Syntheses of γ-Ionone Analogues. V. 8, 9-cis-4, 5, 6-Trimethyloctahydroisobenzofuran and its Derivatives[1]

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(Received July 6, 1961)

In the preceding paper[2] we briefly described an oil, $C_{11}H_{20}O$, which was obtained as one of the hydrogenolysis products of the ethylene acetal of 6-benzyloxymethyl-2, 3, 4-trimethyl-3-cyclohexenylmethanal (V). The infrared spectrum and some properties of this compound resembled those of octahydroisobenzofuran[3] and it showed bands in the infrared region (Fig. 1) at 905 and 886 cm^{-1} characteristic of a tetrahydrofuran ring and at 1053 cm^{-1} indicative of an ether group. M^me^ Mousseron-Canet and her co-laborators[4] have pointed out

1) Presented partly before the Meeting of Hokkaido district of the Chemical Society of Japan, Sapporo, July, 1960.

2) A. Arai and I. Ichikizaki, This Bulletin, 35, 504 (1962).

3) J. Entel, C. H. Ruof and H. C. Howard, *J. Am. Chem. Soc.*, 74, 441 (1952).

4) M. Mousseron-Canet and M. Granier, *Bull. soc. chim.*, 1959, 473; M^me^ Mousseron, M. Mousseron and M. Granier, ibid., 1960, 1418.

in their study on the infrared spectra of the octahydroisobenzofuran series that the absorption band of a C–O–C group at 1000 to 1100 cm^{-1} offers an available information to determine the conformation of cyclic oxide, and they have shown by pertinent comparison with the two stereoisomers of tricyclic oxide which are derivatives of the gem. dimethyloctaline that the cis isomer indicates a characteristic band at 1056 to 1060 cm^{-1}, whereas the trans shows a band at 1020 cm^{-1}. Thus, the structure of 8, 9-*cis*-4, 5, 6 - trimethyloctahydroisobenzofuran (I) was assigned for the oil and it was supported also by the succeeding experimental evidences as described below.

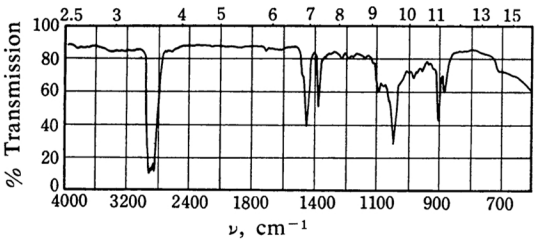


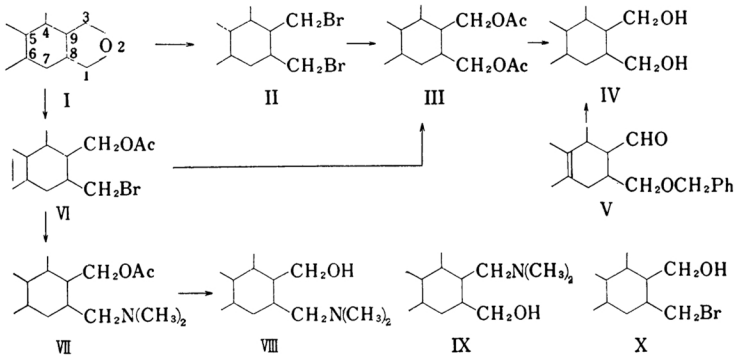
Fig. 1. Infrared spectrum of 8,9-*cis*-4,5,6-trimethyloctahydroisobenzofuran (I).

The compound I reacted with hydrogen bromide in glacial acetic acid at 100°C to give a mixture of dibromide II and a small amount of any acetoxy compounds which showed an infrared absorption band with ν_{max} 1737 cm^{-1}. The mixture could be mostly converted into 1, 2-diacetoxymethyl-3, 4, 5-trimethylcyclohexane (III) on being heated under reflux in glacial acetic acid containing potassium acetate and acetic anhyride and simultaneously gave a considerable amount of I. On alkaline hydrolysis III afforded a high yield of 1, 2-dihydroxymethyl-3, 4, 5-trimethylcyclohexane (IV) which was identical with the hydrogenation product[2] of the compound V. On the other hand, with acetyl bromide in the presence of zinc chloride I reacted to give a bromo acetate, $C_{13}H_{23}O_2Br$, in an expellent yield, which upon further acetylation followed by saponification yielded the diol IV. Although it has been well-known that tetrahydro-furans and -pyrans are generally cleaved by hydrogen halides[5-8] or acid halides[8-10] to give the corresponding dihalides or haloesters, no study on the cleavage of the asymmetric oxide ring as in I has been reported. Now it becomes interesting for us whether the cleavage takes place at the C(1)–O or it does at the C(3)–O linkage.

On treatment with an excess of anhydrous dimethylamine in absolute methanol the bromo acetate obtained above afforded 30% yield of an amino acetate, $C_{15}H_{29}O_2N$, and 35% yield of the parent oxide I, while the starting substance was also recovered in part. Alkaline hydrolysis of this amino acetate gave a high yield of the corresponding amino alcohol, $C_{13}H_{27}ON$, whose infrared absorption bands in almost all regions have close resemblance to those of *N*, *N*-dimethyl-6-hydroxymethyl-2, 3, 4-trimethylcyclohexylmethylamine (IX)[2]. Its methiodide, m. p. 202~203°C, resembled that of IX melted at 204~206°C in many respects, but the mixture melting point showed a marked depression. It is, therefore, no doubt that the amino alcohol is to be a structural isomer of IX and that in it the hydroxymethyl and the *N*, *N*-dimethylaminomethyl groups are reversely located as compared with IX. Thus, we assigned *N*, *N*-dimethyl-2-hydroxymethyl-3, 4, 5-trimethylcyclohexylmethylamine (VIII) for this compound. *N*, *N*-Dimethyl-2-acetoxymethyl - 3, 4, 5 - trimethylcyclohexylmethylamine (VII) and 2-acetoxymethyl-1-bromomethyl-3, 4, 5-trimethylcyclohexane (VI) were accordingly assigned for the amino acetate and the bromo acetate, respectively. Furthermore, it became clear that the fission of the tetrahydrofuran ring in I with acetyl bromide occurs essentially in the 1, 2-position. And in the course of reaction involving the ring fission and the reverse cyclization it has been proved that the configuration of oxide I is completely retained still in the derivatives as stated for octahydroisobenzofuran[8]. The compound V is believed to have a 1, 6-*cis* conformation according to the Alders' rule authorized by a number of investigators[11,12]. The 8, 9-*cis* conformation previously proposed for the oxide by its infrared spectral analysis, therefore, received further support from the fact that I as well as V gives the same diol IV.

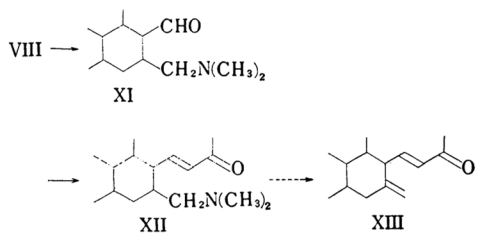
The formation of I in the course of amination of the bromo acetate VI may be conveniently explained by considering the bromo alcohol X as an intermediate, which would be formed readily by the interaction of the acetoxyl group and dimethylamine and converted into oxide I by the base promoted elimination of hydrogen bromide, since such

5) S. Fried and R. D. Kleene, *J. Am. Chem. Soc.*, **62**, 3258 (1940); **63**, 2691 (1941).
6) A. Lüttringhaus and A. Brechlin, *Ber.*, **92**, 2271 (1959).
7) S. F. Birch, R. A. Dean and E. V. Whitehead, *J. Org. Chem.*, **19**, 1449 (1954).
8) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, **1953**, 389, 408.
9) G. Sieber, *Ann.*, **631**, 180 (1960).
10) J. B. Cloke and F. J. Pilgrim, *J. Am. Chem. Soc.*, **61**, 2667 (1939).
11) M. C. Kloetzel, "Organic Reactions", Vol. IV, John Wiley and Sons, Inc., New York (1948), p. 1.
12) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960).



halo alcohols have been commonly used for the most effective preparation of the oxides in this series[8].

The amino alcohol VIII was oxidized by a modified Oppenauer procedure with *p*-benzyloxybenzaldehyde as a hydrogen acceptor[2] to give a high yield of *N*, *N*-dimethyl-2-formyl-3, 4, 5 - trimethylcyclohexylmethylamine (XI), which afforded on condensation with acetone in the presence of sodium hydride 4-(6′-*N*, *N*-dimethylaminomethyl - 2′, 3′, 4′ - trimethylcyclohexyl)-but-3-en-2-one (XII) in 59% yield. Two compounds XI and XII were fully identified by the infrared spectrum. The latter compound would seem to be an intermediate to 4-(6′-methylene - 2′, 3′, 4′ - trimethylcyclohexyl)-but-3-en-2-one (XIII), an analogue of γ-irone, but further investigation has not been performed.



Experimental[13]

8, 9-*cis*-4, 5, 6 - Trimethyloctahydroisobenzofuran (I).—Compound I was previously obtained[2] as one of the hydrogenolysis products of the ethylene acetal of 6-benzyloxymethyl-2, 3, 4-trimethyl-3-cyclohexenylmethanal (V). A sample having b. p. 66～68°C/1.8 mmHg and n_D^{27} 1.4739 was used for the next experiments. Its infrared spectrum is shown in the theoretical part.

1, 2 - Dibromomethyl-3, 4, 5-trimethylcyclohexane (II).—A mixture of oxide I (6.7 g.) and acetic acid (20 ml.) containing anhydrous hydrogen bromide (9.0 g.) was heated for 5 hr. at 100°C in a 50 ml. glass bomb. Hydrogen bromide and acetic acid were distilled off and the remaining oil was dissolved in chloroform (15 ml.). The chloroform solution was washed with 20% aqueous sodium bicarbonate and with water and dried over sodium sulfate. The solvent was removed and the residue was distilled to give a colorless pleasant smelling liquid (7.5 g.), b. p. 106～107.5°C/0.8 mmHg, n_D^{11} 1.5248, whose infrared spectrum showed the presence of an acetate group (1737 cm^{-1}) and no hydroxyl group.

Found: C, 46.46; H, 7.20. Calcd. for $C_{11}H_{20}Br_2$ (II): C, 42.31; H, 6.41%.

From the above infrared spectrum and elemental analysis it was believed that the product consists of 1,2-dibromomethyl-3,4,5-trimethylcyclohexane (II) and a considerable amount of any acetoxy derivative.

1,2-Diacetoxymethyl-3, 4, 5-trimethylcyclohexane (III).—The crude dibromide (4.3 g.) obtained above was heated under reflux with acetic acid (60 ml.) containing potassium acetate (15 g.) and acetic anhydride (3 ml.) for 37 hr. After the bulk of acetic acid was removed under reduced pressure, the residue was extracted with ether and the ether extract was washed with a 20% aqueous sodium carbonate solution and with water, dried over sodium sulfate and evaporated. Distillation of the residue gave a fore-run (0.9 g.) consisting largely of the oxide I, b. p. 65～67°C/1.65 mmHg, and a high-boiling oil (1.8 g.) had b. p. 105～107°C/0.6 mmHg and n_D^{15} 1.4760, which gave on redistillation through a 10 cm. Vigreux column the diacetate III, b. p. 108°C/0.75 mmHg, n_D^{18} 1.4740. ν_{max} (liquid film) 1737 (ester, C=O), 1237 (ester, C-O-C) and 1035 cm^{-1} (C-O).

Found: C, 66.45; H, 9.76. Calcd. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%.

2-Acetoxymethyl-1-bromomethyl-3, 4, 5-trimethylcyclohexane (VI).—A mixture of I (4.4 g.), freshly distilled acetyl bromide (4.0 g., 125%), and zinc chloride (0.2 g.) was heated under reflux for 1.5 hr. in which time boiling had ceased. The dark-brown reaction mixture was dissolved in chloroform and the chloroform solution was washed with aqueous sodium bicarbonate and with water, dried and evaporated. The remaining oil was distilled to afford the bromo acetate VI (5.4 g., 71%) as a pale yellow, pleasant smelling oil, b. p. 102～105°C/

13) All melting points and boiling points are uncorrected. Infrared spectra were measured with a Nippon Bunkō model IR-S double-beam recording spectrophotometer with sodium chloride optics.

0.65 mmHg, n_D^{11} 1.5032. For analysis a sample was redistilled through a 8 cm. Vigreux column; b. p. 104~104.5°C/0.5 mmHg, 121~122°C/1.2 mmHg, n_D^{12} 1.5090. ν_{max} (liquid film) 1738 (ester, C=O), 1234 (ester, C-O-C), 1034 (C-O) and 1384, 1372 cm^{-1} (doublet, CH_3 and O-$COCH_3$ groups).

Found: C, 53.38; H, 7.85. Calcd. for $C_{13}H_{23}O_2$·Br: C, 53.60; H, 7.92%.

1,2-Dihydroxymethyl-3,4,5-trimethylcyclohexane (IV).—*a) Alkaline Hydrolysis of III.*—A solution of the diacetate III (0.55 g.) and potassium hydroxide (0.3 g.) in methanol (7 ml.) was allowed to stand for 41 hr. at room temperature. The reaction mixture was neutralized with 2 N sulfuric acid under cooling and then extracted, after the removal of the bulk of methanol, with ether. The ether extract was washed with water and dried over sodium sulfate. Removal of the solvent followed by distillation of the residue and yielded diol IV (0.35 g., 92.5%) as a viscous oil, b. p. 128~130°C/0.65 mmHg, n_D^6 1.4925. ν_{max} (liquid film) ~3300 and ~1045 cm^{-1} (OH).

Found: C, 70.99; H, 11.76. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90%.

The bis-*p*-nitrobenzoate crystallized from methanol in needles, m. p. 161~162°C, which gave no melting point depression on admixture with that of the diol obtained previously[2] from 6-benzyloxymethyl-2,3,4-trimethyl-3-cyclohexenylmethanal (V).

Found: C, 61.88; H, 5.96. Calcd. for $C_{25}H_{28}O_8N_2$: C, 61.97; H, 5.83%.

b) Further Acetylation Followed by Alkaline Hydrolysis of VI.—A mixture of the bromo acetate VI (2.2 g.), acetic acid (25 ml.), potassium acetate (10 g.) and acetic anhydride (1.8 ml.) was heated under reflux for 20 hr. The bulk of acetic acid and acetic anhydride was removed under reduced pressure, and the orange-brown residue was dissolved in solution of potassium hydroxide (3.0 g.) in 90% methanol (15 ml.) and the solution was set aside for 24 hr. at room temperature. The reaction mixture was treated with the same method as described for a) to afford VI (0.8 g., 56.8%), b. p. 140~142°C/2.1 mmHg, n_D^{29} 1.4870, whose infrared spectrum and solid derivative were identical with those of the diol IV prepared in the method of a).

Reaction of the Bromo Acetate VI with Dimethylamine.—A solution of the bromo acetate VI (3.4 g.) and anhydrous dimethylamine (6.5 g., 10 times of the theoretical amounts) in absolute ethanol (17 ml.) was allowed to stand for 10 days at room temperature in a 50 ml. amber glass bomb. After removal of the solvent and dimethylamine under reduced pressure, the residue was dissolved in ether (30 ml.). The ethereal solution was extracted with three 10 ml. portions of 2 N hydrochloric acid and the combined extracts were washed once with light petroleum and then made to basic with 10% aqueous alkali under cooling. The organic base regenerated was taken up in ether and the ether layer was washed with an aqueous saturated salt solution, dried over sodium sulfate and evaporated. Distillation of the residue to give a slightly yellow oil (0.75 g.), b. p. 90~91°C/0.5 mmHg, n_D^{16} 1.4808, whose infrared spectrum showed characteristic absorptions of the acetyl group at 1739 and 1240 cm^{-1} and *tert*-amino group at 2846, 2800 and 2755 cm^{-1}, and weak bands the hydroxyl group at of ~3390 and ~3200 cm^{-1}.

Found: C, 70.88; H, 11.36; N, 5.62. Calcd. for $C_{15}H_{29}O_2N$: C, 70.54; H, 11.45; N, 5.48%.

It is believed, therefore, that above oil consists of *N,N*-dimethyl-2-acetoxymethyl-3,4,5-trimethylcyclohexylmethylamine (VII) contaminated with a small amount of its hydrolyzed product VIII.

The ethereal solution remained was washed with water, dried over sodium sulfate and evaporated. The residue was distilled to give the oxide I (0.7 g., 35%), b. p. 51~52°C/0.5 mmHg, n_D^{12} 1.4803, (Found: C, 78.61; H, 11.82%), and to recover the unchanged VI (0.5 g., 14.7%), b. p. 104~105°C/0.5 mmHg.

***N,N*-Dimethyl-2-hydroxymethyl-3,4,5-trimethylcyclohexylmethylamine (VIII).**—A solution of the amino acetate VII (0.3 g.) and potassium hydroxide (0.3 g.) in methanol (5 ml.) was kept for 40 hr. at room temperature. Ether (50 ml.) was added to the reaction mixture and the resultant solution was washed with a saturated aqueous salt solution, dried over potassium carbonate and evaporated. Distillation gave the amino alcohol VIII (0.24 g.) as a colorless liquid, b. p. 87~89°C/0.5 mmHg, n_D^{10} 1.4852. ν_{max} (liquid film) 3395, 3200, 1041 (OH); 2840, 2790, 2750 (-$N(CH_3)_2$); 848, 833 cm^{-1} (unassigned).

Found: C, 73.17; H, 12.82; N, 6.62. Calcd. for $C_{13}H_{27}ON$: C, 73.18; H, 12.76; N, 6.57%.

In a separate preparation from VI without isolation of the amino acetate VII, 35% over-all yield of VIII was obtained.

The methiodide crystallized from methanol-ethyl acetate in leaflets, m. p. 202~203°C, which showed a marked depression in the mixed melting point determination with that of *N,N*-dimethyl-6-hydroxylmethyl-2,3,4-trimethylcyclohexylmethylamine (IX) melted at 204~206°C.

Found: C, 47.28; H, 8.74; N, 3.83. Calcd. for $C_{14}H_{30}ONI$: C, 47.30; H, 8.50; N, 3.95%.

***N,N*-Dimethyl-2-formyl-3,4,5-trimethylcyclohexylmethylamine (XI).**—To the amino alcohol aluminate prepared from IX (1.5 g.) and aluminum isopropoxide (0.55 g., 115%) *p*-benzyloxybenzaldehyde (2.4 g., 160%) was added and the resultant mixture was distilled under nitrogen with the same method as described for the oxidation of the isomeric amino alcohol IX[2] to give an oil (1.23 g.), redistillation of which through an 8 cm. Vigreux column afforded the aminoaldehyde XI (1.05 g., 81%) as a colorless oil, b. p. 87~89°C/0.85 mmHg, n_D^{20} 1.4744, whose infrared spectrum showed the presence of C=O (1711), -$N(CH_3)_2$ (2844, 2798, 2753), and no hydroxyl group.

Found: C, 73.52; H, 11.98; N, 6.61. Calcd. for $C_{13}H_{25}ON$: C, 73.88; H, 11.92; N, 6.63%.

Treatment of this oil with picric or picrolonic acids gave an orange-red oil which could not be induced to crystallize. An attempt to prepare the analytical sample of the 2,4-dinitrophenylhydrazone of XI was unsuccessful.

4-(6'-*N,N*-Dimethylaminomethyl-2',3',4'-trimethylcyclohexyl)-but-3-en-2-one (XII).—The amino aldehyde XI (1.0 g.) in freshly distilled acetone

(5 ml.) was added to a cold solution of sodium hydride (30 mg.) in acetone (15 ml.) with vigorous stirring under a nitrogen atmosphere. The resultant mixture was stirred for additional 3 hr. at room temperature, and evaporated under reduced pressure to remove the bulk of acetone. The residue was dissolved in ether and the ethereal solution was extracted twice with 10% hydrochloric acid. The combined extracts were basified with 10% aqueous alkali, after being washed once with light petroleum, to regenerate the organic base which was taken up in ether. The ethereal solution was washed with water, dried over potassium carbonate and concentrated. Distillation gave the amino ketone XII (0.7 g., 59%) as a pale yellow oil, b. p. 122~125°C/0.7 mmHg, n_D^{23} 1.4842. For analysis a sample was redistilled; b. p. 122~125°C/0.65 mmHg, n_D^{25} 1.4852.

ν_{max} (liquid film) 1680 (C=O, conju.); 1622 (C=C, conju.); 984 (-CH=CH-, trans); 2839, 2800, 2752 ($-N(CH_3)_2$); 1259 (=C-CO-); 1381 (CH_2); 1361 ($COCH_3$); 840 cm^{-1} (unassigned).

Found: C, 76.22; H, 11.78. Calcd. for $C_{16}H_{29}ON$: C, 76.44; H, 11.63%.

An attempt to prepare the 2,4-dinitrophenylhydrazone of this compound was unsuccessful.

The authors are indebted to Dr. Asaji Kondo of the Tokyo Institute of Technology for the microanalyses.

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