

**Santonin and Related Compounds. IX. 6-Methyl-2-cyclohexen-1-one<sup>1</sup>**

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6-Methyl-2-cyclohexen-1-one (IV) was prepared by an unequivocal method, and was well characterized.

In 1911, Kötzt and Steinhorst<sup>2</sup> claimed the preparation of 6-methyl-2-cyclohexen-1-one (IV) from 2-methylcyclohexan-1-one by bromination with bromine and subsequent dehydrobromination with aniline. The evidence for the reported structure was based on the analysis of its semicarbazone, m.p. 177–179°, and the non-identity with the 2-methyl isomer (V), forming the semicarbazone, m.p. 207–208°, and with 2-methylenecyclohexan-1-one. Recently, Rinne, *et al.*<sup>3</sup> reported that the 6-methyl isomer was obtained from the same starting ketone by the procedure somewhat different from that reported by the German workers.<sup>2</sup> Two other routes to the 6-methyl isomer (IV) from the different starting materials are recorded in the literature. Birch<sup>4</sup> effected the reduction of N-dimethyl-*o*-toluidine or *o*-cresol methyl ether with sodium and liquid ammonia to form the 6-methyl isomer, which was considered by this author to be identical with that of the earlier workers.<sup>2</sup> Bowman, *et al.*<sup>5</sup> also obtained the same monoënone (IV) by oxidative hydrolysis of 1-bromo-2-methyl-5-cyclohexene.

It was previously shown<sup>6</sup> that the result for the 6-methyl isomer (IV) reported by Rinne, *et al.*<sup>3</sup> could not be repeated and that the sole product in the reaction was the 2-methyl isomer (V). This finding cast doubt on the 6-methyl structure (IV) for the unsaturated ketone of the German workers.<sup>2</sup> On repetition of their reaction, it was found that it also gave only the 2-methyl isomer (V), characterized as the semicarbazone, m.p. 207–208°. Consequently, it may be assumed that the discrepancy of the melting points of these two semicarbazones is merely due to dimorphism.

Now, it became desirable to prepare 6-methyl-2-cyclohexen-1-one (IV) by an unambiguous route. Following the method published by Mukherjee,<sup>7</sup> which was available to us only in abstract, ethyl 1-

methyl-3-cyclohexen-2-onecarboxylate (III) was prepared from ethyl 1-methyl-2-cyclohexanonecarboxylate (I) by bromination and subsequent dehydrobromination with quinoline. In this sequence, dehydrobromination of the monobromo ketone (II) always gave, in addition to the predominant III, a lower-boiling fraction in about 10% yield. This fraction exhibited the ultraviolet absorption spectrum,  $\lambda_{\max}^{\text{EtOH}}$  227 m $\mu$  ( $\epsilon$  8,770), showing that it consisted mainly of the 6-methyl isomer (IV). This situation is further proved by the observations that the fraction gave  $\alpha$ -methylglutaric acid on permanganate oxidation and yielded 4-methyl-3-cyclohexanoneacetic acid (VII) on hydrolysis and decarboxylation of the Michael addition product (VI) with ethyl malonate. However, this fraction formed a complicated mixture of 2,4-dinitrophenylhydrazones, from which the derivative of the 2-methyl isomer (V) was relatively readily isolated in about 20% yield and the derivative of the expected 6-methyl isomer (IV), which is described below, was obtained in a much smaller yield only after chromatography on alumina. The formation of V in this reaction may be due to the double bond migration occurring during the dehydrobromination of the monobromo ketone (II) followed by hydrolysis-decarboxylation of the resulting ester (III).

The unsaturated ester (III) was hydrolyzed with hydrochloric acid in acetic acid with concurrent decarboxylation. An oil, separated only in a low yield from a large quantity of resinous products, formed a semicarbazone, m.p. 183–185°, obviously different from that of the 2-methyl isomer (V). The 6-methyl structure (IV) for this ketone was proved by the ultraviolet absorption spectrum,  $\lambda_{\max}^{\text{EtOH}}$  225 m $\mu$  ( $\epsilon$  10,480), characteristic for the  $\alpha,\beta$ -unsaturated ketones with no substituents.<sup>8</sup> Concentration of the mother liquor of the semicarbazone by heating gave a semicarbazino-semicarbazone (VIII, R = H), the structure of which was based on the analytical figures and the ultraviolet absorption spectrum,  $\lambda_{\max}^{\text{EtOH}}$  229 m $\mu$  ( $\epsilon$  10,280), closely similar to that of the semicarbazone of 2-methylcyclohexan-1-one. This behavior of IV against semicarbazide is in sharp contrast to that of the 2-methyl isomer (V), which afforded a quantitative yield of the normal

(1) This work was supported in part by the grant in aid for Scientific Research from the Ministry of Education of Japan.

(2) Kötzt and Steinhorst, *Ann.*, **379**, 17 (1911).

(3) Rinne, Deutsch, Bowman, and Joffe, *J. Am. Chem. Soc.*, **72**, 5759 (1950).

(4) Birch, *J. Chem. Soc.*, 593 (1946).

(5) Bowman, Joffe, Rinne, and Wilkes, *Chem. Abstr.*, **45**, 2880 (1951).

(6) Yanagita and Inayama, *J. Org. Chem.*, **19**, 1724 (1954); *Cf.* Warnhoff and Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953).

(7) Mukherjee, *Chem. Abstr.*, **43**, 2605 (1949).

(8) Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corporation, New York, 1949, p. 190.

semicarbazone more readily.<sup>6</sup> Furthermore, the unsaturated ester (III) formed, as the sole product, the corresponding semicarbazino-semicarbazone, whose analytical data and ultraviolet spectrum,  $\lambda_{\max}^{\text{EtOH}}$  230 m $\mu$  ( $\epsilon$  10,230), are in good agreement with the structure (VIII, R = COOC<sub>2</sub>H<sub>5</sub>).

The 6-methyl isomer (IV) in pure form gave a difficulty separable mixture of 2,4-dinitrophenylhydrazones, from which two forms were isolated only in low yields. These derivatives are probably dimorphs, since the one, m.p. 122–125°, was transformed to the other, m.p. 161–163°, by repeated recrystallizations. In view of the facile migration of the double bond in cyclic systems by acid, it was suspected that, due to the comparably high concentration of the sulfuric acid in the 2,4-dinitrophenylhydrazine solution, IV might have been partly isomerized to V giving the complicated hydrazone mixture. This possibility was excluded by the observation that the crude hydrazone mixture from the 6-methyl isomer regenerated the parent ketone, the ultraviolet absorption spectrum of which remains practically unchanged. Birch<sup>4</sup> reported the 6-methyl-2-cyclohexen-1-one, 2,4-dinitrophenylhydrazone, m.p. 157°, which probably is impure. Furthermore, this author disclosed the formation of 2,4-dinitrophenylhydrazino-2,4-dinitrophenylhydrazone from IV on treatment with the alcoholic solution of hydrazine and concentrated sulfuric acid at reflux temperature, but this derivative was not obtained at ordinary temperature.

It was found that the bromo ketone (II) on reaction with 2,4-dinitrophenylhydrazine in methanol gave rise to a tetrahydroindazolone derivative (IX) bearing the methoxy group in the place of bromine. The structure of IX was assigned on the basis of the analytical figures and the ultraviolet spectrum, which resembles that of the 2,4-dinitrophenylhy-

drazone of 2-methylcyclohexanone rather than those of the same derivatives of the unsaturated ketones (IV and V), but showed no distinct peaks in the region of 240–300 m $\mu$  (Fig. 1). Contrary to the monobromo ketone (II), the related ketones, I, III, and ethyl 2-cyclohexanonecarboxylate quantitatively formed the normal 2,4-dinitrophenylhydrazone under comparable conditions.

During the progress of this investigation, Grob and Rumpf<sup>9</sup> published results on the formation of a tetrahydroindazolone derivative from I on brief treatment with *p*-nitrophenylhydrazine in refluxing acetic acid. Even under such conditions, the above three ketones gave only the normal 2,4-dinitrophenylhydrazones.

#### EXPERIMENTAL<sup>10</sup>

"6-Methyl-2-cyclohexen-1-one" of Kötze and Steinhorst. Following the procedure reported by the authors named,<sup>2</sup> 2-methylcyclohexan-1-one was brominated with a stream of dry air containing bromine to give the monobromide (54%), a colorless oil of b.p. 65–67° at 4.5 mm., which was dehydrobrominated with aniline in ether. The oily product (17%), b.p. 59–61° at 13 mm.,  $\lambda_{\max}^{\text{EtOH}}$  235 m $\mu$  ( $\epsilon$  5,686), formed, in 75% yield, a 2,4-dinitrophenylhydrazone which was recrystallized from ethanol; red leaflets, m.p. 198–202°. It showed no depression of the m.p. on admixture with the same derivative of 2-methyl-2-cyclohexen-1-one (V).<sup>5</sup>

Ethyl 1-methyl-2-cyclohexanonecarboxylate (I). This was prepared by a slight modification of the procedure reported previously.<sup>11</sup> To a stirred solution of 0.74 g. of sodium in 10 cc. of absolute ethanol was added dropwise, under ice-cooling, 5.5 g. of ethyl 2-cyclohexanonecarboxylate followed by 1.2 g. of methyl iodide. After being stirred for an additional 10 minutes at room temperature, the clear yellow solution was refluxed for 3 hours and worked up in the usual manner. There was obtained 5.52 g. (93%) of a pale yellow oil (I), b.p. 85–86° at 3 mm. Reported,<sup>11</sup> b.p. 113° at 11 mm.

It formed, in 60% yield, a semicarbazone, m.p. 158–159.5°, after recrystallization from ethanol. Reported, m.p. 152°<sup>11</sup> and 157–159°.<sup>9</sup>

Anal. Calc'd for C<sub>11</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>: N, 17.43. Found: N, 17.38.

With an equimolar amount of 2,4-dinitrophenylhydrazine in 20% ethanolic sulfuric acid, the oil (I) formed quantitatively, a 2,4-dinitrophenylhydrazone, m.p. 136–138°, which was recrystallized from ethanol to lustrous yellow scales, m.p. 138–139.5°;  $\lambda_{\max}^{\text{EtOH}}$  265 m $\mu$  ( $\epsilon$  7,870) and 360 m $\mu$  ( $\epsilon$  22,525).

Anal. Calc'd for C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>: C, 52.72; H, 5.35; N, 15.38. Found: C, 52.50; H, 5.79; N, 15.54.

Ethyl 1-methyl-3-cyclohexen-2-onecarboxylate (III). This was prepared from the above keto ester (I) by the procedure reported by Mukherjee.<sup>7</sup> The keto ester (96 g.) was treated with 83.4 g. of bromine to give a quantitative yield of the 3-bromo compound (II), which was used without further purification for the following step. The monobromide was heated with 100 g. of pure quinoline at 170–180° for 20 minutes. There was obtained 62 g. of an oil, which, after washing with alkali, was distilled into two fractions; a colorless oil (9.2 g.),

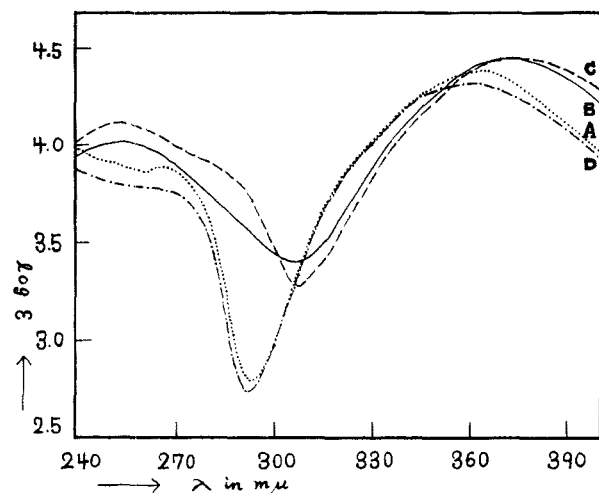


FIG. 1.—ULTRAVIOLET ABSORPTION SPECTRA OF THE 2,4-DINITROPHENYLHYDRAZONES OF: (A) 2-METHYLCYCLOHEXAN-1-ONE, (B) 2-METHYL-2-CYCLOHEXEN-1-ONE (V), (C) 6-METHYL-2-CYCLOHEXEN-1-ONE (IV); AND (D) 9-METHYL-2-(2',4'-DINITROPHENYL)-7-METHOXY-4,5,6,7-TETRAHYDRO-3-INDAZOLONE (IX).

(9) Grob and Rumpf, *Helv. Chim. Acta*, **37**, 1489 (1954).

(10) All temperatures are uncorrected. Microanalyses were made by Miss Shibuya, and ultraviolet measurements by Miss Suzuki, both of this school.

(11) (a) Kötze and Michels, *Ann.*, **350**, 212 (1906). (b) Chuang, Tien, and Huang, *Ber.*, **68**, 864 (1935). (c) Bachmann and Kishner, *J. Am. Chem. Soc.*, **65**, 1963 (1943).

b.p. 71–74° at 24 mm., and an aromatic oil (48.2 g., 50%), b.p. 114–117° at 11 mm.

The fraction of the lower boiling point will be described in the following paragraph. The fraction of the higher boiling point (III, 0.5 g.) was reacted with semicarbazide (0.6 g.) in ethanolic acetic acid at room temperature for a week. There was obtained 340 mg. (54%) of a *semicarbazino-semicarbazone* (VIII, R = COOC<sub>2</sub>H<sub>5</sub>), as white crystals, m.p. 196–199°. Recrystallization from ethanol raised the m.p. to 202–203°;  $\lambda_{\text{max}}^{\text{EtOH}}$  230 m $\mu$  ( $\epsilon$  10,250).

Anal. Calc'd for C<sub>12</sub>H<sub>22</sub>N<sub>6</sub>O<sub>4</sub>: C, 45.85; H, 7.05; N, 26.64. Found: C, 46.37; H, 7.25; N, 26.66.

The fraction of III formed quantitatively a *2,4-dinitrophenylhydrazone*, m.p. 115–121°, which was recrystallized from ethanol to yellow scales, m.p. 121–124°;  $\lambda_{\text{max}}^{\text{EtOH}}$  251 m $\mu$  ( $\epsilon$  8,500) and 366 m $\mu$  ( $\epsilon$  23,340).

Anal. Calc'd for C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>6</sub>: C, 53.03; H, 5.01; N, 15.46. Found: C, 52.70; H, 5.09; N, 15.26

The crude  $\alpha$ -bromo ketone (II, 95 mg.) was added to a solution of 80 mg. of 2,4-dinitrophenylhydrazine and 0.1 cc. of concentrated sulfuric acid in 2 cc. of ethanol, and allowed to stand for 36 hours at room temperature. There was obtained a tetrahydroindazolone (IX) (110 mg., 70%), melting in the range of 85–123°, which was recrystallized twice from ethanol to lustrous golden yellow needles, m.p. 143–145°;  $\lambda_{\text{max}}^{\text{EtOH}}$  362 m $\mu$  ( $\epsilon$  20,800).

Anal. Calc'd for C<sub>15</sub>H<sub>15</sub>N<sub>4</sub>O<sub>6</sub>: C, 51.71; H, 4.63; N, 16.09. Found: C, 51.85; H, 4.81; N, 16.40.

*6-Methyl-2-cyclohexen-1-one* (IV). (a) A solution of 20 g. of the unsaturated ester (III) in 400 cc. of acetic acid was added to 300 cc. of 24% hydrochloric acid, and heated to a gentle reflux in an oil-bath for 14 hours. After cooling, the reaction mixture was poured into water, neutralized with sodium carbonate, and extracted with ether. Washing with aqueous alkali, drying, and evaporation of the ether extract gave an oily residue (7.0 g.), which was distilled to give a colorless oil (2.64 g., 26%), b.p. 69–71° at 18 mm. or 46–49° at 9 mm.;  $\lambda_{\text{max}}^{\text{EtOH}}$  225 m $\mu$  ( $\epsilon$  10,480).

The oil (0.22 g.) was added to a solution of semicarbazide in ethanolic acetic acid (from 0.46 g. of semicarbazide hydrochloride) and allowed to stand overnight at room temperature. A *monosemicarbazone* (0.12 g., 36%), m.p. 162–174°, was filtered and recrystallized from ethanol to lustrous prisms, m.p. 182–185°;  $\lambda_{\text{max}}^{\text{EtOH}}$  232 m $\mu$  ( $\epsilon$  9,390) and 269 m $\mu$  ( $\epsilon$  13,230).

Anal. Calc'd for C<sub>8</sub>H<sub>13</sub>N<sub>3</sub>O: N, 25.13. Found: N, 25.27.

The mother liquor of the semicarbazone was concentrated in a water-bath and allowed to stand giving a *semicarbazino-semicarbazone* (VIII, R = H), as white crystals (105 mg., 22%), m.p. 176–181°. Recrystallization from a large quantity of ethanol afforded microscopic crystals, m.p. 193–195°;  $\lambda_{\text{max}}^{\text{EtOH}}$  229 m $\mu$  ( $\epsilon$  10,280).

Anal. Calc'd for C<sub>9</sub>H<sub>13</sub>N<sub>6</sub>O<sub>2</sub>: N, 34.69. Found: N, 34.31.

As described above for the keto ester (I), this oil gave quantitatively a mixture of 2,4-dinitrophenylhydrazones, m.p. 124–129°, from which on repeated crystallization from ethanol and then from ethyl acetate one form of the *2,4-dinitrophenylhydrazone* of IV was obtained as orange needles (20%), m.p. 162–164°;  $\lambda_{\text{max}}^{\text{EtOH}}$  255 m $\mu$  ( $\epsilon$  10,240) and 362 m $\mu$  ( $\epsilon$  27,120). Reported, m.p. 156–157°<sup>4</sup> and m.p. 158°.<sup>5</sup>

Anal. Calc'd for C<sub>13</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>: C, 53.77; H, 4.86; N, 19.33. Found: C, 54.17; H, 5.01; N, 19.03.

From the mother liquors of recrystallizations of the above hydrazone, another form of the *2,4-dinitrophenylhydrazone* was obtained as orange scales, m.p. 122–125.5°, after recrystallization from ethanol.

Anal. Calc'd for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>: C, 53.77; H, 4.86; N, 19.33. Found: C, 53.65; H, 5.34; N, 19.19.

On persistent recrystallization from ethanol, the latter form of the lower m.p. was suddenly converted to the former of the higher m.p.

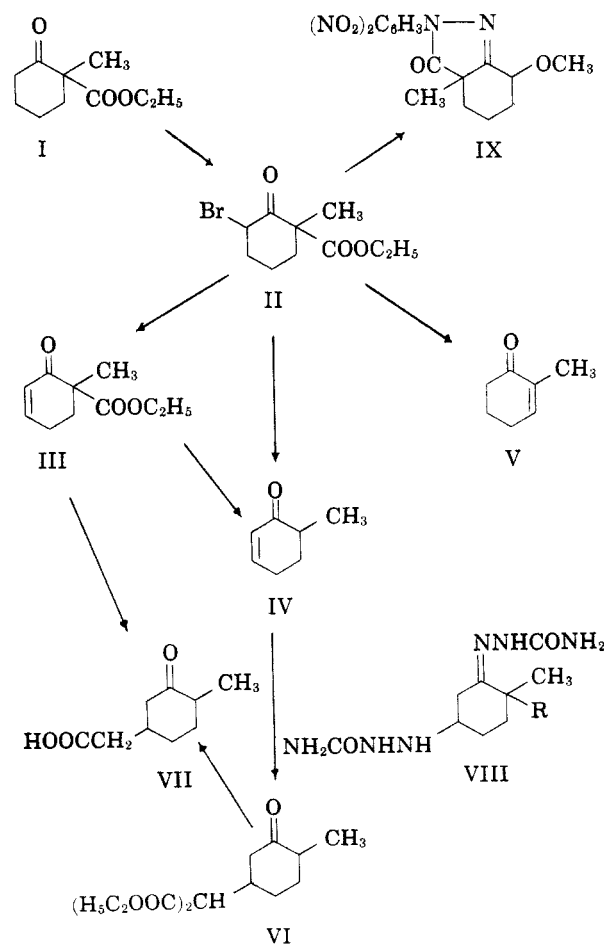
The above crude mixture of 2,4-dinitrophenylhydrazones of IV with pyruvic acid gave back the parent ketone, showing  $\lambda_{\text{max}}^{\text{EtOH}}$  225 m $\mu$  ( $\epsilon$  9,900). IV was rapidly hydrogenated in

ethanol over palladium-charcoal to give 2-methylcyclohexanone, identified as its 2,4-dinitrophenylhydrazone, m.p. 135–136°, undepressed on admixture with a sample prepared from 2-methylcyclohexanone.

(b) The lower-boiling fraction of the dehydrobromination product from the  $\alpha$ -bromo ketone (II), described above, showed  $\lambda_{\text{max}}^{\text{EtOH}}$  227 m $\mu$  ( $\epsilon$  8,770) and formed quantitatively a complicated mixture of 2,4-dinitrophenylhydrazones, melting in the range of 150–163°. Fractional crystallization from ethanol afforded the derivative, m.p. 202–205°, of 2-methyl-2-cyclohexen-1-one (V, 20%), as less soluble crystals, and the derivative, m.p. 161–163° (after chromatography on alumina), of 6-methyl-2-cyclohexen-1-one (IV), as more soluble crystals. The melting points of these 2,4-dinitrophenylhydrazones were not depressed on admixture with the respective samples from the preceding experiment.

On reaction with semicarbazide as described above, this fraction gave only the semicarbazone (33%), m.p. and mixture m.p. 202–206° (after recrystallization from ethanol) of 2-methyl-2-cyclohexen-1-one (V).

To a stirred mixture of 0.5 g. of this fraction in 20 cc. of water was added, dropwise, a solution of potassium permanganate (2.4 g.) in acetone with ice-cooling. After the addition, the stirring was continued for another 2 hours at room temperature, the reaction mixture was heated in a water-bath for 20 minutes, and worked up in the usual manner. There was obtained 0.19 g. (32%) of a bicarbonate-soluble oil, which soon solidified, m.p. 67–70°. Recrystallization from water and then from benzene-petroleum ether gave white prisms, m.p. 71–74°. It showed no depression of the m.p. on admixture with  $\alpha$ -methylglutaric acid, m.p.



72–74°, prepared by the method reported by Ansell and Hey.<sup>12</sup>

*Anal.* Calc'd for  $C_6H_{10}O_4$ : C, 49.31; H, 6.90. Found: C, 49.37; H, 7.32.

To a stirred solution of sodium ethoxide, prepared from 46 mg. of sodium and 7.5 cc. of absolute ethanol, was added, dropwise, 1 g., of this fraction, and then 1.76 g. of ethyl malonate, under chilling with ice-salt mixture. After the stirring was maintained for an additional 2 hours, the reaction mixture was worked up as usual. The neutral oily product (1.5 g.) was distilled to give two fractions, a colorless oil (0.35 g.), b.p. 95–98° at 23 mm., and a viscous oil (1.12 g., 50%), b.p. 168–169° at 7 mm. The former fraction of the lower boiling point formed a small quantity of 2,4-

dinitrophenylhydrazone, m.p. and mixture m.p. 201° (after recrystallization from ethanol), of 2-methyl-2-cyclohexen-1-one (V). The fraction of the higher boiling point (1 g.), which consisted mainly of the diester (VI), was heated with 5 cc. of concentrated hydrochloric acid in a water-bath for 39 hours. The reaction mixture was extracted with ether, and the ether extract was shaken with aqueous sodium bicarbonate. The bicarbonate solution was acidified and extracted with ether. Evaporation of the dried ether solution left an oil (460 mg., 80%), which solidified, m.p. 80–87°. Recrystallization from ether-petroleum ether afforded thick prisms, m.p. 91–94°, undepressed on admixture with 4-methyl-3-cyclohexanoneacetic acid (VII) prepared from the Michael adduct of the unsaturated ester (III) with malonate, which will be reported in the near future.

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(12) Ansell and Hey, *J. Chem. Soc.*, 1683 (1950).

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