karrer, *ibid.*, **32**, 1371 (1949).

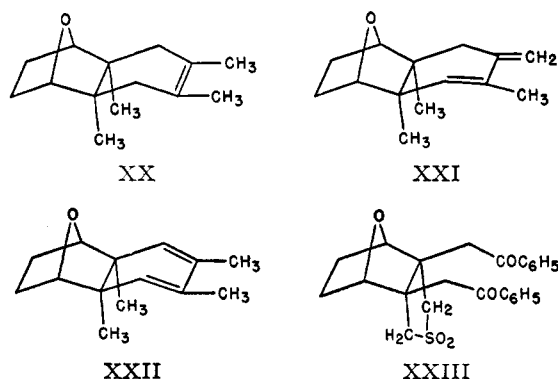
(21) As would be expected, the oxide (XVIII) is also formed by treatment of the diol (XV) with one equivalent of methanesulfonyl chloride in pyridine.

(22) Direct desulfurization of XIX was not satisfactory because simultaneous reduction of the double bond could not be prevented.

to protect the double bond against reduction with the Raney nickel by increasing its substitution (through the initial use of 2,3-dimethyl- or 2,3-diphenylbutadiene in the addition to IX) had given unsatisfactory results,<sup>23</sup> hydroxylation of the double bond proved a better alternative. Treatment of the dithioethyl compound (XIX) with one equivalent of osmium tetroxide in the presence of pyridine afforded the glycol (XXIV) which was desulfurized with active Raney nickel in refluxing alcohol to the desired dimethyl glycol (XXV), m.p. 107–109°, in 75% yield (68% from XIX). The structure of this glycol is as shown in XXV because its method of formation requires that it be a *cis*-glycol, and since only one of the two possible *cis*-glycols is formed, it clearly must be the one resulting from the approach of OsO<sub>4</sub> from the less hindered side of the molecule.

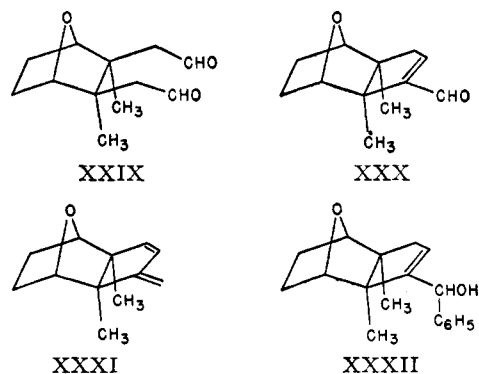
With the conversion of the original adduct (X) to the dimethyl compound (XXV), the introduction of the two angular methyl groups in their proper steric relationship to the oxide bridge was achieved. There remained only to convert the dihydroxy-cyclohexene system into the anhydride ring of cantharidin, an operation that required as the immediate objective the transformation of XXV into the type of system shown in XXVI, which would be expected to yield cantharidin by appropriate oxidation.<sup>24</sup>

(23) For instance, while the dimethyl analog of X, Xa (from 2,3-dimethylbutadiene and IX), after conversion to its cyclic sulfide (XVIIa), gave smooth desulfurization with the expected retention of the tetrasubstituted double bond, attempts to degrade the dimethyl-cyclohexene system remained unavailing: thus, the elimination of HBr from the product of the reaction of the desulfurized substance (XX) with *N*-bromosuccinimide gave the diene system shown in XXI rather than the desired 1,3-cyclohexadiene derivative (XXII), to which it could not be isomerized. In the diphenyl series it was found that desulfurization could not be effected completely with partially deactivated Raney nickel, while active catalyst simultaneously reduced the cyclohexene double bond. Ozonolysis before desulfurization gave a nicely crystalline dibenzoyl sulfone (XXIII) which could not be satisfactorily oxidized further.



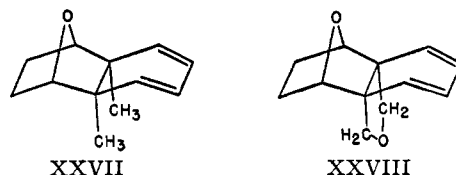
(24) Possibly the most obvious way of accomplishing this would be the thermolysis of a suitable diester of XXV to the 1,3-cyclohexadiene derivative (XXVII) by analogy with the well-established *cis* eliminations encountered in the thermal decomposition of monoesters (cf. D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949)). The feasibility of this method of synthesis of cyclic dienes was established in the present work by the smooth conversion of the diesterate of *cis*-1,2-cyclohexanediol at 360° to 1,3-cyclohexadiene, isolated as its maleic anhydride addition product in 42% yield. The compound XXVIII, which is closely related to XXVII, was prepared by this method, but the approach was not pursued when it was found that its ozonolysis gave mainly lactonic material, possibly the result of initial 1,4-addition of O<sub>3</sub> or O<sub>2</sub> to the homoannular diene. It is this difficulty which led to

This change was achieved in the following manner: cleavage of the dimethyl glycol (XXV) proceeded readily with periodic acid in aqueous dioxane to yield the expected dialdehyde (XXIX), which was cyclized to the cyclopentenealdehyde (XXX), m.p. 75–77°,  $\lambda_{\text{max}}^{\text{EtOH}}$  237–238 m $\mu$ ,  $\epsilon_{\text{max}}$  14,500, in agreement with the expected absorption.<sup>26</sup> This was further characterized by its orange phenylhydrazone, m.p. 190–192°. From the cyclopentenealdehyde (XXX) the desired goal (see footnote 24) of a *trans* dienic system, illustrated by the partial formula XXXI, was easily reached.



Addition of phenyllithium to the cyclopentenealdehyde (XXX) gave rise to the phenylcyclopentenylcarbinol (XXXII), m.p. 105–106°, in 73% yield, along with a small amount of non-crystalline epimer. Since it was essential to avoid skeletal rearrangements during the removal of the elements of water from XXXII,<sup>27</sup> it was decided to have recourse to a thermal elimination process.

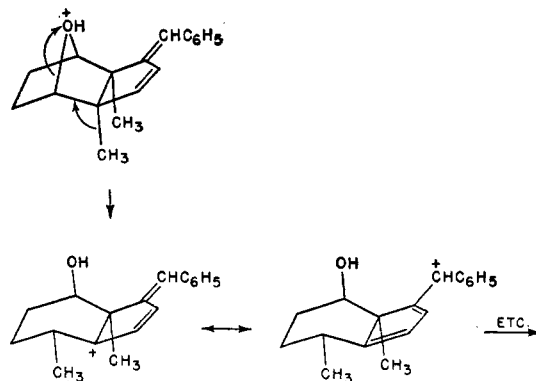
the decision to prepare a system XXVI in which the double bonds form a *trans* diene system as in XXXI.



(25) Cf. the cyclization of adipaldehyde to  $\Delta^1$ -cyclopentenealdehyde (J. B. Brown, H. B. Henbest and E. R. H. Jones, *ibid.*, 3634 (1940)).

(26)  $\Delta^1$ -Cyclopentenealdehyde has  $\lambda_{\text{max}}^{\text{EtOH}}$  237–238 m $\mu$ ,  $\epsilon_{\text{max}}$  13,500.<sup>26</sup>

(27) The opportunity for such rearrangements in this system would appear to be excellent during the course of ionic dehydrations because of the steric disposition of the methyl groups in relation to the oxide bridge and because (in contrast to the situation with cantharidin itself which is stable to acid) the cation resulting from methyl migration is of relatively low energy as a result of conjugation with the benzene ring



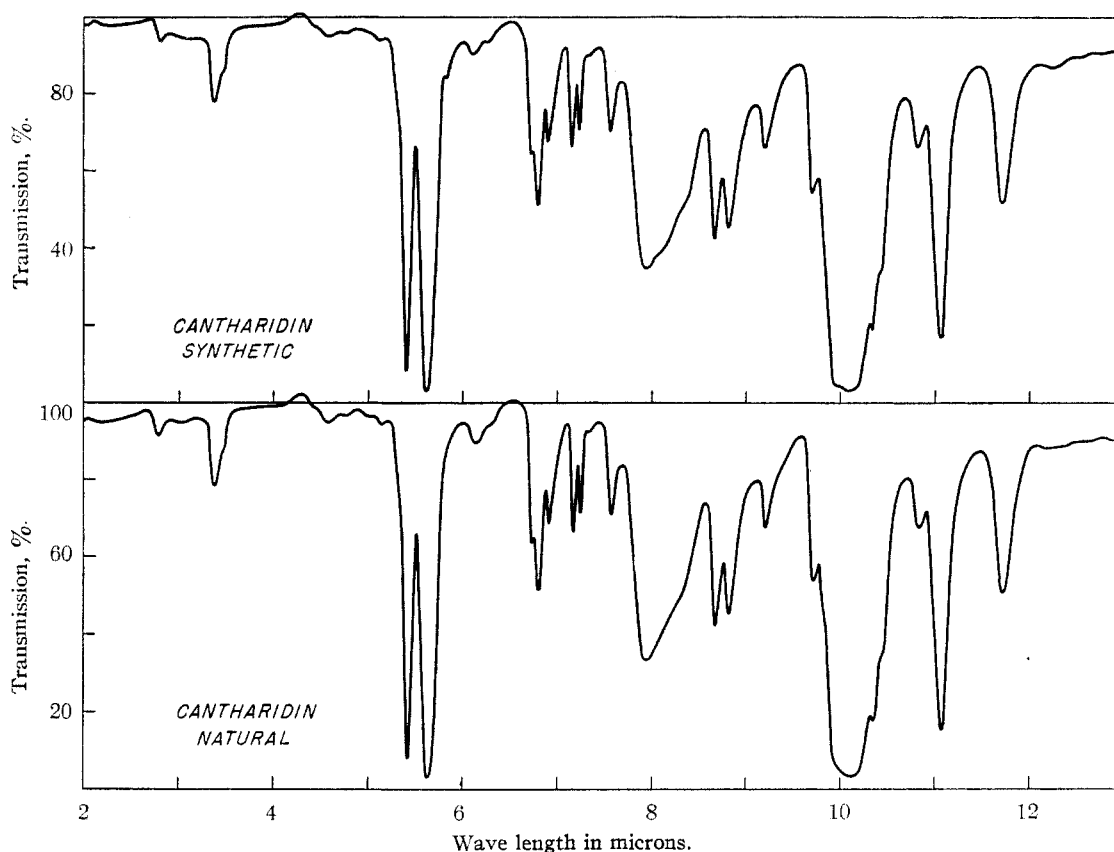
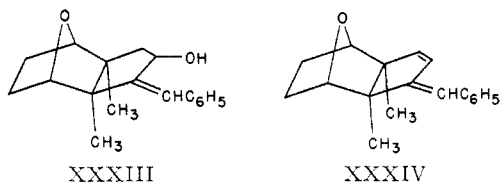


Fig. 1.—Infrared spectra in chloroform.

To that end, the carbinol (XXXII) was subjected to anionotropic rearrangement<sup>28</sup> to the benzylidene-cyclopentanol derivative (XXXIII), one isomer of which was obtained crystalline, m.p. 165–167°,  $\lambda_{\text{max}}^{\text{EtOH}}$  251–252 m $\mu$ ,  $\epsilon_{\text{max}}$  30,500.<sup>29</sup> Pyrolysis of the stearate of crystalline XXXIII gave the desired diene (XXXIV),  $\lambda_{\text{max}}^{\text{EtOH}}$  283 m $\mu$ ,  $\epsilon_{\text{max}}$  22,500.<sup>29</sup> This same diene was also obtained from the stearate of the non-crystalline isomer of XXXIII, so that the total yield of XXXIV from crystalline XXXII was 64%.



Ozonolysis of the diene (XXXIV), followed by decomposition with hydrogen peroxide,<sup>30</sup> gave directly crystalline cantharidin (Ia), m.p. 209–212°, raised by recrystallization to 212–213°. Mixed melting point determination as well as comparison of infrared spectra (Fig. 1) and X-ray powder

(28) Cf. E. A. Braude, E. R. H. Jones and E. S. Stern, *J. Chem. Soc.*, 1087 (1947); also E. A. Braude and W. F. Forbes, *ibid.*, 1755 (1951).

(29) Braude and Forbes<sup>28</sup> give for benzylidenecyclopentanol-2  $\lambda_{\text{max}}^{\text{EtOH}}$  251, 256 m $\mu$ ,  $\epsilon_{\text{max}}$  19,000; and for benzylidenecyclopentene-2  $\lambda_{\text{max}}^{\text{EtOH}}$  288 m $\mu$ ,  $\epsilon_{\text{max}}$  20,300.

(30) This sequence of reactions may constitute a useful degradation of certain cyclohexene systems. The degradation of cyclohexene itself to succinic acid, which served as a model for the degradation of XXXIII to cantharidin, is described in the Experimental section.

diagrams established the identity of our synthetic product with natural cantharidin.

#### Experimental<sup>31</sup>

**Furan-Dimethyl Acetylene Dicarboxylate Adduct (Dimethyl 3,6-Epoxy-3,6-dihydrophthalate).**—Acetylenedicarboxylic acid monopotassium salt, prepared by the method of reference 32, was converted to the corresponding dimethyl ester by the following procedure patterned after the esterification technique of Clinton and Laskowski.<sup>33</sup> A mixture of 15 ml. of concd. sulfuric acid and 5 ml. of 30% fuming sulfuric acid was added cautiously, with cooling, to a solution of 200 ml. of ethylene dichloride and 80 ml. of absolute methanol. Following the addition of 49 g. (0.32 mole) of finely powdered monopotassium acetylenedicarboxylate, the mixture was refluxed for 20 hours. After cooling and washing with water and 5% sodium bicarbonate solution, the organic layer was distilled, giving 30.2 g. (66.5%) of dimethylacetylenedicarboxylate, b.p. 93–97° (15 mm.) (reported b.p. 98° (20 mm.)<sup>34</sup>).

The addition of furan to dimethyl acetylenedicarboxylate was carried out by the following modification of the method of Diels and Olsen.<sup>11</sup> A solution of dimethyl acetylenedicarboxylate (44 g., 0.31 mole) and furan (26 g.) in benzene (50 ml.) was refluxed in a closed system for 14 hours. Distillation furnished 50 g. (77%) of the adduct, b.p. 130–133° (2 mm.) (reported b.p. 130–135° (0.9 mm.)<sup>35</sup>).

(31) Infrared spectra were recorded on a Baird model B spectrophotometer. Ultraviolet absorption data were determined in 95% ethanol solution on a Beckmann quartz spectrophotometer.

(32) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 10.

(33) R. O. Clinton and S. C. Laskowski, *THIS JOURNAL*, **70**, 3135 (1948).

(34) H. Mommaerts, *Bull. soc. chim. Belg.*, **52**, 79 (1943).

(35) In handling this substance it is well to keep in mind the very powerful lachrymatory and vesicatory properties of the esters of acetylenedicarboxylic acid.

(36) Reference 11. These authors, however, were not able to obtain a satisfactory analysis for this substance.

*Anal.* Calcd. for  $C_{10}H_{10}O_8$  (210.18): C, 57.14; H, 4.80. Found: C, 57.06; H, 5.02.

The semi-hydrogenation of this adduct must be performed without delay, as the substance is rapidly decomposed on standing.

**Dimethyl 3,6-Epoxy-3,4,5,6-tetrahydrophthalate (IX).**—A solution of 50 g. (0.24 mole) of freshly distilled furan adduct in 200 ml. of acetone was shaken with 0.3 g. of 10% palladium-charcoal catalyst at room temperature (water cooling) in a Parr hydrogenator. The required amount of hydrogen was absorbed in 20 minutes, and the dihydro adduct (IX) was obtained in 78% yield as large prismatic needles, m.p. 51–51.5°, on crystallization from ligroin (60–90°); the reported m.p. is 52°. <sup>11</sup>

On a larger scale the following procedure was found to be convenient: a solution of 1.0 mole of dimethyl acetylenedicarboxylate and 1.25 mole of furan in 150 ml. of benzene was refluxed for six hours under an atmosphere of nitrogen. At the end of this time most of the excess furan was allowed to distil off by heating on the steam-bath, and the resulting solution immediately reduced catalytically in acetone as described above. The over-all yield of recrystallized dihydro adduct, m.p. 51–51.5°, on this scale was 51%.

**Diene Additions to Dimethyl 3,6-Epoxy-3,4,5,6-tetrahydrophthalate.**—**A. Butadiene.**—Dimethyl 3,6-epoxy-3,4,5,6-tetrahydrophthalate (IX, 39.1 g., 0.185 mole) was added together with 0.2 g. of hydroquinone to a solution of 60 g. of butadiene in 80 ml. of absolute ethanol cooled in an acetone-Dry Ice-bath. The resulting solution was then transferred to an autoclave and heated to 100°. After 24 hours at this temperature, the vessel was opened, and the excess butadiene was removed by heating on the steam-bath. The remaining solution was cooled in ice and the crystalline adduct (X) was collected and washed with cold petroleum ether; yield 42 g. (86%), m.p. 78.5–79°, unchanged after recrystallization from ligroin-ethanol. A further quantity (3 g.) of this same adduct was obtained by concentration of the mother liquors, bringing the total yield of X to 92%.

*Anal.* Calcd. for  $C_{14}H_{18}O_5$  (226.28): C, 63.14; H, 6.81. Found: C, 63.36; H, 6.11.

Hydrolysis of this diester with methanolic KOH, followed by acidification, furnished the corresponding anhydride, m.p. 162°, identical with the product obtained previously by Alder and Backendorf<sup>17</sup> from the reaction of butadiene with 3,6-epoxy-3,4,5,6-tetrahydrophthalic acid.

**B. 2,3-Dimethylbutadiene.**—A solution of 117 g. (0.55 mole) of IX, 87 g. of 2,3-dimethylbutadiene<sup>37</sup> and 0.3 g. of hydroquinone in 150 ml. of 95% ethanol was refluxed on the steam-bath for 55 hours. The reaction mixture was filtered hot after the addition of 50 ml. of petroleum ether. Upon cooling, the dimethyl adduct (Xa) crystallized in a condition of analytical purity, m.p. 95–95.5°, yield 152 g. (94%).

*Anal.* Calcd. for  $C_{16}H_{22}O_5$  (294.34): C, 65.29; H, 7.53. Found: C, 65.53; H, 7.24.

**C. 2,3-Diphenylbutadiene.**—A solution of 1.0 g. (0.0047 mole) of IX, 1.35 g. (0.0065 mole) of 2,3-diphenylbutadiene (prepared by the dehydration<sup>38</sup> of 2,3-diphenyl-2,3-butenediol<sup>39</sup>) and a few crystals of hydroquinone in 5 ml. of benzene was heated in a sealed tube for 24 hours at 100°. After evaporation of the solvent, the diphenyl adduct (Xb) crystallized on the addition of ligroin. Recrystallization from a mixture of ethanol (3 ml.) and 60–90° ligroin (10 ml.) afforded 1.25 g. (63% from IX) of product, m.p. 131–131.5°, raised by recrystallization from 95% ethanol to 132.5–133°.

*Anal.* Calcd. for  $C_{26}H_{26}O_5$  (418.47): C, 74.62; H, 6.26. Found: C, 74.82; H, 6.27.

This adduct is stable to potassium permanganate in acetone solution in the cold. On standing in methanol with acetone-deactivated Raney nickel, the material was recovered unchanged; with fully active catalyst, after one-half hour, the corresponding dihydro compound, m.p. 138–138.5° after recrystallization from ligroin, resulted.

(37) L. P. Kyriakides, *THIS JOURNAL*, **36**, 987 (1914).

(38) A. Mustafa, *ibid.*, **71**, 1878 (1949). In small runs (2–4 g.), yields of 30–35% were obtained by this procedure, while larger batches gave considerably lower yields.

(39) K. Sisido and H. Nozaki, *ibid.*, **70**, 776 (1948).

*Anal.* Calcd. for  $C_{26}H_{26}O_5$  (420.48): C, 74.26; H, 6.71. Found: C, 73.99; H, 6.64.

**Lithium Aluminum Hydride Reduction of the Butadiene Adduct Diester (X) to the Diol (XV).**—A solution of 40 g. of X in 150 ml. of anhydrous ether was treated with 15 g. of lithium aluminum hydride in the usual fashion. After completion of the reduction, crushed ice was cautiously added until the vigorous reaction had ceased, followed by the addition of a cold solution of 40 ml. of concd. sulfuric acid in 200 ml. of water, with thorough stirring. The diol (XV), which formed a solid, curdy layer at the water-ether interface, was collected by filtration and dried at 100°. The crude diol product thus obtained in 80–85% yield is sufficiently pure for conversion to the dimesylate (next section). Crystallization from absolute alcohol-benzene gave small needles, m.p. 154–154.5°.

*Anal.* Calcd. for  $C_{12}H_{18}O_3$  (210.36): C, 68.54; H, 8.63. Found: C, 68.68; H, 8.60.

The dimethyl adduct (Xa), when reduced in the same manner, similarly afforded 64% of the corresponding diol (XVa), which had m.p. 188–190° after recrystallization from methanol.

*Anal.* Calcd. for  $C_{14}H_{22}O_3$  (238.32): C, 70.55; H, 9.31. Found: C, 70.64; H, 9.80.

The reduction of the diphenyl adduct (Xb) was performed in tetrahydrofuran solution, and the product, diol (XVb), was isolated by ether extraction of the hydrolyzed reaction mixture in 95% yield, m.p. 229–230° (cor.) after recrystallization from pyridine-ethanol.

*Anal.* Calcd. for  $C_{24}H_{28}O_3$  (362.45): C, 79.53; H, 7.23. Found: C, 79.32; H, 7.32.

**Conversion of the Adduct Diol (XV) to the Dimesylate (XVI).**—The diol (XV, m.p. 152–154°, 19.7 g.) was dissolved, with heating, in 75 ml. of dry pyridine and an equal volume of dry benzene. To this solution, after rapid cooling to 5°, a freshly prepared mixture of methanesulfonyl chloride<sup>40</sup> (35 g.) and pyridine (30 ml.), chilled to 0°, was added in several portions, with stirring, while the temperature was maintained below 10°. After standing six hours at 5°, the yellowish mixture was poured onto an excess of crushed ice and water, and the product recovered by extraction with chloroform (three 500-ml. portions), followed successively by washing with dilute acid, sodium bicarbonate solution and water, and finally drying over magnesium sulfate. Upon removal of the solvent and recrystallization of the residue from benzene-ethanol, 30.8 g. (90%) of colorless product, m.p. 152–154° (slow dec.), was obtained. Recrystallization from ethanol furnished a pure sample as fine prisms, m.p. 154–154.5° (slow dec.).

*Anal.* Calcd. for  $C_{14}H_{22}O_7S_2$  (366.44): C, 45.88; H, 6.05. Found: C, 45.98; H, 5.76.

In the same manner the dimethyl diol (XVa) was converted to its dimesylate (XVIa) in 73% yield, m.p. 168° (dec.) after recrystallization from ethanol.

*Anal.* Calcd. for  $C_{16}H_{26}O_7S_2$  (394.39): C, 48.72; H, 6.62. Found: C, 48.41; H, 6.58.

Similarly, the diphenyl diol (XVb) gave a quantitative yield of the corresponding dimesylate (XVIb) m.p. 187–189°, after recrystallization from pyridine-ethanol.

*Anal.* Calcd. for  $C_{26}H_{30}O_7S_2$  (518.62): C, 60.21; H, 5.83. Found: C, 60.77; H, 5.88.

**Attempted Preparation of the Cyclic Sulfide (XVII) and Related Experiments.**—A solution of 30 g. (0.082 mole) of the dimesylate XVI (m.p. 152–154°) and 27 g. of sodium sulfide nonahydrate in 300 ml. of ethanol was refluxed on the steam-bath for three days. After cooling and removal of the sodium methanesulfonate deposit, the solution was concentrated *in vacuo* and the residue taken up in ether. The ether layer was washed several times with water and the product recovered by distillation, giving 9.2 g. (ca. 50%) of a material boiling over the range 115–130° (0.4 mm.). This fraction did not, however, give a satisfactory analysis for the cyclic sulfide (XVII). *Anal.* Calcd. for  $C_{12}H_{16}OS$  (208.31): C, 69.21; H, 7.74. Found: C, 69.68; H, 7.59. The slightly high carbon value was apparently due to the presence of some of the corresponding cyclic oxide (XVIII), as was made evident by the fact that Raney nickel de-

(40) C. R. Noller and P. J. Hearst, *ibid.*, **70**, 3955 (1948); *cf. Org. Syntheses*, **30**, 58 (1950).

sulfurization of the impure sulfide with an active catalyst did not afford the epoxy-9,10-dimethyldecalin, but a crystalline product, m.p. 43–46°, whose low (1.4%) carbon analysis indicated the presence of the **dihydro derivative** of the cyclic oxide (XVIII). *Anal.* Calcd. for  $C_{12}H_{20}O$  (180.28): C, 79.94; H, 11.18. Found: C, 78.53; H, 10.87. Final confirmation for this conclusion was obtained by the isolation (through fractional sublimation of the desulfurization product) of the pure dihydro cyclic oxide, m.p. 80–81°, identical with the dihydro derivative of the pure cyclic oxide prepared as described below.

*Anal.* Calcd. for  $C_{12}H_{18}O_2$  (194.26): C, 74.19; H, 9.34. Found: C, 74.05; H, 9.28.

The cyclic oxide (XVIII), formed as a by-product in the above reaction with sodium sulfide, can be prepared in high yield in the following way: A solution of 12.5 g. of the dimesylate (XVI) in 90 ml. of tetrahydrofuran is stirred into a solution of 3.5 g. of lithium aluminum hydride in 20 ml. of the same solvent. After refluxing for 4 hours, the reaction mixture is decomposed with cold aqueous sulfuric acid and extracted with ether. The crude material obtained after removal of the solvent is then sublimed at 100° (0.1 mm.), giving 5.5 g. (83%) of colorless crystals, m.p. 45.5–46°.

*Anal.* Calcd. for  $C_{12}H_{16}O_2$  (192.25): C, 74.97; H, 8.39. Found: C, 75.11; H, 8.59.

This same compound can also be prepared, though in lower yield, by treatment of the diol (XV) with exactly one mole of methanesulfonyl chloride in pyridine at room temperature for eight hours.

In the dimethyl adduct series, reaction of the **dimethyl dimesylate (XVIIa)** with sodium sulfide produced an impure **cyclic sulfide (XVIIa)**, m.p. 71–72.5° after recrystallization from nitromethane, which also gave an unsatisfactory analysis (*Anal.* Calcd. for  $C_{14}H_{20}OS$  (236.36): C, 71.15; H, 8.53. Found: C, 71.87; H, 8.48). This again appeared to be contaminated with the corresponding cyclic oxide, as an acceptable C–H analysis was also not obtained after desulfurization with freshly prepared W-4 Raney nickel,<sup>41</sup> although the product again was nicely crystalline, m.p. 81–84°. Since the material decolorized potassium permanganate in acetone at the same rate as the dicarbomethoxy adduct (Xa), the olefinic linkage had, as expected, survived the desulfurization. Further experiments in this series, however, were discontinued after it was found that treatment of this dimethylcyclohexene with N-bromosuccinimide, followed by collidine dehydrobromination, led to a substance which appeared to be a methylenecyclohexene (XXI) ( $\lambda_{\max}^{EIOH}$  243 m $\mu$ , log 4.4) rather than the desired dimethylcyclohexadiene (XXII), which, conceivably, might in part have been oxidizable to cantharidin (see, however, experiments in the cyclic oxide series described later). Attempts to rearrange this diene with acid to the homoannular isomer resulted only in recovery of starting material.

In the diphenyl adduct series the preparation of the cyclic sulfide afforded a product which, in contrast to the above, appeared to be largely the homogeneous **diphenyl cyclic sulfide (XVIIb)**, m.p. 155–156° after recrystallization from ethanol, yield 45%.

*Anal.* Calcd. for  $C_{24}H_{24}OS$  (360.49): C, 79.96; H, 6.71. Found: C, 80.42; H, 6.53.

This material could not, however, be completely desulfurized using acetone-deactivated Raney nickel, while saturation of the cyclohexene double bond could not be prevented with a fully active catalyst (*cf.* reduction of the diphenyl adduct itself (Xb) with Raney nickel at room temperature described above). Oxidation of this diphenyl cyclic sulfide (XVIIb) with ozone in chloroform solution, followed by treatment with zinc dust in acetic acid, gave an oily product, which, on titration with ethanol, furnished, in 12% yield, the corresponding **dibenzoyl cyclic sulfone (XXIII)**, m.p. 232–233° (*cor.*). The infrared spectrum of this substance exhibited intense absorption at 5.9  $\mu$  and at 7.6 and 8.9  $\mu$ , characteristic, respectively, of the carbonyl and sulfone groups.

*Anal.* Calcd. for  $C_{24}H_{24}O_3S$  (424.49): C, 67.90; H, 5.70. Found: C, 67.19; H, 5.65.

**Sequence to Cantharidin.** A. *exo*-5,8-Epoxy-9,10-**cis**-dimethylthioethyloctalin-2 (XIX).—To a solution of an-

hydrous potassium *t*-butoxide (30 g., 0.77 g. at., of metallic potassium dissolved in 600 ml. of anhydrous *t*-butyl alcohol) an excess of ethyl mercaptan (55 g., 0.89 mole) was added with cooling in the hood. When the slight reaction produced by this operation had subsided, 30.3 g. (0.0825 mole) of the dimesylate (XVI), m.p. 152–154.5°, dissolved in 150 ml. of dry benzene, was added in one portion, and the reaction mixture heated to gentle reflux, with stirring. In the course of a few hours the initial yellow color disappeared, and the solution gradually acquired a nearly colorless gelatinous condition. After three days the reaction mixture was worked up by pouring into ice-water and the neutral product was recovered by ether extraction. Distillation of this material afforded two fractions:

(A) B.p. 80–115° (mostly 108–112°) at 0.5 mm., identified as the **cyclic oxide (XVIII)**, which crystallized readily from petroleum ether as large prisms, m.p. 44–45.5°, total yield 7.0 g. (46.5%). Reduction with Raney nickel afforded the dihydro cyclic oxide described above (m.p. and mixed m.p. 80–82°) in high yield.

(B) B.p. 125–170° (mostly 160–165°) at 0.3 mm., identified as the desired **dithioethyl compound (XIX)**, which crystallized completely on standing; yield 11.6 g. (47%). On dissolving in a small amount of petroleum ether and cooling to 0°, this material crystallized as colorless, flat needles, m.p. 45–45.5°.

*Anal.* Calcd. for  $C_{16}H_{26}OS_2$  (298.49): C, 64.39; H, 8.77. Found: C, 64.35; H, 9.01.

B. *exo*-5,8-Epoxy-9,10-**cis**-dimethyl-2,3-dihydroxydecalin (XXV).—Hydroxylation of the olefinic linkage in XIX (10.5 g., 0.0352 mole, from the fraction (B) above) with osmium tetroxide (9.0 g., 0.0352 mole) in anhydrous ether (250 ml.) containing a catalytic amount of pyridine (2.5 ml.) was allowed to proceed over three days in the dark at room temperature. Reduction of the deep brown osmate ester with aqueous alcoholic sodium sulfite<sup>42</sup> gave, after concentration of the alcoholic filtrates and extraction with chloroform, the desired **dithioethyl glycol (XXIV)** as a viscous tan oil.

For the reductive desulfurization to XXV, 10 g. of this crude dithioethyl glycol was dissolved in 200 ml. of 95% ethanol and stirred at reflux with 120 g. of W-6 Raney nickel<sup>43</sup> under nitrogen<sup>44</sup> for one hour. After cooling and filtration from the catalyst, removal of the solvent *in vacuo* on the steam-bath, and, finally, distillation of the colorless residue, 5.0 g. of the **dimethyl glycol (XXV)**, b.p. (bath temp.) 170–175° (0.3 mm.), was obtained. This on crystallization from 25 ml. of benzene-cyclohexane (1:1) furnished 4.80 g. (75%, or 68% from XIX) of small, colorless, jagged prisms, having a characteristic camphoraceous odor and melting at 104–106°. The analytical sample was crystallized from the same solvent pair to constant m.p. of 107–109°.

*Anal.* Calcd. for  $C_{12}H_{20}O_3$  (212.28): C, 67.89; H, 9.50. Found: C, 68.13; H, 9.51.

C. *exo*-1-Formyl-4,7-epoxy-8,9-**cis**-dimethyl-4,5,6,7,8,9-hexahydroindene (XXX).—To a solution of 4.50 g. (0.0212 mole) of the above dimethyl glycol (XXV), m.p. 104–106°, in 60 ml. of pure dioxane cooled to 10°, 4.90 g. (0.0216 mole) of periodic acid ( $HIO_4 \cdot 2H_2O$ ) dissolved in a minimum amount of water (*ca.* 15 ml.) was added in one portion with stirring. Immediately following there occurred a copious deposit of iodic acid, accompanied by slight warming. After standing for eight hours at room temperature, the colorless reaction mixture was diluted with 150 ml. of water and aqueous sodium chloride, neutralized with sodium bicarbonate solution, and the product recovered by extraction with chloroform in six 75-ml. portions. The infrared spectrum of the dialdehyde (XXIX) obtained by removal of the solvent (after drying) on the steam-bath under reduced pressure showed the expected saturated carbonyl band at 5.78  $\mu$ .

The following procedure, patterned after the general method of Kuhn and collaborators,<sup>45</sup> was found to be

(42) *Cf. inter alia*, L. H. Sarett, *ibid.*, **70**, 1690 (1948); **71**, 2443 (1949).

(43) *Org. Syntheses*, **29**, 24 (1949).

(44) Without this expedient, considerable carbonyl-bearing material was produced in this step, presumably the result of catalyzed aerial oxidation.

(45) R. Kuhn, W. Badstübner and C. Grundmann, *Ber.*, **69**, 98 (1936), and later papers. *Cf.* also R. B. Woodward, *et al.*, *This Journal*, **74**, 4223 (1952).

(41) H. Adkins and A. A. Pavlic, *This Journal*, **69**, 3039 (1947).



superior to the previously reported<sup>16</sup> cyclization of the dialdehyde to the cyclopentenealdehyde (XXX) with aqueous dioxane at elevated temperatures. To 100 ml. of a benzene solution of the total dialdehyde (XXIX) obtained above was added, with stirring under nitrogen, 2 ml. of 20% piperidine acetate in benzene. The solution became cloudy within a few seconds and water gradually collected on the sides of the flask. When the reaction mixture was heated to 60–70° for one hour, a reddish-tan color developed and the reaction appeared to be essentially complete (5.78  $\mu$  band in the infrared spectrum replaced after this time with the conjugated carbonyl band at 5.93  $\mu$ ). After washing the benzene layer with dilute acid, sodium bicarbonate solution, water, drying over magnesium sulfate, and, finally, removal of the solvent, there was obtained, on distillation of the residue, 3.05 g. (75%) of the cyclopentenealdehyde (XXX), b.p. (bath temp.) 110–115° (0.2 mm.), which crystallized as distilled to a nearly colorless, pleasant smelling mass, m.p. 74–77°. Redistillation, accompanied by considerable sublimation, raised this m.p. to 75–77°, b.p. (bath temp.) 110–113° (0.2 mm.). The ultraviolet absorption spectrum of this product had  $\lambda_{\text{max}}^{\text{EtOH}}$  237–238 m $\mu$ ,  $\epsilon_{\text{max}}$  14,600.<sup>26</sup>

The aldehyde was characterized as its phenylhydrazone, crystallizing from ethanol as orange prisms, m.p. 190–192°.

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{12}\text{O}_2$  (282.37): C, 76.56; H, 7.85. Found: C, 76.24; H, 8.10.

**D. *exo*-4,7-Epoxy-8,9-*cis*-dimethyl-4,5,6,7,8,9-hexahydroindenyl-1-phenylcarbinol (XXXII).**—To a solution of excess phenyllithium (0.04 mole) in 200 ml. of ether cooled to 0°, 2.70 g. (0.0140 mole) of the above cyclopentenealdehyde (XXX, m.p. 75–77°) dissolved in 25 ml. of anhydrous ether was added, under nitrogen, with efficient stirring, over a ten-minute period. After one hour the reaction mixture was allowed to come to room temperature for an additional two hours. It was then poured onto crushed ice and the ether layer separated, washed with a saturated sodium chloride solution and dried over magnesium sulfate. Upon removal of the solvent, the residue gradually became crystalline (m.p. 95–103°). Recrystallization from benzene-petroleum ether afforded 2.75 g. (72.5%) of XXXII as colorless needle clusters or platelets, m.p. 104.5–105.5°; concentration of the mother liquors yielded no further crystalline material. The infrared spectrum of the crude product contained no bands in the carbonyl region; the ultraviolet absorption of the crystalline fraction had  $\lambda_{\text{max}}^{\text{EtOH}}$  253 and 259 m $\mu$ , with  $\epsilon_{\text{max}}$  170 and 210, respectively; for comparison to similar compounds, cf. ref. 28.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{20}\text{O}_2$  (270.36): C, 79.96; H, 8.20. Found: C, 80.25; H, 8.49.

**E. *exo*-2-Hydroxybenzylidene-4,7-epoxy-8,9-*cis*-dimethyl-4,6,7,8,9-hexahydroindane (XXXIII).**—Both the crystalline carbinol from the above section (XXXII, 2.60 g., m.p. 104–105.5°) and the non-crystalline mother liquor material were subjected (separately) to anionotropic rearrangement in aqueous dioxane according to the directions of Braude and his collaborators.<sup>28</sup> The direct product obtained on working up the former crystallized in part after scratching under petroleum ether: yield 0.70 g. (27%), m.p. 149–153°. On recrystallization from benzene-petroleum ether, this material formed shiny plates, m.p. 165–167° (softening at 155°). Its ultraviolet absorption had  $\lambda_{\text{max}}^{\text{EtOH}}$  251–252 m $\mu$ ,  $\epsilon_{\text{max}}$  30,500.<sup>29,46</sup>

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{20}\text{O}_2$  (270.36): C, 79.96; H, 8.20. Found: C, 80.13; H, 8.047.

The product remaining in the mother liquors from the above crystalline isomer could not be induced to crystallize further; its infrared spectrum, and also its ultraviolet absorption ( $\lambda_{\text{max}}^{\text{EtOH}}$  251–252 m $\mu$ ,  $\epsilon_{\text{max}}$  ca. 22,000), indicated that it was probably a stereoisomeric modification of the crystalline material (cf. data and comments on the corresponding stearates and pyrolysis products below). The product from the rearrangement of the non-crystalline mother liquor carbinol (XXXII) afforded an additional 50 mg. of the crystalline isomer (XXXIII), m.p. 149–151°; the remaining fraction did not crystallize ( $\lambda_{\text{max}}^{\text{EtOH}}$  251–252 m $\mu$ ,  $\epsilon_{\text{max}}$  ca. 15,000).

(46) The molecular extinction coefficient normally associated with a styrene chromophore of this type is around 20,000 (cf. ref. 28); what feature in the present instance gives rise to the abnormally high intensity observed is not clear.

**F. *exo*-1-Benzylidene-4,7-epoxy-8,9-*cis*-dimethyl-4,5,6,7,8,9-hexahydroindene (XXXIV).**—Esterification of the three benzylidenecyclopentanol fractions from the preceding section (A, 0.60 g. of the crystalline isomer (XXXIII), m.p. 149–153°; B, 1.95 g. of the liquid material from the mother liquors of the crystalline isomer; and C, ca. 1.0 g. of the liquid product obtained from the anionotropic rearrangement of the non-crystalline carbinol (XXXII) was conducted by means of the appropriate equivalent of stearoyl chloride in excess pyridine-benzene (1:2) at room temperature for 12 hours. The infrared spectra of the neutral products obtained exhibited only slight absorption in the 2.7–3.0  $\mu$  region (–OH absent), and had the typical ester carbonyl absorption at 5.78  $\mu$ ; the spectra of the products from fractions A and B appeared to be identical. No attempt was made to crystallize or purify these stearate esters.

On heating each of these samples to 275–340° (salt-bath temperature), thermal decomposition to the desired diene (XXXIV) proceeded smoothly, with the product and stearic acid co-distilling under reduced pressure (25–35 mm.) as formed. The stearic acid was removed from the distillates by extraction from ether with 5% aqueous KOH, and the dried neutral portions were then purified by eluting from a 30-fold excess of activated (basic) alumina with petroleum ether-benzene (3:1) until only trace amounts of material were collected. Infrared comparison of the products thus obtained from the first two samples (A and B above) revealed them to be identical. Accordingly, they were combined and distilled *in vacuo* to give the diene (XXXIV), b.p. (bath temp.) 145–150° (0.5 mm.), yield 1.51 g. (63.5%) of viscous, pale yellow oil ( $\lambda_{\text{max}}^{\text{EtOH}}$  283 m $\mu$ ,  $\epsilon_{\text{max}}$  22,500<sup>29</sup>). A sample after redistillation for analysis, (b.p. (bath temp.) 148–150° (0.5 mm.),  $n_D^{25}$  1.5932) still gave low carbon values.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{20}\text{O}$  (252.34): C, 85.67; H, 7.99. Found: C, 84.27; H, 8.44.

From the distillation of the product from the third sample (C above) 0.48 g. (52%) of what appeared to be largely the same diene was obtained ( $\lambda_{\text{max}}^{\text{EtOH}}$  283 m $\mu$ ,  $\epsilon_{\text{max}}$  21,500).

**G. *exo*-1,2-*cis*-Dimethyl-3,6-epoxy-hexahydrophthalic anhydride (Cantharidin, Ia).**—A slow stream of ozone (ca. 7–10 mmole/hr.) was passed through a solution of the above diene (XXXIV, 1.60 g., 6.35 mmoles) in 25 ml. of ethyl acetate at –40 to –50° until no more was consumed (1.25 hour). After removal of the solvent under reduced pressure at 30–40°, the colorless, glassy residue was taken up in 15 ml. of aqueous acetic acid, together with an equal volume of 20% aqueous hydrogen peroxide, and the resulting solution was refluxed vigorously for three hours. The mixture was then diluted with water to a volume of 75 ml. and the neutral material recovered by extraction with chloroform (sodium bicarbonate wash). After drying (magnesium sulfate) and evaporation of the solvent under reduced pressure, the product crystallized readily on trituration with a few ml. of ether. The m.p. of the crude cantharidin (Ia) thus obtained was 209–212°; on recrystallization from acetone it melted at 212–213° (uncor.), alone or mixed with an authentic sample.<sup>47</sup> The yield of pure product was 195 mg. (16% from the diene), plus an additional 90 mg. obtained from the mother liquors after redigestion with basic hydrogen peroxide (total yield 23%).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_4$  (196.20): C, 61.21; H, 6.17. Found: C, 61.49; H, 6.43.

The identity of this synthetic cantharidin was further established by comparison of its infrared spectrum and X-ray powder diffraction pattern<sup>48</sup> with those of natural cantharidin, (cf. Fig. 1).

**Model Degradation. Succinic Acid from Cyclopentene-1-aldehyde.**—This aldehyde, b.p. 51.5–52° (20 mm.), prepared from *trans*-1,2-cyclohexanediol according to the directions of Brown, Henbest and Jones,<sup>49</sup> was added slowly, with stirring, to an excess of phenyllithium in ether at 0° under nitrogen. After the reaction mixture had been allowed to warm up to room temperature for several hours, it was

(47) British Drug House "Cantharidinum."

(48) We are grateful to Prof. Clifford Frondel and his staff of the Harvard Department of Mineralogy for performing this determination.

(49) Reference 25; cf. also J. English, Jr., and G. W. Barber, *THIS JOURNAL*, **71**, 3310 (1949).



poured into crushed ice and the product recovered by ether extraction. The infrared spectrum had strong absorption in the -OH region ( $2.8 \mu$ ) and was entirely devoid of bands in the carbonyl region (absence of 1,4-addition).

On a preparative scale the dehydration of this carbinol to benzylidenecyclopentene-2, m.p.  $46-48^\circ$ ,<sup>28</sup> by distillation over potassium bisulfate in a manner similar to that described subsequently by Braude and Forbes,<sup>30</sup> proved to be the most satisfactory and convenient method: yield 60-65%. Also examined but found unsatisfactory (poor yields) were dehydration attempts using thionyl chloride and also phosphorus oxychloride in pyridine and in triethylamine. Ozonization of this diene (1.40 g., 9.0 mmoles) in ethyl acetate (25 ml.) at  $-50$  to  $-60^\circ$  or at  $-10$  to  $15^\circ$ , followed by decomposition of the resulting ozonide with aqueous hydrogen peroxide (15-20% solution), gave, as the direct crystalline acidic product, succinic acid (0.43 g., 40%), m.p.  $180-183^\circ$ , undepressed on admixture with an authentic sample (m.p.  $184-186^\circ$ ).

As an alternative procedure, dehydration of the above carbinol subsequent to anionotropic rearrangement,<sup>28</sup> was also investigated in some detail. Conversion of the rearranged carbinol, benzylidenecyclopentanol-2<sup>28</sup> to its acetate, benzoate, xanthate and stearate esters was conducted according to standard procedures. Pyrolytic decomposition of the first three of these derivatives, although yielding varying amounts of the desired diene, benzylidenecyclopentene-2, gave it in only rather poor yields. Thermal decomposition of the stearate, however, proceeded smoothly on heating to  $230-270^\circ$  (25 mm.) to give this diene, m.p.  $45-48^\circ$ , in fair yield (30%) after purification by redistillation.

**Experiments in the Cyclic Oxide Series. A. Preparation of the Cyclic Oxide Diene (XXVIII) via NBS.**—A solution of 0.4 g. of the cyclic oxide (XVIII), m.p.  $44-46^\circ$ , 0.4 g. of N-bromosuccinimide and 40 mg. of benzoyl peroxide in 10 ml. of dry carbon tetrachloride was refluxed for 30 minutes. After filtration of the succinimide and removal of the solvent, the remaining oil was refluxed for 15 minutes with 5 ml. of dry 2,4,6-collidine. Addition of ether, followed by washing with dilute hydrochloric acid and sodium bicarbonate solution, and, finally, removal of the solvent gave a product which crystallized on cooling. The solid was recrystallized from petroleum ether and further purified by vacuum sublimation at  $100^\circ$  to give XXVIII, m.p.  $107-108^\circ$ , yield 90 mg. (23%). The ultraviolet absorption spectrum showed the expected broad peak with  $\lambda_{\max}^{\text{EtOH}}$   $254 \text{ m}\mu$  ( $\log \epsilon$  3.8) and  $264 \text{ m}\mu$  (3.8).

(50) Reference 18. These authors prepared the cyclopentenyl-phenylcarbinol by the action of cyclopentenyllithium on benzaldehyde.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_2$  (190.23): C, 75.76; H, 7.42. Found: C, 76.16; H, 7.70.

**B. 1,3-Cyclohexadiene from cis-1,2-Cyclohexanediol.**—This experiment served as a model for an alternative synthesis of the above diene (XXVIII). *cis*-1,2-Cyclohexanediol<sup>51</sup> was converted to its distearate by the general method of Smith and Rouault.<sup>52</sup> This was then heated to  $360^\circ$  for 1.5 hour. The distillate, which was collected in an ice-cooled receiver, was treated with the appropriate amount of maleic anhydride in benzene at room temperature to give the cyclohexadienemaleic anhydride adduct in 42% yield from the diol. It melted at  $146-146.5^\circ$  (reported m.p.  $147^\circ$ ).<sup>53</sup>

**C. cis- and trans-Glycols from the Cyclic Oxide (XVIII).**—The preparation of the *cis*-cyclic oxide glycol in 54% yield was performed as described above in the case of the dithioethyl compound (XXIV, Sequence to Cantharidin, B). Recrystallization of the crude diol from chloroform gave the pure substance, m.p.  $169-171^\circ$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_4$  (226.26): C, 63.70; H, 8.02. Found: C, 64.06; H, 8.05.

The corresponding *trans*-glycol was produced when the cyclic oxide (XVIII) was hydroxylated with formic acid-hydrogen peroxide,<sup>54</sup> followed by hydrolysis with methanolic potassium hydroxide. It had m.p.  $147-149^\circ$  after recrystallization from chloroform-benzene.

*Anal.* Calcd. as above. Found: C, 63.28; H, 8.00.

Pyrolysis of the distearate of the above *cis*-glycol, m.p.  $169-171^\circ$ , was performed as described above in the preparation of 1,3-cyclohexadiene. The diene obtained was identical with the product (XXVIII) produced in the N-bromosuccinimide sequence described above.

Cleavage of 0.3 g. of this *cis*-glycol with lead tetraacetate (0.7 g.) in chloroform in the presence of potassium carbonate (0.25 g.) afforded the corresponding dialdehyde (carbonyl absorption at  $5.78 \mu$ ), which was cyclized to the cyclic oxide cyclopentenaldehyde analog of XXX (carbonyl at  $5.93 \mu$ ) in aqueous solution under nitrogen at  $100^\circ$  for 50 hours. For lack of sufficient material no further studies were made with this product; it was characterized as its bright orange 2,4-dinitrophenylhydrazine, m.p.  $265^\circ$  (dec.).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}_6\text{N}_4$  (386.36): C, 55.95; H, 4.70; N, 14.50. Found: C, 56.38; H, 5.22; N, 14.49.

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(51) W. Markownikoff, *Ann.*, **302**, 21 (1898); cf. G. Wagner, *Ber.*, **21**, 1230 (1888).

(52) L. I. Smith and G. F. Rouault, *This Journal*, **65**, 745 (1943).

(53) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

(54) Cf. *Org. Syntheses*, **28**, 35 (1948); also ref. 25.