

This material gave a yellow 2,4-dinitrophenylhydrazone, m.p. 89–89.5° (ethanol) and a semicarbazone, m.p. 91–92° (ethanol).

From the above constants and derivatives it is believed that the above material is DL-dihydrocitronellal (VI) contaminated with some citral.

The literature<sup>11</sup> reports for VI, b.p. 81° (12 mm.),  $n_D^{20}$  1.4257,  $d_4^{20}$  0.8253, 2,4-dinitrophenylhydrazone, m.p. 93.5°, semicarbazone, m.p. 91–92°.

*Wolff-Kishner reduction of DL-hydroxycitronellal.* Hydrazine hydrate (85%; 44 g., 0.76 mole) was added in 1 hr. to a solution of DL-hydroxycitronellal (43 g., 0.25 mole) in diethylene glycol (200 ml.). The temperature rose to 52° during the addition. Potassium hydroxide (15 g., 0.27 mole) was added and the temperature slowly raised so that 45 g. of azeotrope (33 g. of water) b.p. 105–115° was collected over 2 hr. Water (200 ml.) was added to the residue in the flask. The organic layer was separated and the water layer was washed with benzene (75 ml., twice). The combined organic layers

(including that from the azeotrope) were distilled through a 6-in. packed column. There was obtained 29.7 g. (75.2%) of DL-2,6-dimethyl-2-octanol (IV), b.p. 69.0–69.5° (4.0 mm.),  $n_D^{20}$  1.4338,  $d_4^{20}$  0.8275. Authentic<sup>6</sup> IV has a b.p. 75–76° (7.0 mm.),  $n_D^{20}$  1.4336,  $d_4^{20}$  0.8273.

The infrared spectrum of the above alcohol was identical with the known 2,6-dimethyl-2-octanol.

This gave a phenylurethane, m.p. 84.8–85.2° which failed to depress the melting point of the phenylurethane obtained from an authentic sample<sup>6</sup> of DL-2,6-dimethyl-2-octanol.

*Acknowledgment.* The author wishes to express his appreciation to Prof. Harry Wasserman of Yale University and Mr. Irwin Sommer of our analytical department for valuable assistance during this work.

EAST RUTHERFORD, N. J.

[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJYU UNIVERSITY]

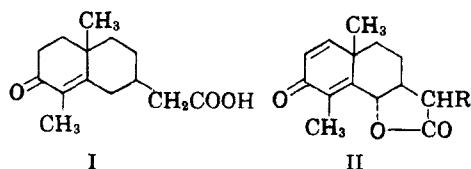
## Santonin and Related Compounds. XV.<sup>1</sup> Preparation of *trans*- and *cis*-4,9-Dimethyl- $\Delta^4$ -3-octalol-6-acetic Acids<sup>2</sup>

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The Michael addition of diethyl malonate to 3-keto-4,9-dimethyl- $\Delta^{4,5}$ -hexahydronaphthalene (III) with sodium *tert*-butoxide gave two stereoisomers of the adduct (IV). The relative yield of these isomers depended on the conditions employed. One isomer, which was predominantly obtained on prolonged reaction at room temperature, may be assigned the *trans*-structure (IVA) with the malonate side chain at an axial position. Another isomer, formed chiefly under more severe conditions, must possess the *cis*-structure (IVB). Hydrolysis and decarboxylation of each isomer of the substituted malonate (IV) gave, respectively, the corresponding monoacid (IA or IB) through the diacid (V). The formation of two isomers on Michael addition does not conform to the earlier belief. From this view, the Michael reactions in the same or closely related systems reported previously were examined. It was reported that addition of diethyl methylmalonate to III under similar conditions gave exclusively the stable *cis*-adduct even at room temperature. An alternative route to the monoacid (I) involved the Robinson reaction of 4-methylcyclohexan-3-one-1-acetate (VIII, R=CH<sub>3</sub>) with the Mannich base (VII), giving chiefly the ester of the *trans*-acid (IA). This aspect of the stereochemistry agrees with the earlier postulates. A possible mechanism is offered for explanation of the steric course of Robinson reactions of this type.

From the viewpoint of stereochemical research on the  $\alpha$ -propionic acid side chain of the lactone in the santonin molecule (II, R = CH<sub>3</sub>), it was desirable to prepare, as a model compound, 4,9-dimethyl- $\Delta^4$ -3-octalol-6-acetic acid (I) in a state of stereochemical purity. This acid, moreover, will represent a useful intermediate for the synthesis of a simple santonin analog such as II



(R = H). Since this work was initiated, certain papers<sup>3–6</sup> have appeared in which the same ground

is covered. Abe, *et al.*<sup>7</sup> announced the total synthesis of natural santonins and of their stereoisomers, which provided the basis for discussion of configuration at the asymmetric centers in santonin (II, R = CH<sub>3</sub>).

A route to the acid (I) involving the reaction sequence III → IV → V was first disclosed by Matsui, *et al.*<sup>3</sup> The Michael addition of diethyl malonate to the  $\Delta^{4,5}$ -dienone (III) was effected at relatively low temperature, and a semisolid product (IV) on hydrolysis was said to give two acids (V), a solid and a liquid, which were each decarboxylated

(4) F. J. McQuillin, *Chem. & Ind. (London)*, 311 (1954).

(5) T. Miki, *J. Pharm. Soc. Japan*, **75**, 395 (1955).

(6) F. D. Gunstone and A. P. Tulloch, *J. Chem. Soc.*, 1130 (1955).

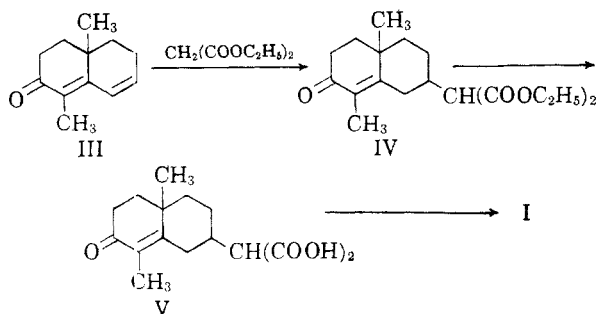
(7) (a) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **75**, 2567 (1953). (b) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1416 (1956). (c) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956). *Cf.*, reference 3 and J. K. Chakrabarti, P. Dutt, and P. C. Dutta, *J. Chem. Soc.*, 4978 (1956).

(1) Paper XIV, R. Futaki, *J. Org. Chem.*, **23**, 451 (1958).

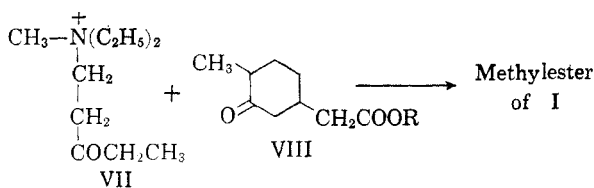
(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

(3) M. Matsui, K. Toki, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Chem. Soc. Japan*, **27**, 7 (1954).

to the corresponding monoacid (I). Almost at the same time, McQuillin<sup>4</sup> mentioned that the same



reaction at a relatively high temperature furnished an oily adduct (IV), which was characterized as its 2,4-dinitrophenylhydrazone. Soon after, Miki<sup>5</sup> reported the isolation of one isomer of the adduct (IV) in crystalline form on prolonged reaction at ordinary temperature. A diacid (V) and monoacid (I), derived from the solid adduct, show melting points different from those of the corresponding compounds reported by Matsui, *et al.*<sup>3</sup> (Table I). Simultaneously, Gunstone and Tulloch<sup>6</sup> published an alternative route to the acid (I) through the Robinson condensation of 1-diethylaminopentan-3-one methiodide (VII) with the cyclohexanone-acetate (VIII, R = CH<sub>3</sub>), followed by hydrolysis of the resulting monoester. The melting point of the acid so obtained is the same as that of one of the acids of Matsui, *et al.*<sup>3</sup> (Table I).



The compounds reported in the previous papers have as yet not been correlated. No information has been recorded concerning the configuration of these compounds, except an equatorial assignment by Miki<sup>5</sup> to the malonate side chain in his solid adduct (IV). The present paper deals with the preparation of isomeric pairs of the products in pure state by the above two different courses, and the establishment of the spatial arrangement of these compounds. Furthermore, based on our data, the interpretation for the stereochemistry of santonin suggested previously, is discussed.

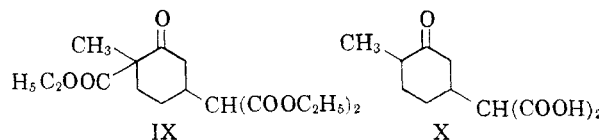
When the paper of Gunstone and Tulloch<sup>6</sup> appeared describing the preparation of I by the Robinson reaction, our studies along the same lines had already been completed. For comparison purposes, it seems worth while to mention our results, which include certain new findings. The starting acid (VIII, R = H), as described previously,<sup>6,9</sup>

(8) S. M. Mukherjee, *J. Ind. Chem. Soc.*, **25**, 155 (1948); *Chem. Abstr.*, **43**, 2605 (1949).

(9) M. Yanagita, S. Inayama, and R. Kitagawa, *J. Org. Chem.*, **21**, 612 (1956).

was prepared by Michael addition of diethyl malonate to ethyl 1-methyl-3-cyclohexen-2-one-1-carboxylate, followed by hydrolysis and decarboxylation of the resulting triester (IX). In this Michael reaction, the intermediates, a monoester (VIII, R = C<sub>2</sub>H<sub>5</sub>) and a diacid (X), both formed in minute amounts, were isolated and characterized.

Gunstone and Tulloch<sup>6</sup> reported that the Robinson reaction of VIII (R = CH<sub>3</sub>) and the Mannich base (VII) with sodium methoxide in methanol led to a rather low yield (11.5%) of methyl ester of I. We used absolute ethanol instead of methanol. There was obtained, besides the predominant neutral product in better yield, a small amount (12%) of an octalone-acetic acid (IA), m.p. 135–136°. Hydrolysis of the neutral product with alkali gave in 34% yield the same acid (IA), which was the sole product isolated previously.<sup>6</sup> However, from



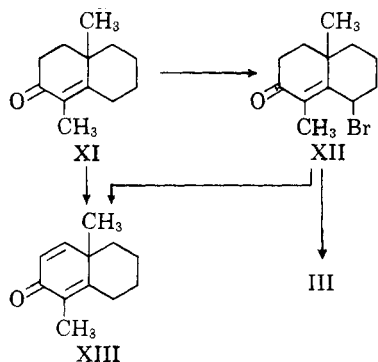
the mother liquor of IA, another isomer (IB), m.p. 144–145°, was consistently isolated, though in a small amount.

As an alternative route to I, the above cited Michael reaction of the  $\Delta^{4,5}$ -dienone (III) with diethyl malonate was explored. As first reported by Gunstone and Heggie,<sup>10</sup> the dienone (III) was prepared by bromination of the monoenone (XI) and subsequent dehydrobromination of the resulting monobromide (XII) with pyridine. Careful examination of the oily product showed that the dienone fraction (III) was contaminated, together with starting ketone (XI), with a small amount of the known cross-conjugated dienone (XIII),<sup>10,11</sup> characterized as its 2,4-dinitrophenylhydrazone. The latter, which was hitherto accessible only with difficulty, was readily prepared by oxidation of the monoenone (XI) with selenium dioxide in refluxing *tert*-butanol. It has been stated<sup>10,11b,12</sup> that the dienone-phenol rearrangement of XIII with acetic anhydride and concentrated sulfuric acid, which are the most common reagents for this reaction, led frequently to an unidentifiable oily mixture. It is found now that this rearrangement to the *ar*-2-tetralol can be readily effected by warming the dienone (XIII) with dilute sulfuric acid. Similarly, rearrangement of 2,4,4-trimethylcyclohexa- $\Delta^{2,5}$ -di-

(10) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.* 1437 (1952).

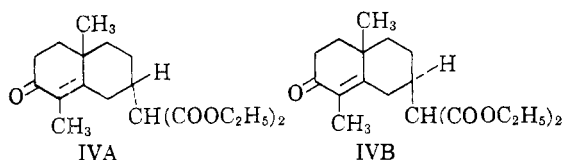
(11) (a) P. R. Hill and F. J. McQuillin, *J. Chem. Soc.*, 4060 (1953). (b) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956). (c) M. Sumi, *Pharm. Bull. Japan*, **4**, 147 (1956). T. Miki claimed the preparation of XIII from XI with selenium dioxide in glacial acetic acid, but no details of experimentation had been described [*J. Pharm. Soc. Japan*, **75**, 403 (1955)].

(12) M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954).



enone to pseudocumenol proceeded much more readily with dilute sulfuric acid than with acetic anhydride-sulfuric acid as reported previously.<sup>12</sup> It has been reported from our laboratory<sup>13</sup> that the reaction of 5-bromo-9-methyl- $\Delta^4$ -3-octalone with anhydrous sodium acetate furnished, along with the predominant  $\Delta^{4,5}$ -dienone (XVII), the rearranged  $\Delta^{1,4}$ -dienone in a minute amount. The formation of XIII from XII represented an additional instance of such rearrangement during dehydrobromination with a base.

The Michael reaction of the dienone (III) with diethyl malonate in the presence of potassium *tert*-butanol was extensively examined under a variety of the reaction conditions. When the mixture was allowed to react at room temperature for 2 days and then at 80–90° for 2 hours, one adduct (IVA), m.p. 70–71°, was obtained in 32% yield as the chief product. In addition, a small amount of crystals (IVB), m.p. 75–76°, showing melting point depression with IVA, was isolated from the mother

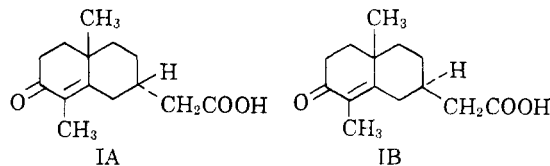


liquor of IVA. This result is somewhat surprising, since the Michael reaction of such type had been claimed<sup>7</sup> to give only the more stable isomer of the possible two adducts, independent of the conditions employed. On prolongation of the reaction at refluxing temperature, the higher-melting isomer (IVB) was chiefly obtained in 28% yield. Based on these results, the lower-melting adduct may be possibly assigned the *trans*-configuration (IVA) with the malonate side chain in an axial conformation, and the higher-melting isomer the *cis*-configuration (IVB) with an equatorial side chain. It may be predicted that each isomer of the malonate adducts (IVA and IVB) would be selectively produced under control of the reaction conditions. This prediction was confirmed. Thus, when the reaction was conducted at room temperature for 10 days, the yield of the *trans*-isomer (IVA) was raised to 51%, while

(13) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955).

refluxing of the mixture for 10 hours led in a 39% yield to the *cis*-isomer (IVB).

The *trans*-diester (IVA) was hydrolyzed to a diacid (VA), which on pyrolysis gave the substituted acetic acid (IA), m.p. 135–136°. The latter was



identified with the aforementioned acid obtained from the chief product of the Robinson condensation. Similarly, the *cis*-diester was converted through a diacid (VB) into the *cis*-monoacid (IB), m.p. 143–145°, identical with the acid from the minor product of the Robinson reaction. It is clear that the Robinson reaction of the 4-substituted 2-methylcyclohexanone with the Mannich base favors the formation of the octalone with the C<sub>6</sub>-substituent in an axial position.

The melting points of the compounds noted in this and earlier papers of this series are compared in Table I. The close agreement of the melting points leaves no doubt that the Michael reaction adduct (IV) and the derived diacid (V) of Miki<sup>5</sup> have the C<sub>6</sub>-side chain in an axial position, contrary to the previous assignment by this worker. That the substituted acetic acid (I) reported by Miki<sup>5</sup> possesses a melting point higher than those of IA of others is hard to understand. It is clear that Matsui, *et al.*<sup>3</sup> had in hand the two pure isomers of the monoacid (IA and IB) from the Michael adduct (IV), and that the compounds of McQuillin<sup>4</sup> and of Gunstone and Tulloch<sup>6</sup> are in the *trans*-series.

In the total synthesis of santonin (II, R = CH<sub>3</sub>), Abe, *et al.*<sup>7</sup> reported the preparation of the C<sub>11</sub>-methyl homologs (XV) of IV, as an intermediate, by the Michael reaction of diethyl methylmalonate to the dienone (III) at room temperature. It has been inferred by certain workers<sup>7a,14</sup> that, by analogy with previous work,<sup>15</sup> this mode of reaction permits an equatorial assignment to the introduced side chain in XV, suggesting stereospecificity of the Michael reactions. Hydrolysis and decarboxylation of the diester (XV) gave rise to two epimers of the monoacid (XVIB), each of which was respectively transformed to  $\alpha$ - or  $\beta$ -santonin in few steps. This result was considered<sup>7a,14</sup> to give strong support for an equatorial position of the  $\alpha$ -propionic group of the lactone ring in santonin. The two monoacids (XVIA), prepared previously by the Robinson reaction of methyl 4-methylcyclohexan-3-one-1- $\alpha$ -propionate and the Mannich base (VII), are isomeric at the 6-position with XVIB, and would be assigned the *trans*-structure.<sup>7a</sup>

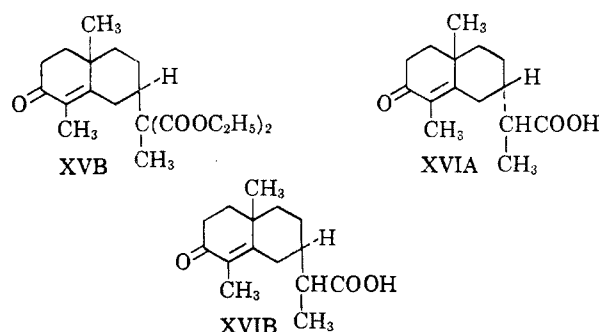
(14) (a) R. B. Woodward and P. Yates, *Chem. & Ind. (London)*, 1391 (1954). (b) E. J. Corey, *J. Am. Chem. Soc.*, **77**, 1044 (1955).

(15) J. W. Ralls, *J. Am. Chem. Soc.*, **75**, 2123 (1953).

TABLE I

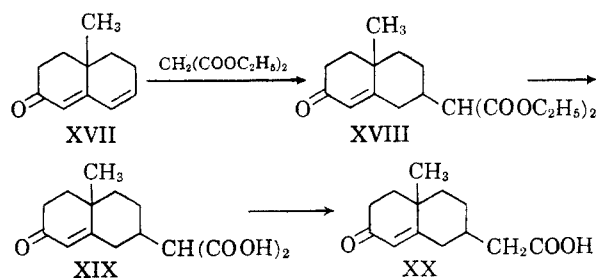
	Present Work	Matsui, <sup>3</sup> <i>et al.</i>	McQuillin <sup>4</sup>	Miki <sup>5</sup>	Gunstone <sup>6</sup> <i>et al.</i>
<i>trans</i> -Monoacid (IA)	135–136°	135°		139°	135°
<i>cis</i> -Monoacid (IB)	143–145°	143–145°			
<i>trans</i> -Diacid (VA)	174–176°	oil		173°	
<i>cis</i> -Diacid (VB)	185–186°	185°			
<i>trans</i> -Diester (IVA)	70–71°			71°	
2,4-Dinitrophenylhydrazone of IVA	174–176°		170°	177°	
<i>cis</i> -Diester (VB)	75–76°				
2,4-Dinitrophenylhydrazone of VB	129–130°				

However, the above cited basis for the *cis*-assignment of the stereoformula (XVIB) does not seem valid, in view of the present observation that the Michael addition reaction in most closely related systems is not wholly stereospecific, but forms the isomeric adducts in varying relative yields. Particularly, the foregoing fact that, like the *trans*-substituted malonate (IVA), the methylmalonate adduct (XV) was preferentially formed by the Michael reaction at ordinary temperatures, would favor the *trans*-configuration (XVA) for this adduct. Nevertheless, an equatorial character of the  $\alpha$ -propionic acid side chain in santonin had been well established by other means,<sup>16,17</sup> and hence, the formulas (XV, XVIA, and XVIB) should be correct. These formulas were strongly supported by our finding that the *cis*-malonate adduct (IVB) was transformed into XVB by methylation with methyl iodide and sodium *tert*-butoxide. It is remarkable that the Michael additions of diethyl malonate and methylmalonate to the dienone (III) proceed through different steric courses under similar reaction conditions. On the other hand, it can be seen that the Robinson reactions showed stereospecificity to yield predominantly the *trans*-product. This agrees with the earlier work.<sup>18</sup>



The marked influence of the methyl group in the malonate anion on the stereochemical pattern in the Michael reaction prompted us to investigate the same malonate addition reaction to the  $\Delta^{4,5}$ -dienone (XVII), the lower homolog of III. It has been reported by Gunstone and Tulloch<sup>6</sup> that the

Michael reaction of the dienone (XVII) with diethyl malonate and sodium ethoxide in refluxing ethanol gave rise to a liquid adduct (XVIII), characterized as a 2,4-dinitrophenylhydrazone, m.p. 146–150°. The diester (XVIII) was converted through a diacid (XIX) to the substituted acetic acid (XXB), m.p. 85–88°, which was reported to be not obtained in an analytically pure state.<sup>6</sup> On repetition of this reaction sequence, it was found that the malonate adduct of the reported boiling point was not sterically pure, and formed a mixture of 2,4-dinitrophenylhydrazones, from which one form, m.p. 143–145°, was isolated, accompanied by a small amount of a second form, m.p. 145–150°. Hydrolysis of the diester mixture (XVIII) gave the diacid (XIX), possessing the melting point (dec.) identical with that reported previously.<sup>6</sup> On decarboxylation of the diacid (XIX), the monoacid (XXB), m.p. 90–94°, was chiefly obtained, along with a small amount of the isomer (XXA), m.p. 113–115°. The lower-melting acid, which gave satisfactory analyses, is probably identical with the acid, m.p. 85–88°, of Gunstone and Tulloch.<sup>6</sup> When the addition reaction was carried out with sodium *tert*-butoxide in *tert*-butanol at room temperature for 7 days, there was chiefly obtained a solid adduct



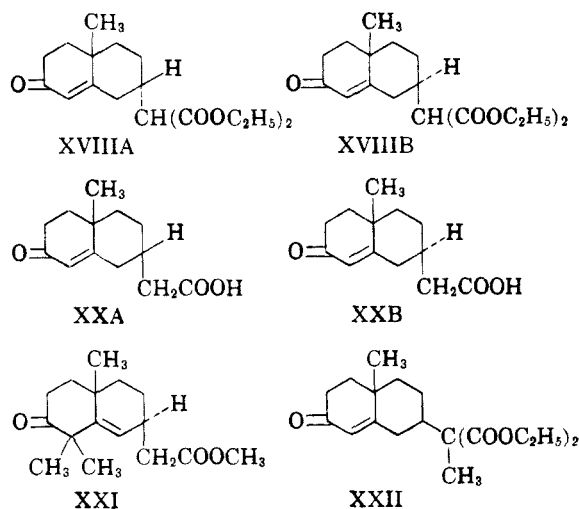
(XVIII), forming the 2,4-dinitrophenylhydrazone of the higher melting point. In addition, a minute amount of the liquid isomer (XVIII B) was detected as its 2,4-dinitrophenylhydrazone after chromatography. This steric result completely parallels that of the same reaction with III, clearly indicating that the solid adduct (XVIII A) and its liquid isomer (XVIII B) possess, respectively, the malonate side chain in axial and equatorial positions. It is to be noted that when the above Michael addition was performed in refluxing *tert*-butyl alcohol, the *trans*-isomer (XXA), contrary to the

(16) A. Tahara, *J. Org. Chem.*, **21**, 442 (1956).

(17) W. Cocker and T. B. H. McMurry, *Chem. & Ind. (London)*, 1954, 1199; M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).

(18) E. J. McQuillin, *J. Chem. Soc.*, 528 (1955).

reaction in refluxing ethanol, was chiefly obtained, but in much lower yield than that of the reaction at ordinary temperature. The solid diester (XV-III A) was converted through a diacid (XIX A) to the higher-melting monoacid (XX A). This acid



showed the same melting point as that of the acid derived previously from the Robinson condensation product of VIII and diethylaminobutan-3-one methiodide.<sup>6</sup> To prove unequivocally the configuration of the side chain in XX A, an effort was made to convert the *trans*-monoacid into IA by monomethylation at the 4-position. After model experiments, which will be reported in the following paper, the methyl ester of XX A was reacted with methyl iodide and potassium *tert*-butoxide in *tert*-butyl alcohol. Chromatographic separation of the oily product furnished, together with the predominant 4,4,9-trimethyl compound (XXI), a minute amount of the methyl ester of IA which was identified as its 2,4-dinitrophenylhydrazone.

The Michael addition of methylmalonate to the dienone (XVII) in the presence of sodium ethoxide in ethanol has been reported by Harukawa.<sup>19</sup> It proceeded at ordinary temperature with ease comparable to that observed in its addition to III. The only product (XXII), which may be assigned the *cis*-structure, was converted to an isomer of the two possible monoacids. This acid was shown to be different from the acid prepared by the Robinson condensation of methyl 4-methylcyclohexan-3-one-1- $\alpha$ -propionate and diethylaminobutan-3-one methiodide, followed by hydrolysis.<sup>19</sup> It is not clear whether this discrepancy is due to a different configuration at two asymmetric centers or at only one. However, as proposed previously, the *trans*-assignment to the acid from the Robinson condensation product seems correct.

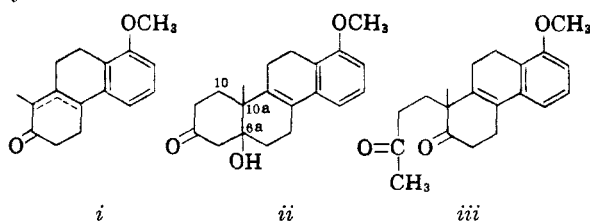
We should like to offer a possible explanation for the steric course of the Robinson reaction described in the present work. It has been stated by Johnson<sup>20</sup>

that in the formation of a tricyclic ketone by the Robinson method, alkylation of carbanion of the bicyclic methyl ketone involves preferential attack so that the incoming alkyl group assumes an axial conformation. This is in line with the steric consideration for bromination of cyclic ketones suggested by Corey.<sup>21</sup> On application of this rule to the Robinson reaction cited above, it may be assumed that the carbanion (XXIII) of VIII (R = CH<sub>3</sub>) may be attacked selectively by the Mannich base from the axial side to form XXIV. The latter can be inverted to XXV which is less favored by one more skew interaction than XXIV. The diketone (XXIV) may be intramolecularly cyclized to the *cis*-decalol (XXVI). Isolation of a cyclic ketol of similar type has been reported by McQuillin<sup>18</sup> in the synthesis of cyperones by the Robinson procedure. Transformation of XXVI to the observed octalones (as IA) with inversion of the side chain would be expected to proceed through a hypothetical unsaturated intermediate (XXVII) where the angular methyl group is equatorial to the ring with the side chain. Such an octalone, as shown by molecular models, requires a boat form for the unsaturated ring. It is more plausible to infer that the elimination would take place in the inverted form (XXVIII) of XXVI, which gives directly the observed octalone (as IA). Similar cyclization of the diketone (XXV) may lead to *cis*- and *trans*-decalonols (XXVIII and XXIX), the latter forming the same octalone (as IA). On the other hand, an equatorial attack of the alkylating reagent at the carbanion (XXIII) may give rise to the *cis*-monoacid (as IB) through a *trans*-decalonol bearing the acetate side chain equatorial.<sup>22</sup>

Based on the results of his cyperone studies, McQuillin<sup>18</sup> declared that in the Robinson reaction of 5-substituted 2-methylcyclohexanone, the formation of each isomer of the intermediate decalonol, corresponding to XXVI, is in proportion to the

(21) E. J. Corey, *J. Am. Chem. Soc.*, **76**, 175 (1954).

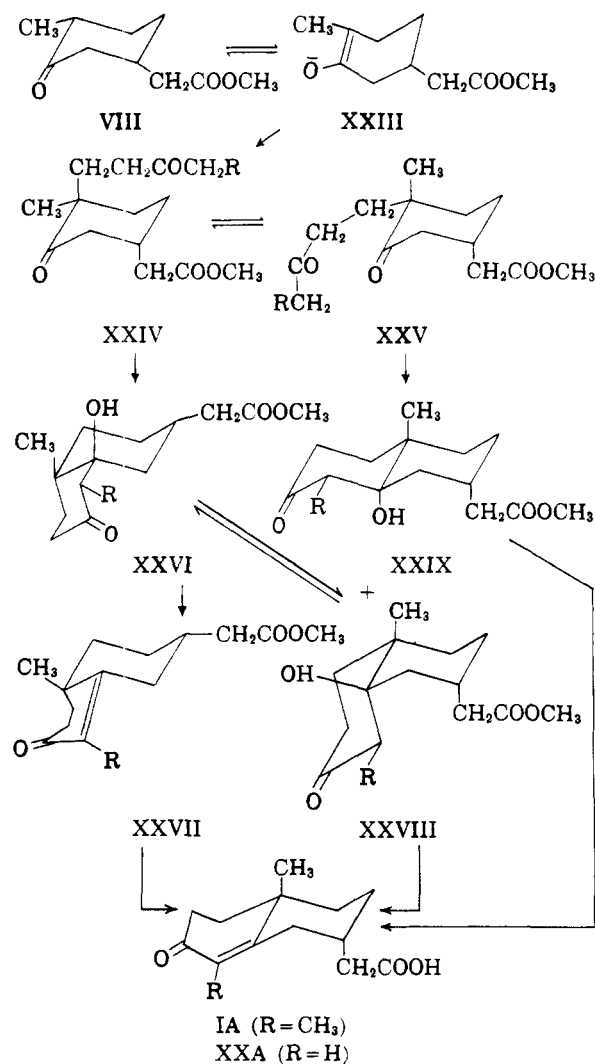
(22) Johnson *et al.* [*J. Am. Chem. Soc.*, **78**, 6302 (1956)] reported that the base-catalyzed condensation of methyl vinyl ketone with the tricyclic ketone (*i*) gave a mixture of isomers of the tetracyclic ketol (*ii*) which are different in configuration at C<sub>6a</sub>. This result clearly indicated the equatorial attachment of the bond 10-10a at the angular carbon in *ii*. It is reasonable to consider that according to the above generality,<sup>20</sup> an attack of methyl vinyl ketone at the anionic ketone at the anionic center of *i* would occur preferentially from the axial side, and the resulting intermediate (*iii*), possessing only one asymmetric carbon, may be immediately inverted to the stable form under migration of the axial ketone side chain into the equatorial position, and then cyclized to *ii*.



(19) T. Harukawa, *J. Pharm. Soc. Japan.*, **75**, 521 (1955).

(20) W. S. Johnson, *Chem. & Ind. (London)*, 167 (1956).

population of the two conformations of the cyclohexanone used. A survey of the literature<sup>23</sup> indicates that in polycyclic systems, a cyclohexanone ring in which ring inversion is impossible because of rigid fixation by other rings, also reacted with the alkylating reagent to give an epimeric mixture, as in the case described above. Obviously, this sug-



gests the occurrence of an alkylation from either side of a cyclic ketone in only one conformation. Therefore, the postulation of McQuillin<sup>18</sup> for the steric course of the Robinson reaction seems unlikely.

#### EXPERIMENTAL<sup>24</sup>

All temperatures are uncorrected.

*Diethyl 4-methyl-4-ethoxycarbonyl-3-cyclohexanone-1-malonate* (IX). This was prepared by a slight modification of the procedure reported by Mukherjee. To a stirred mixture of sodium metal (4 g.) and diethyl malonate (40 g.) in 150 cc.

(23) For example see L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos, and G. E. Arth, *J. Am. Chem. Soc.*, **75**, 2112 (1953).

(24) Microanalyses were carried out by Miss Ch. Shibuya and the ultraviolet measurement by Miss M. Suzuki.

of absolute ethanol was added, dropwise, ethyl 1-methyl-3-cyclohexen-2-one-1-carboxylate<sup>9</sup> (30 g.) with ice-salt cooling and the stirring was kept up for 2 hr. Working up of the reaction mixture as usual gave the adduct (IX, 44 g., 78%) as a colorless viscous oil, b.p. 185–189° at 3 mm. (Reported,<sup>8</sup> b.p. 192° at 5 mm.).

On prolonged standing with semicarbazide in dilute acetic acid, the semicarbazone was obtained in 54% yield. Recrystallization from dilute ethanol furnished colorless prisms, m.p. 128–129°. Reported,<sup>8</sup> m.p. 126°.

*4-Methyl-3-cyclohexanone-1-acetic acid* (VIII, R = H). According to the procedure reported previously,<sup>8</sup> the above substituted malonate (IX, 50 g.) was heated with concentrated hydrochloric acid on a boiling water bath for 26 hr. The oily product, which solidified mostly, was treated with cold ethyl acetate to give 10.1 g. (40.7%) of crude monoacid (VIII, R = H), m.p. 89–93°. Recrystallization from benzene-hexane furnished colorless prisms, m.p. 96–98° (reported, m.p. 95–99°<sup>6</sup> and 91–94°<sup>9</sup>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>14</sub>O<sub>3</sub>: C, 63.51; H, 8.39. Found: C, 63.70; H, 8.82.

The semicarbazone, formed almost quantitatively, was recrystallized from ethanol to colorless prisms, m.p. 198–200° (reported,<sup>6</sup> m.p. 193–195°).

*Anal.* Calcd. for C<sub>10</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: N, 18.49. Found: N, 18.62. The acid formed almost quantitatively the 2,4-dinitrophenylhydrazone, m.p. 106–110°, which was recrystallized from ethanol to orange needles, m.p. 118–119°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O<sub>6</sub>: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.90; H, 5.01; N, 15.62.

The mother liquor of the monoacid (VIII, R = H) gave a dark red oil (19.2 g.), which was dissolved in ether and shaken with aqueous sodium carbonate. Acidification of the carbonate solution furnished an additional 4.7 g. (total 60%) of the crude monoacid (VIII, R = H). The neutral fraction, a pale yellow oil (4.2 g.), was distilled to give 3.7 g. (13%) of a colorless oil, b.p. 117–120° at 25 mm. It formed in 88% yield a 2,4-dinitrophenylhydrazone, m.p. 104–108°. Recrystallization from ethanol furnished orange silky needles, m.p. 117–119°, undepressed on admixture with the same derivative of ethyl ester (VIII, R = C<sub>2</sub>H<sub>5</sub>) of the monoacid, described below.

In another run, a mixture of the diester (IX, 30 g.) and concentrated hydrochloric acid (240 cc.) was heated for 4 hr. The product, a brown oil, was treated with ether to give a diacid (X, 0.5 g.), as sparingly soluble crystals, m.p. 153–156°. Washing with warm ether gave analytically pure sample, m.p. 165–168°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>5</sub>: C, 56.07; H, 6.59. Found: C, 56.07; H, 6.94.

The mother liquor of the diacid gave the crude monoacid (VIII, R = H) (10.4 g., 69%), m.p. 82–90°.

A *methyl ester* (VIII, R = CH<sub>3</sub>) was prepared by methylation of the acid with diazomethane in ether solution. A colorless oil, b.p. 126–129° at 5 mm., was obtained in 96% yield. A sample, prepared from the acid with sulfuric acid and methanol, was reported to have the b.p. 136–137° at 13 mm.<sup>6</sup>

The ester formed almost quantitatively a *semicarbazone*, m.p. 138–142°, which was recrystallized from ethanol to white fine scales, m.p. 148–150°. On drying under reduced pressure at 100° for 6 hr., it showed m.p. 141–143°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.58; H, 7.72; N, 17.24.

The methyl ester formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 108–112°, which was recrystallized from ethanol to orange needles, m.p. 127–129°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.69; H, 5.02; N, 15.69.

An *ethyl ester* (VIII, R = C<sub>2</sub>H<sub>5</sub>) was prepared by refluxing the monoacid (0.1 g.) with concentrated sulfuric acid (1 drop) in absolute ethanol (0.5 cc.) for 6 hr. The neutral product, a pale yellow oil, was fractionated to a colorless oil (0.05 g.), b.p. 119° at 4 mm. (bath temperature).

It formed almost quantitatively a *semicarbazone*, m.p. 162–166°, which was recrystallized from ethanol to prisms, m.p. 168–170°.

*Anal.* Calcd. for  $C_{12}H_{21}N_3O_3$ : N, 16.46. Found: N, 16.93.

The ethyl ester formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 99–104°, which was once recrystallized from ethanol to silky orange needles, m.p. 117–119°.

*Anal.* Calcd. for  $C_{17}H_{22}N_4O_6$ : C, 53.96; H, 5.86; N, 14.81. Found: C, 53.73; H, 5.95; N, 14.56.

*Preparation of 4,9-dimethyl- $\Delta^4$ -3-octalone-6-acetic acid (IA) by the Robinson reaction.* This was carried out by an improvement of the procedure reported previously.<sup>6</sup> Diethylaminopentan-3-one (6.3 g., VII) was treated with methyl iodide (5.8 g.) under cooling, and the above cyclohexanone-acetate (VIII, R = CH<sub>3</sub>) (3.7 g.) was added dropwise, followed by a solution of sodium methoxide (from 0.95 g. sodium) in absolute methanol (30 cc.). The mixture was allowed to stand at room temperature overnight, and refluxed for 40 min. with stirring. After cooling, the reaction was acidified with acetic acid, then evaporated under reduced pressure, the residue was diluted with water and extracted with ether. The ether solution was shaken successively with aqueous sodium bicarbonate, sodium carbonate, and water.

(a) *Acid product.* Acidification of the carbonate solution gave a pale yellow oil (1.2 g.), which mostly solidified. Treatment with ethyl acetate–petroleum ether furnished 0.56 g. (12%) of the *trans*-acetic acid compound (IA), m.p. 127–130°, which was recrystallized from the same solvent mixture to white prisms, m.p. 135°;  $\lambda_{\text{max}}^{\text{EtOH}}$  248 m $\mu$  (log  $\epsilon$  4.18). Reported,<sup>6</sup> m.p. 135°.

It formed almost quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 225–228° (dec.), which was recrystallized from ethyl acetate and then acetic acid to red fine scales, m.p. 234–236°;  $\lambda_{\text{max}}^{\text{CHCl}_3}$  260 m $\mu$  (log  $\epsilon$  4.31), 290 m $\mu$  (log  $\epsilon$  4.11) (infl.), and 392 m $\mu$  (log  $\epsilon$  4.51).

*Anal.* Calcd. for  $C_{20}H_{24}N_4O_6$ : C, 57.68; H, 5.81; N, 13.46. Found: C, 57.41; H, 5.70; N, 13.00.

A *semicarbazone*, m.p. 229–232°, obtained almost quantitatively, was recrystallized from ethanol to white prisms, m.p. 235–236°.

*Anal.* Calcd. for  $C_{15}H_{23}N_3O_3$ : C, 61.41; H, 7.90; N, 14.33. Found: C, 61.23; H, 7.70; N, 14.16.

(b) *Neutral product.* The above ether solution, washed with aqueous sodium carbonate, was dried and evaporated to leave a pale yellow oil (3.25 g.), which was fractionated. A forerun of the starting material (1.2 g., 46%), b.p. 111–125° at 4 mm., was followed by the octalone–acetic ester (I, R = CH<sub>3</sub>) (1.7 g.), b.p. 170–195° at 5 mm. Refractionation gave 1.43 g. (29%) of a pale yellow viscous oil, b.p. 170–191° at 5 mm. This oil formed, in 85% yield, a *2,4-dinitrophenylhydrazone*, melting in the range of 139° and 155°. Repeated recrystallizations from ethyl acetate furnished deep red fine needles, m.p. 178–180°;  $\lambda_{\text{max}}^{\text{CHCl}_3}$  260 m $\mu$  (log  $\epsilon$  4.26), 295 m $\mu$  (log  $\epsilon$  4.03) (infl.), and 392 m $\mu$  (log  $\epsilon$  4.46). It melted at 182–183° on admixture with the same derivative of the methyl ester of the *trans*-monoacid (IA), described below (reported,<sup>6</sup> m.p. 176–177°).

The above ester fraction (1.0 g.) was heated to reflux with potassium hydroxide (1.0 g.) in methanol (10 cc.) for 2 hr. The crude acid (I) was obtained as a pale yellow viscous oil, which soon solidified partly. Crystallization from ether–petroleum ether gave 0.44 g. (47%) of the *trans*-monoacid (IA) as yellowish crystals, m.p. 122–129°. Recrystallization from ethyl acetate furnished colorless prisms, m.p. and mixed m.p. 133–135°.

The mother liquor of crystallization of IA gave the *cis*-isomer (IB) (0.14 g.), melting in the range of 108–119°. Recrystallization from ethyl acetate to colorless prisms, m.p. 144–145°, undepressed with the authentic sample described below.

*Bromination-dehydrobromination of 4,9-dimethyl- $\Delta^4$ -3-octalone (XI).* This reaction was previously performed by two procedures<sup>10</sup> to yield the  $\Delta^4$ -dienone (III). The one in-

volves bromination of the monoeneone (XI) with *N*-bromosuccinimide and subsequent elimination of the bromide (XII) with hot pyridine, and the other consists of the bromine treatment of the monoeneone (XI) and distillation of the resulting bromide (XII) after standing at room temperature. On repetition, it was found that the latter procedure was unfavorable, since distillation of the bromide was always accompanied with evolution of white smoke, giving a distillate which soon colored deeply.

By combination of these procedures, a convenient method for the  $\Delta^4$ -dienone (III) was developed.

The monobromide (XII), prepared from the monoeneone (XI, 15.0 g.) with bromine (14.1 g.) in carbon tetrachloride (50 cc.), was heated to reflux with dried pyridine (30 cc.) for 4 hr. The product, a red brown oil (13.9 g.), was fractionated to a pale yellow oil (9.3 g., 63%), b.p. 110–111° at 3 mm., and a yellowish oil (2.4 g., 16%), b.p. 113–127° at 3 mm.; both had  $\lambda_{\text{max}}^{\text{EtOH}}$  288 m $\mu$  (log  $\epsilon$  4.29). These fractions, consisting mainly of the  $\Delta^4$ -dienone (III), formed the same *2,4-dinitrophenylhydrazone*, m.p. 200–205°. Recrystallization from ethyl acetate–ethanol furnished dark red plates, m.p. and mixed m.p. 212–214°;  $\lambda_{\text{max}}^{\text{CHCl}_3}$  266 m $\mu$  (log  $\epsilon$  4.20), 312 m $\mu$  (log  $\epsilon$  4.15), and 402.5 m $\mu$  (log 4.54) (reported,<sup>10</sup> m.p. 216°).

The higher-boiling fraction formed in about 70% yield the *semicarbazone* of the  $\Delta^4$ -dienone (III), m.p. 220–222°, after recrystallization from ethanol. It had  $\lambda_{\text{max}}^{\text{EtOH}}$  300 m $\mu$  (log  $\epsilon$  4.55) [reported,<sup>10</sup> m.p. 216–217°;  $\lambda_{\text{max}}^{\text{EtOH}}$  300 m $\mu$  (log  $\epsilon$  4.55)].

To the mother liquor of crystallization of the *semicarbazone* was added Brady's reagent (an ethanolic solution of *2,4-dinitrophenylhydrazone* and concentrated sulfuric acid), and the red crystals, m.p. 198–205°, which separated, were recrystallized from ethyl acetate–ethanol to dark red plates, m.p. 218–220°;  $\lambda_{\text{max}}^{\text{CHCl}_3}$  263 m $\mu$  (log  $\epsilon$  4.22), 315 m $\mu$  (log  $\epsilon$  3.87), and 406 m $\mu$  (log  $\epsilon$  4.52). The sample showed no depression of the melting point on admixture with the same derivative, m.p. 226–227°, of the  $\Delta^4$ -dienone (XIII).<sup>11b</sup>

*Anal.* Calcd. for  $C_{18}H_{20}N_4O_4$ : C, 60.66; H, 5.66; N, 15.72. Found: C, 60.49; H, 5.50; N, 15.38.

*Oxidation of 4,9-dimethyl- $\Delta^4$ -3-octalone (XI) with selenium dioxide.* The monoeneone (XI, 1.78 g.) was heated to reflux in a stream of nitrogen with 1.2 g. of freshly sublimed selenium dioxide in 100 cc. of *tert*-butyl alcohol and 1 cc. of glacial acetic acid for 48 hr. After filtration of the selenium, the reaction mixture was evaporated under reduced pressure, the residual oil was mixed with ether, and again filtered to remove the remaining selenium. The ether solution was washed with aqueous sodium hydroxide and then with water. Evaporation of the dried ether solution left a brown oil (2.05 g.), which was fractionated to 1.1 g. (62.5%) of the  $\Delta^4$ -dienone (XIII) as a pale yellow oil, b.p. 108–112° at 2 mm. Refractionation gave an almost colorless oil (1.0 g.), b.p. 109–111° at 2 mm.;  $n_D^{20}$  1.5449;  $\lambda_{\text{max}}^{\text{EtOH}}$  241 m $\mu$  (log  $\epsilon$  3.95) and 265 m $\mu$  (log  $\epsilon$  3.79) (infl.);  $\lambda_{\text{C=C}}^{\text{CCl}_4}$  6.0  $\mu$  ( $\alpha,\beta,\alpha',\beta'$ -diunsaturated ketone),  $\lambda_{\text{C-C}}^{\text{CCl}_4}$  6.11  $\mu$ , 6.195  $\mu$  (reported<sup>11a</sup>, b.p. 108–110° at 1 mm.;  $n_D^{20}$  1.5322).

The oil formed quantitatively the *2,4-dinitrophenylhydrazone*, m.p. 225–228°, which is higher than the melting point of the pure sample of one form reported from our laboratory.<sup>11b</sup> Recrystallization from ethyl acetate–ethanol and then ethyl acetate alone gave deep red scales, m.p. 232–234°. It had  $\lambda_{\text{max}}^{\text{CHCl}_3}$  260 m $\mu$  (log  $\epsilon$  4.39), 312 m $\mu$  (log  $\epsilon$  3.98), and 407 m $\mu$  (log  $\epsilon$  4.67), which is practically identical with the reported value,<sup>10</sup> but somewhat different from the value of the lower-melting form described above.

*Anal.* Calcd. for  $C_{18}H_{20}N_4O_4$ : C, 60.66; H, 5.66; N, 15.72. Found: C, 60.94; H, 5.40; N, 15.50.

*Dienone-phenol rearrangement of 3-keto-4,9-dimethyl- $\Delta^4$ -4-hezahydronaphthalene (XIII) and related compound.* A mixture of the above dienone (XIII, 0.10 g.) and dilute sulfuric acid (5 cc. each of concentrated sulfuric acid and water) was warmed at 50–60° on a water bath for 9 hr. with stirring. After cooling, the reaction mixture, which precipitated a



brown oil, was poured onto water and extracted with ether. Evaporation of the dried ether solution left 0.04 g. of 1,4-dimethyl-*ar*-2-tetralol, m.p. 103–104°, after recrystallization from petroleum ether. It showed no depression of the melting point on admixture with the authentic sample reported previously.<sup>11b</sup> This material had  $\lambda_{\text{max}}^{\text{EtOH}}$  217 m $\mu$  (10 g.  $\epsilon$  3.90) and 285.5 m $\mu$  (log  $\epsilon$  3.29).

Similarly, 2,4,4-trimethylcyclohexa- $\Delta^{2,5}$ -dienone (0.1 g.)<sup>12</sup> was warmed with dilute sulfuric acid for 13 hr. The reaction mixture was diluted with water, extracted with ether, and the ether solution was shaken with 10% aqueous sodium hydroxide. Acidification of the alkaline solution gave pseudocumol as a brown oil (0.07 g.) which soon solidified almost completely, m.p. 50–54°. Recrystallization from petroleum ether furnished white silky prisms, m.p. and mixed m.p. 70.5–72.5°.

*Michael addition of diethyl malonate to 3-keto-4,9-dimethyl  $\Delta^{4,5}$ -hexahydronaphthalene (III).* (a) at room temperature for 2 days and then at 80–90° for 2 hr. To a stirred potassium *tert*-butoxide paste, prepared from 0.22 g. of potassium metal and 5 cc. of absolute *tert*-butyl alcohol, 3.65 g. of diethyl malonate and then 2.0 g. of the  $\Delta^{4,5}$ -dienone (III) were added dropwise with ice cooling. The mixture was allowed to react with occasional stirring at room temperature for 48 hr. and then heated at 80–90° (water bath temperature) for 2 hr. The deep brown solution was neutralized with acetic acid, evaporated to a small volume, acidified with hydrochloric acid, and extracted with ether. The ether solution was washed with aqueous sodium hydroxide and with water. Evaporation of the dried ether solution left a brown oil (5.25 g.), which was fractionated. With a forerun of the starting materials, the adduct (IV) was obtained as a pale yellow viscous oil (2.01 g.), b.p. 188–201° at 3 mm., which almost completely solidified. On washing ether–petroleum ether 1.22 g. (32%) of the *trans*-adduct (IVA) was obtained as crystals, m.p. 55–61°, which was recrystallized from ethyl acetate–petroleum ether as colorless large prisms, m.p. 70–71°;  $\lambda_{\text{max}}^{\text{EtOH}}$  246 m $\mu$  (log  $\epsilon$  4.25). Miki<sup>5</sup> reported m.p. 71° and  $\lambda_{\text{max}}^{\text{EtOH}}$  246 (log  $\epsilon$  4.15) for his adduct which was considered to be *cis*.

*Anal.* Calcd. for C<sub>19</sub>H<sub>20</sub>O<sub>5</sub>: C, 67.83; H, 8.39. Found: C, 67.70; H, 8.07.

The 2,4-dinitrophenylhydrazone had the m.p. 174–176° (red-orange prisms), after recrystallization from ethyl acetate:  $\lambda_{\text{max}}^{\text{CHCl}_3}$  261 m $\mu$  (log  $\epsilon$  4.25), 295 m $\mu$  (log  $\epsilon$  4.03) (infr.), and 392 m $\mu$  (log  $\epsilon$  4.47) (reported,<sup>5</sup> m.p. 177°).

IVA quantitatively formed a *semicarbazone*, m.p. 152–156°, which was recrystallized from dilute ethanol to fine prisms, m.p. 160–162°.

*Anal.* Calcd. for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>: C, 61.05; H, 7.94; N, 10.68. Found: C, 61.11; H, 7.98; N, 10.56.

The mother liquor of IVA gave a pale yellow, viscous oil (0.7 g.), which was distilled to 2 fractions, a pale yellow oil (0.12 g.), b.p. 190–220° (bath temperature), and a yellowish oil (0.45 g.), b.p. 195–205°, both at 3 mm. After standing for about 1 month, the former fraction furnished an additional 0.05 g. of the crude *trans*-adduct (IVA), and the latter fraction gave 0.1 g. of the *cis*-isomer (IVB), m.p. 61–67°. Recrystallization from ethyl acetate–petroleum ether furnished crystals, m.p. and mixed m.p. 75–76° with the authentic sample described below (c).

(b) at room temperature for 3 days and then refluxing for 48 hr. A mixture of potassiummalonate (from 1.38 g. of potassium, 15 cc. of *tert*-butyl alcohol, and 21.9 g. of diethyl malonate) and 12.0 g. of the  $\Delta^{4,5}$ -dienone (III) was reacted at room temperature for 3 days, and then was heated to reflux for 48 hr. Worked up as described in (a), a red brown oily product (25 g.) was fractionated to a pale yellow viscous oil (14.9 g.), b.p. 170–220° at 5 mm., which slowly solidified. Treatment with petroleum ether gave the *cis*-adduct (IVB, 11.5 g.), melting in the range of 56–70°. On one recrystallization from ethyl acetate, 6.5 g. (28.4%) of white prisms, m.p. 71–74°, was obtained, which was further recrystallized from the same solvent to raise the m.p. to

75–76°;  $\lambda_{\text{max}}^{\text{EtOH}}$  246 m $\mu$  (log  $\epsilon$  4.23). It showed obvious depression (15–20°) of the melting point on admixture with the *trans*-adduct (IVA).

*Anal.* Calcd. for C<sub>19</sub>H<sub>20</sub>O<sub>5</sub>: C, 67.83; H, 8.39. Found: C, 67.42; H, 8.38.

A *semicarbazone*, m.p. 172–177°, prepared quantitatively, was recrystallized from dilute ethanol to fine prisms, m.p. 176–178°.

*Anal.* Calcd. for C<sub>20</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>: C, 61.05; H, 7.94; N, 10.68. Found: C, 61.35; H, 7.78; N, 10.46.

A 2,4-dinitrophenylhydrazone, m.p. 123–125°, prepared quantitatively, was recrystallized from ethyl acetate–ethanol to reddish-orange plates, m.p. 129–130°;  $\lambda_{\text{max}}^{\text{EtOH}}$  260 m $\mu$  (log  $\epsilon$  4.24), 295 m $\mu$  (log  $\epsilon$  4.03), and 392 m $\mu$  (log  $\epsilon$  4.46).

*Anal.* Calcd. for C<sub>25</sub>H<sub>32</sub>N<sub>4</sub>O<sub>5</sub>: C, 58.13; H, 6.24; N, 10.85. Found: C, 58.26; H, 6.59; N, 10.97.

(c) at room temperature for 10 days. A mixture of potassiummalonate (from 1.0 g. of potassium, 25 cc. of *tert*-butyl alcohol, and 16.4 g. of diethyl malonate) and 8.9 g. of the  $\Delta^{4,5}$ -dienone (III) was stirred at room temperature for 10 days. The solid slowly dissolved to form a yellowish-brown fluorescent solution. The oily reaction mixture was fractionated to a pale yellow oil (11.65 g.), b.p. 192–196° at 1.2 mm., which mostly solidified. Washing with petroleum ether and recrystallization from ethyl acetate by addition of petroleum ether furnished (6.52 g., 33%) the *trans*-adduct (IVA) as colorless large prisms, m.p. 70–71°. The mother liquor of crystallization of IVA gave an additional 2.24 g. (total 51%) of the crude IVA.

(d) at reflux temperature for 10 hr. A mixture of potassiummalonate (from 1.25 g. of potassium metal, 30 cc. of *tert*-butyl alcohol, and 20 g. of diethyl malonate) and 11.0 g. of the  $\Delta^{4,5}$ -dienone (III) was refluxed for 10 hr. and worked up as above. The reaction mixture was fractionated to a pale yellow viscous oil (12.7 g.), b.p. 180–190° at 0.025 mm., which slowly crystallized on addition of a little hexane. Washing with hexane and recrystallization from ethyl acetate furnished 8.12 g. (39%) of the *cis*-adduct (IVB), m.p. and mixed m.p. 74–76°. Hydrolysis and decarboxylation of the mother liquor of IVB, as will be described in the following paragraph, furnished only the *trans*-monoacid (IA, 1.01 g.), m.p. and mixed m.p. 133–135°, after recrystallization from ethyl acetate.

*Hydrolysis and decarboxylation of diethyl-trans-4,9-dimethyl- $\Delta^{4,5}$ -octalone-6-malonate (IVA).* This reaction was carried out by improvement of a reported procedure<sup>6</sup> to raise the yield of the products.

To a solution of 8.0 g. of the *trans*-malonate adduct (IVA) in 30 cc. of methanol was added a solution of 8.0 g. of potassium hydroxide in 10 cc. of water and 40 cc. of methanol with cooling. After standing overnight at room temperature, the solution was heated to reflux for 40 min. The chilled reaction mixture was neutralized with acetic acid and evaporated under reduced pressure. The residue was dissolved in water and acidification with 20% hydrochloric acid separated a dirty green oil. On standing, the *trans*-diacid (VA) (6.5 g., 97%) deposited as needles, m.p. 166–169° (dec.). Recrystallization from dilute methanol and then ethyl acetate raised the melting point to 174–176° (dec.);  $\lambda_{\text{max}}^{\text{EtOH}}$  247.5 m $\mu$  (log  $\epsilon$  4.24).

*Anal.* Calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>5</sub>: C, 64.27; H, 7.19. Found: C, 63.96; H, 7.22.

Pyrolysis of the diacid (VA, 6.25 g.) at 170–180° (oil bath temperature) for 10 min. in a stream of nitrogen gave a red brown oil (sublim.), which solidified on cooling. Recrystallization from ethyl acetate with active carbon gave the *trans*-monoacid (IA, 4.63 g., 89%), m.p. 132–134°. Recrystallization from ethanol furnished colorless prisms, m.p. 135–136°;  $\lambda_{\text{max}}^{\text{EtOH}}$  248 m $\mu$  (log  $\epsilon$  4.20). It showed no depression of the melting point on admixture with the above sample, prepared by the Robinson reaction.

*Anal.* Calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>3</sub>: C, 71.16; H, 8.53. Found: C, 70.91; H, 8.17.



This acid was methylated with diazomethane in ether solution. A methyl ester had the b.p. 153–155° at 2 mm.;  $\lambda_{\text{max}}^{\text{EtOH}}$  247 m $\mu$  (log  $\epsilon$  4.21).

It formed almost quantitatively a 2,4-dinitrophenylhydrazone as deep red fine needles, m.p. 171–178°. Recrystallization from ethyl acetate–ethanol and then glacial acetic acid raised the m.p. to 182–184°.

Anal. Calcd. for  $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_6$ : C, 58.59; H, 6.09; N, 13.02. Found: C, 58.87; H, 5.97; N, 12.98.

*Hydrolysis and decarboxylation of diethyl cis-4,9-dimethyl- $\Delta^4$ -3-octalone-6-malonate (IVB).* These reactions were carried out exactly as described above for the *trans*-isomer (IVA). The crude *cis*-diacid, m.p. 185° (dec.), was obtained in 98% yield. Recrystallization from ethyl acetate gave white prisms, m.p. 185–186° (dec.);  $\lambda_{\text{max}}^{\text{EtOH}}$  247.5 m $\mu$  (log  $\epsilon$  4.23). Matsui *et al.*<sup>8</sup> gave the m.p. 185° for one isomer of the diacid (V).

Anal. Calcd. for  $\text{C}_{16}\text{H}_{20}\text{O}_5$ : C, 64.27; H, 7.19. Found: C, 63.88; H, 7.52.

Pyrolysis of the diacid gave in 91% yield the *cis*-monoacid, melting in the range of 128–137°. Recrystallization from ethyl acetate gave colorless prisms, m.p. 143–145°;  $\lambda_{\text{max}}^{\text{EtOH}}$  248 m $\mu$  (log  $\epsilon$  4.19).

Anal. Calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_3$ : C, 71.16; H, 8.53. Found: C, 70.92; H, 8.23.

It formed almost quantitatively a 2,4-dinitrophenylhydrazone, m.p. 231–234°, which was recrystallized from ethyl acetate and then from glacial acetic acid to red silky needles, m.p. 243–245°;  $\lambda_{\text{max}}^{\text{EtOH}}$  261.5 m $\mu$  (log  $\epsilon$  4.30), 295 m $\mu$  (log  $\epsilon$  4.08) (infl.), and 392 m $\mu$  (log  $\epsilon$  4.51).

Anal. Calcd. for  $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_6$ : C, 57.68; H, 5.81; N, 13.46. Found: C, 57.86; H, 5.44; N, 13.23.

The semicarbazone, m.p. 243–248°, obtained almost quantitatively, was recrystallized from ethanol to white scales, m.p. 249–250°.

Anal. Calcd. for  $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_3$ : C, 61.41; H, 7.90; N, 14.33. Found: C, 61.44; H, 7.49; N, 13.89.

This acid was methylated with diazomethane in ether solution. A methyl ester had b.p. 147–149° at 2 mm.;  $\lambda_{\text{max}}^{\text{EtOH}}$  247 m $\mu$  (log  $\epsilon$  4.20). It formed quantitatively a 2,4-dinitrophenylhydrazone, deep red fine needles, m.p. 180–183°. Recrystallization from ethyl acetate raised the m.p. to 185–187°;  $\lambda_{\text{max}}^{\text{CHCl}_3}$  260.5 m $\mu$  (log  $\epsilon$  4.26), 295 m $\mu$  (log  $\epsilon$  4.05) (infl.), and 392 m $\mu$  (log  $\epsilon$  4.48).

Anal. Calcd. for  $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_6$ : C, 58.59; H, 6.09; N, 13.02. Found: C, 58.52; H, 6.09; N, 12.72.

*Methylation of diethyl cis-4,9-dimethyl- $\Delta^4$ -3-octalone-6-malonate (IVB) with methyl iodide.* To a stirred potassium *tert*-butoxide paste, prepared from 0.12 g. of potassium metal and 10 cc. of *tert*-butyl alcohol, 1.0 g. of the *cis*-malonate adduct (IVA) was added dropwise, followed by 4 cc. of methyl iodide. After refluxing for 1 hr., another 1 cc. of methyl iodide was added, and the refluxing was continued further for 3 hr. The neutral reaction mixture was evaporated under reduced pressure, the residue was dissolved in water, and extracted with ether. The ether solution was washed with sodium bicarbonate solution, dried, and evaporated to leave a pale yellow oil (0.59 g.). Fractionation furnished almost colorless oil (0.4 g.), b.p. 160–162° at 0.02 mm., which was chromatographed on alumina (12 g.) as a petroleum ether solution. Elution with petroleum ether–benzene gave 0.08 g. of crystals, m.p. 53–56°, which was recrystallized from petroleum ether to white prisms, m.p. 59–60°. It showed no depression of the melting point on admixture with the *cis*-methylmalonate adduct (XV), m.p. 61–62°, kindly furnished by Dr. Abe.<sup>7b</sup> The 2,4-dinitrophenylhydrazone had m.p. 125° (after recrystallization from ethanol), undepressed on admixture with the same derivative, m.p. 125°, of the diester (XV) of Abe, who gave the m.p. as 123°.

*Michael addition of diethyl malonate to 3-keto-9-methyl- $\Delta^4$ -5-hexahydronaphthalene (XVII).* The  $\Delta^4$ -dienone (XVII) was prepared by bromination-dehydrobromination of 9-methyl- $\Delta^4$ -3-decalone, as reported previously.<sup>6</sup> The product

contained 20–25% of the unchanged starting ketone, which was used for the Michael reaction without further purification. Its 2,4-dinitrophenylhydrazone was recrystallized from benzene-methanol to deep red plates, m.p. 194–195°;  $\lambda_{\text{max}}^{\text{EtOH}}$  268 m $\mu$  (log  $\epsilon$  4.20), 308.5 m $\mu$  (log  $\epsilon$  4.14), and 402 m $\mu$  (log  $\epsilon$  4.53). Reported, m.p. 187–190°<sup>6</sup> and m.p. 177°.<sup>25</sup>

(a) *at reflux temperature in ethanol.* The Michael reaction of XVII was first carried out by a modification of the procedure reported previously.<sup>6</sup> To a sodium ethoxide solution, prepared from 0.12 g. of sodium metal and 5 cc. of ethanol, 7.0 g. of diethylmalonate was added, followed by 1.80 g. of the ketone (XVII). The mixture was heated to reflux for 90 min. The chilled mixture was acidified with acetic acid (0.5 cc.) and evaporated under reduced pressure. The residue was mixed with water, extracted with ether, and the ether solution was washed with sodium bicarbonate solution and water. Evaporation of the dried ether solution left an oil which was fractionated to a colorless oil (0.37 g.), b.p. 96–100° at 3 mm., and a pale yellow oil (2.04 g.), b.p. 175–180° at 0.05 mm.;  $n_D^{20}$  1.5020 (reported,<sup>6</sup> b.p. 174–180° at 0.05 mm., and  $n_D^{20}$  1.5105).

The former fraction mainly consisted of 9-methyl- $\Delta^4$ -3-octalone, which was characterized as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 168–169°.<sup>26</sup> The latter fraction (0.09 g.) formed 0.12 g. (85%) of 2,4-dinitrophenylhydrazone, melting in the range of 95 and 110°, which was chromatographed on alumina (acid-washed, 5 g.), and eluted with carbon tetrachloride–chloroform (9:1). The more readily eluted fraction gave 0.065 g. of the hydrazone of the *cis*-adduct (XVIII B) as orange red plates, m.p. 143–145° (after recrystallization from benzene–petroleum ether). The less readily eluted fraction gave orange-yellow fine needles (10 mg.), m.p. 149–150° (after recrystallization from ethyl acetate–ethanol), undepressed on admixture with the same derivative of the *trans*-adduct (XVIII A), described below. Reported,<sup>6</sup> m.p. 146–150° (from ethanol).

(b) *at room temperature in tert-butyl alcohol.* To a paste of potassiummalonate, prepared from 0.35 g. of potassium metal, 20 cc. of *tert*-butyl alcohol, and 10.5 g. of diethyl malonate, 2.92 g. of the ketone (XVII) was added and stirred at room temperature for 7 days. The brown solution was worked up as described above (a). The oily mixture was fractionated to give the starting monoene (0.79 g.), 118–122° at 7 mm., and a pale yellow viscous oil (3.06 g.), b.p. 165–172° at 0.02 mm.;  $n_D^{20}$  1.4990. The latter fraction mostly solidified on standing in a refrigerator. Filtration by suction and washing with petroleum ether gave 2.4 g. (57%, based on unrecovered monoene) of the *trans*-adduct (XVIII A) as colorless prisms, m.p. 37–39°.

The *trans*-adduct formed in 90% yielded a 2,4-dinitrophenylhydrazone, melting in the range of 135–144°, which was recrystallized from ethyl acetate–ethanol to orange-yellow needles, m.p. 149–150°. It showed obvious depression (5–10°) of the melting point on admixture with the same derivative of the above *cis*-isomer (XVIII B).

Anal. Calcd. for  $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_6$ : C, 57.36; H, 6.02; N, 11.15. Found: C, 57.65; H, 6.23; N, 11.07.

The mother liquid (0.10 g.) of XVIII A formed 2,4-dinitrophenylhydrazone (0.125 g.), m.p. 102–105°, which was subjected to chromatographic separation on alumina (5 g.) as described above. There were obtained the hydrazone of the *cis*-adduct (XVIII B) (55 mg.), m.p. and mixed m.p. 143–145°, and the hydrazone of the *trans*-adduct (XVIII A) (10 mg.), m.p. and mixed m.p. 149–150°.

(c) *at reflux temperature in tert-butyl alcohol.* A mixture of potassium metal (0.24 g.), *tert*-butyl alcohol (15 cc.), diethyl malonate (8 g.), and the ketone (XVII, 2.00 g.) was heated to reflux on a water bath for 90 min. Worked up as described above, the crude product was fractionated to the starting monoene (0.52 g.) and a pale yellow viscous oil (1.76 g.),

(25) T. Harukawa, *J. Pharm. Soc. Japan*, **75**, 421 (1955).

(26) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

b.p. 172–182° at 0.2 mm.;  $n_D^{20}$  1.5050. The latter fraction was seeded with the *trans*-adduct (XVIII A) and kept in a refrigerator for about 40 days. The partly solidified oil was filtered by suction and washed with petroleum ether to give 0.42 g. (14%) of the *trans*-adduct (XVIII A), m.p. and mixed m.p. 37–39°.

The mother oil of XVIII A amounted to 1.24 g., which (0.10 g.) formed a resinous mixture of 2,4-dinitrophenylhydrazone (0.125 g.). Chromatographic separation on alumina (10 g.) and elution with carbon tetrachloride–chloroform (10:1) afforded the hydrazone of XVIII B (0.06 g.), m.p. and mixed m.p. 143–145°, after recrystallization from benzene–petroleum ether.

*Hydrolysis and decarboxylation of diethyl 9-methyl- $\Delta^4$ -3-octalone-6-malonate (XVIII).* (a) *with the cis-malonate (XVIII B).* The oily malonate adduct, prepared by the method (a) in the preceding paragraph, was hydrolyzed as described for IVA. On standing overnight at room temperature, the alkaline solution of XVIII B became dirty green. The diacid, 164–165° (dec.), was obtained in 67% yield. Recrystallization from dilute ethanol did not alter the melting point (reported,<sup>6</sup> 165–168°).

The diacid (5.80 g.) was heated at 180–190° (bath temperature) for 10 min. The brown mass so obtained was treated with ethyl acetate–petroleum ether to give a light brown solid (3.96 g.), melting in the range of 54–76°. On fractional recrystallization from benzene, the less soluble fraction furnished 2.33 g. (48%) of the *cis* monoacid (XXB) as colorless needles, m.p. 88–92°. Further recrystallization from the same solvent raised the melting point to 90–94°. Gunstone and Tulloch<sup>6</sup> reported the m.p. 88° for the sample which was said to be not analytically pure.

*Anal.* Calcd. for  $C_{13}H_{18}O_3$ : C, 70.24; H, 8.16. Found: C, 70.53; H, 8.15.

An oil collected from the mother liquors of XXB was seeded and gave 0.92 g. (19%) of the *trans*-isomer (XXA), m.p. 105–111°. Recrystallization from benzene gave white crystalline powder, m.p. 113–115°, undepressed on admixture with a sample described below.

(b) *with the trans-malonate (XVIII A).* The above solid adduct (XVIII A) was hydrolyzed as described above. The diacid, m.p. 164–165° (dec.), obtained in 81% yield, was recrystallized from dilute methanol to colorless prisms, m.p. 165–166° (dec.).

*Anal.* Calcd. for  $C_{14}H_{18}O_5$ : C, 63.14; H, 6.81. Found: C, 63.23; H, 6.64.

Decarboxylation of the *trans*-diacid by the procedure described above gave in 93% yield the *trans*-monoacid (XXA), melting in the range of 95–114°. Recrystallization from ethyl acetate–petroleum ether furnished white crystalline powder, m.p. 113–115°. Gunstone and Tulloch<sup>6</sup> reported

the m.p. 113–115° for the monoacid, prepared by the Robinson condensation of VIII and diethylaminobutan-3-one.

XXA was methylated with diazomethane in ether to give almost quantitatively a *methyl ester*, which was distilled to colorless oil, b.p. 156–157° at 3.5 mm.;  $n_D^{20}$  1.5151. It formed a 2,4-dinitrophenylhydrazone, as orange scales, m.p. 160–161°, after recrystallization from benzenemethanol.

*Anal.* Calcd. for  $C_{20}H_{24}N_4O_6$ : C, 57.68; H, 5.81; N, 13.46. Found: C, 57.73; H, 5.90; N, 13.23.

*Methylation of methyl trans-9-methyl- $\Delta^4$ -3-octalone-6-acetate (XXA) with methyl iodide.* To a stirred potassium *tert*-butoxide, prepared from 85 mg. of potassium metal and 3 cc. of *tert*-butyl alcohol, a solution of 0.20 g. of the above methyl ester of the *trans*-monoacid (XXA) in 5 cc. of benzene was added. The solution became brown. Methyl iodide (0.5 g.) was added dropwise, and a white precipitate appeared soon and the color of the solution faded. The mixture was heated to a gentle reflux for 2.5 hr. The solvent was evaporated under reduced pressure, the residue was dissolved in water, and extracted with ether. The ether solution was shaken with sodium bicarbonate solution and then with water. Evaporation of the dried ether solution left a pale yellow oil (0.11 g.), which was chromatographed on alumina (acid-washed, 5 g.) and eluted with benzene and then with benzene–ether (4:1). The first elution with benzene gave the trimethyl ketone (XXIA) (25 mg.), m.p. 39–41°, which was recrystallized from petroleum ether to plates, m.p. 40–40.5°. It had no ultraviolet absorption band corresponding to the  $\alpha,\beta$ -unsaturated ketone.

*Anal.* Calcd. for  $C_{15}H_{24}O_3$ : C, 72.69; H, 9.15. Found: C, 72.28; H, 9.29.

It formed a 2,4-dinitrophenylhydrazone, yellow fine needles, m.p. 153–154°, after recrystallization from ethyl acetate–ethanol.

*Anal.* Calcd. for  $C_{22}H_{28}N_4O_6$ : C, 59.44; H, 6.35. Found: C, 59.69; H, 6.72.

The later elution with benzene gave an oil (10 mg.), which was converted to red 2,4-dinitrophenylhydrazone, melting in the range of 158–168°. Chromatography on alumina (1 g.) and elution with benzene furnished red fine needles, m.p. 180–182°, after recrystallization from ethyl acetate–ethanol. It showed no depression of the melting point on admixture with the same derivative of the *trans*-monoacid (IA) methyl ester, described above.

An oil (30 mg.), eluted with benzene–ether contained the starting keto-ester (XXA), characterized as 2,4-dinitrophenylhydrazone, m.p. 160–161° (after chromatography on alumina and recrystallization from ethyl acetate–ethanol).

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