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95. Hitoshi Minato, Makoto Ishikawa, and Tohru Nagasaki : Studies on Sesquiterpenoids. X.*1 Small Scale Dehydrogenation of Some Perhydro-azulene and -naphthalene Derivatives.

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In studies on sesquiterpenoids, dehydrogenation is an important technique which is often carried out in order to confirm the structures. Our group obtained the fura-

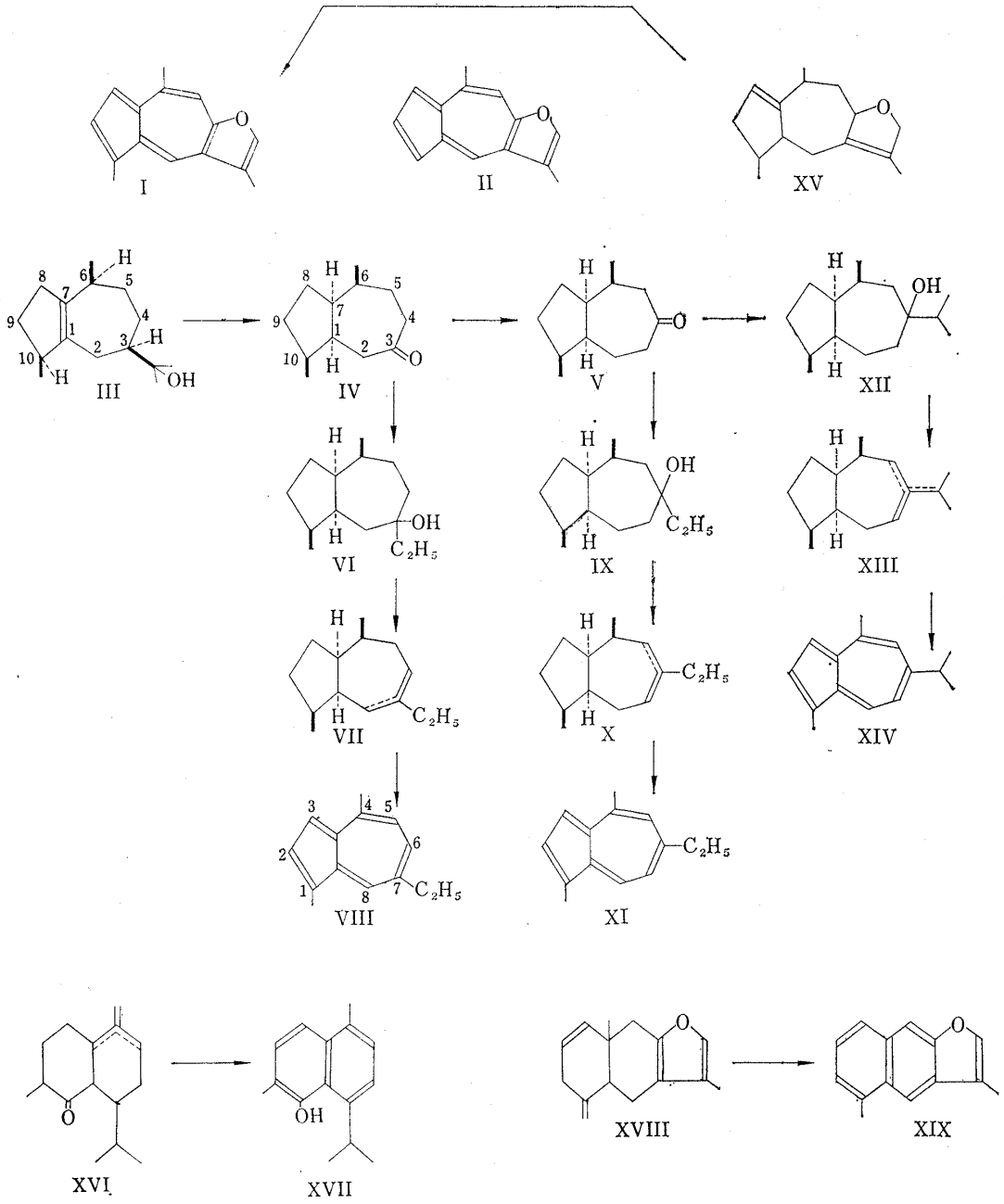

Chart 1.

*1 Part IX. H. Ishii, T. Tozyo, H. Minato : Tetrahedron, in the press.

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noazulenes, linderazulene (I) and ujacazulene (II), by dehydrogenation during studies[1~3] on furanosesquiterpenes. At that occasion, necessity compelled us to develop a micro-technique for dehydrogenation, using palladium-charcoal for this purpose.

In this report, we wish to examine the reaction conditions with perhydroazulene derivatives obtained from guaiol (III).

6,10-Dimethylbicyclo[5,3,0]decan-3-one (IV) was obtained from guaiol (III) as already reported,[4] and converted into VII by treatment with ethylmagnesium iodide followed by dehydration of VI with thionyl chloride-pyridine. Dehydrogenation of VII afforded chamazulene[5,6] (VIII).

6,10-Dimethylbicyclo[5,3,0]decan-4-one[4] (V) was obtained from IV and its structure was elucidated by the fact that V afforded 6-isopropyl-1,4-dimethylazulene[7] (XIV) *via* XII and XIII. Compounds (X and XIII) were obtained by treatment of V with ethylmagnesium iodide or isopropylmagnesium bromide, followed by dehydration of IX or XII. Linderazulene (I) was obtained by dehydrogenation of compound[1] (XV).

General procedure of dehydrogenation is as follows: A mixture of a compound and 10% palladium-charcoal in a test tube (15~20 cm.) is heated at 305~325° in a nitrogen atmosphere, and then azulene which immediately condensed on the upper part of the tube is extracted with light petroleum. The light petroleum extract is extracted with conc. phosphoric acid under ice-cooling, and the phosphoric acid layer is added to ice-water and extracted again with light petroleum to give azulene. With furanoazulene (I or II),

Table I.

Entry No.	Compound	(mg.)	10% Pd-C (mg.)	Ratio of compound and 10% Pd-C	Time (min.)	Dehydrogenation product (mg.)	Azulene	(mg.)	(%)
1	VII	165	300	1 : 1.8	15	90.0		0	0
2	VII	113	120	1 : 1.06	15	71.7	VIII	0.7	0.6
3	VII	162	90	1 : 0.55	15	109.0	VIII	4.5	2.8
4	VII	73	33	1 : 0.45	8	52.0	VIII	4.0	5.5
5	VII	50	20	1 : 0.4	2	23.0	VIII	2.1	4.2
6	VII	109	30	1 : 0.28	10	73.0	VIII	2.5	2.3
7	X	33.3	25	1 : 0.75	1	23.6	XI	4.2	12.6
8	X	73.4	50	1 : 0.68	1	56.7	XI	6.5	8.8
9	X	52	30	1 : 0.58	3	32.1	XI	4.0	7.7
10	XIII	20.5	35	1 : 1.7	2.5	11.0		0	0
11	XIII	27.2	20	1 : 0.74	1	20.6	XIV	3.0	11.0
12	XIII	62.5	42	1 : 0.67	1.5	53.9	XIV	4.5	7.2
13	XIII	45	30	1 : 0.67	1.5	33.2	XIV	4.0	8.9
14	XV	20	100	1 : 5	5	3.0		0	0
15	XV	44	44	1 : 1	5	26.5	I	4.2	10.0
16	XV	15	15	1 : 1	5	10.7	I	1.5	10.3
17	XV	21.4	10.4	1 : 0.5	3	18.3	I	3.8	18.0
18	XV[a]	17.1	8.4	1 : 0.5	3	15.0	I	4.0	23.0
19	XVI	49.8	25	1 : 0.5	1	42.2	XVII	27.2	56.0
20	XVIII	60	60	1 : 1	5	41	XIX	12.5	22.6

a) See reference 1. Entry No. 1~13: Reaction was carried out at 320~325°.
Entry No. 14~18: Reaction was carried out at 305~310°.

1) K. Takeda, H. Minato, M. Ishikawa: J. Chem. Soc., **1964**, 2591.
2) K. Takeda, H. Minato, K. Hamamoto, I. Horibe, T. Nagasaki, M. Ikuta: *Ibid.* **1964**, 3577.
3) K. Takeda, H. Minato, M. Ishikawa: *Ibid.* **1964**, 4578.
4) K. Takeda, H. Minato, T. Terasawa, Ch. Yanaihara: This Bulletin, To be published.
5) F. Šorm, V. Herout, K. Takeda: Collection Czechoslov. Chem. Communs., **19**, 186 (1954).
6) K. Takeda, T. Kubota, W. Nagata: This Bulletin, **1**, 241 (1953).
7) Pl. A. Plattner, A. Fürst. L. Marti: Helv. Chim. Acta, **32**, 2452 (1949).

the purification by conc. phosphoric acid is not carried out and the light petroleum extract is immediately chromatographed on neutral alumina, because treatment with phosphoric acid soils the azulene.

As shown in Table I, (1) dehydrogenation with a large amount of palladium-charcoal does not give azulene (Entry No. 1, 10, or 14), while again it is not satisfactory to use only a very small amount (Entry No. 6). The desirable ratio of the compound and palladium-charcoal is 1:0.75~1:0.5. (2) Prolonging the reaction time it is not significant and may rather lower the yield of azulene (Entry No. 2~6). The favorable reaction time is 1~3 min. (3) It is unfavorable to dehydrogenate a large amount of a compound at once by this technique (Entry No. 3); the desirable amount is to the extent of 50 mg. (4) The optimum reaction temperature is 300~330°. (5) It is probably reasonable to conclude that the yield of I is better than that of Ⅷ, Ⅺ, or XIV, since the dehydrogenated compound (XV) has two ethylenic double bonds in its molecule.

This method is also applicable to perhydronaphthalene derivatives, for instance XVI[8] or XVⅢ[9] and in both cases the yield is extremely satisfactory as shown in Entry No. 19 and No. 20.

Experimental*3

7-Ethyl-1,4-dimethylazulene (Chamazulene) (VIII) (Entry No. 4 in Table I)——When a mixture of 3-ethyl-6,10-dimethylbicyclo[5,3,0]decene[6] (Ⅶ) (73 mg.) and 10% palladium-charcoal (33 mg.) in a test tube (18 cm.) was heated at 320~325° for 8 min. in a nitrogen atmosphere, the azulene immediately condensed on the upper part of the tube and was extracted with light petroleum. The extract was evaporated, leaving a blue oil (52 mg.). The residue was dissolved in light petroleum and the azulene was extracted with 85% H_3PO_4. The H_3PO_4 layer was added to ice-H_2O and extracted again with light petroleum, and the extract was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evaporated, leaving the crude azulene (6.1 mg.). The residue was converted into its 2,4,6-trinitrobenzene adduct and chromatographed on neutral Al_2O_3 to give chamazulene (Ⅷ, 4.0 mg., 5.5% yield). 2,4,6-Trinitrobenzene adduct: Dark purple needles, m.p. 132~133° (from EtOH).

4-Ethyl-6,10-dimethylbicyclo[5,3,0]decan-4-ol (IX)——The Grignard reagent prepared from ethyl iodide (3.9 g.) and magnesium (610 mg.) was applied to the ketone (V, 1.06 g.) in ether solution, decomposed with NH_4Cl solution, and treated in the usual manner by which an oily alcohol (1.036 g.) was obtained. The oil was distilled at 125~130°/1 mm. (bath temperature) to give colorless oil (IX), IR ν_{max}^{film} cm^{-1}: 3380, 1175, 1120, 1000 and 960. *Anal.* Calcd. for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.68; H, 12.40.

6-Ethyl-1,4-dimethylazulene (XI) (Entry No. 7 in Table I)——A mixture of IX (1.02 g.) and thionyl chloride (0.6 ml.) in pyridine (10 ml.) was left at room temperature for 2 hr., poured into ice-H_2O, and extracted with ether. The extract was washed with 2*N* H_2SO_4, 2*N* Na_2CO_3 and H_2O, dried (Na_2SO_4) and evaporated, leaving a yellow oil. The residue was chromatographed on Al_2O_3 to give a colorless oil (X, 695 mg.), b.p_5 120~125°. A mixture of X (33.3 mg.) and 10% Pd-C (25 mg.) was heated at 320~322° for 1 min. in a nitrogen atmosphere and treated under the same manner as Ⅷ to give 6-ethyl-1,4-dimethylazulene (XI, 4.2 mg., 12.6% yield), a blue-violet oil, UV λ_{max} mμ (log ε): 242.5 (4.29), 286 (4.71), 292 (4.72), 343 (3.52), 352 (3.60) and 369 (3.11), and Visible Spectrum λ_{max} mμ (ε): 541 (225), 563 (274), 585 (297), 614 (267), 638 (228), 675 (111) and 708 (68), IR $\nu_{max}^{CS_2}$ cm^{-1}: 1286, 1050, 1015, 860, 825, 790, 775 and 715. 2,4,6-Trinitrobenzene adduct: Dark purple needles, m.p. 116~117° (from EtOH). *Anal.* Calcd. for $C_{14}H_{16}\cdot C_6H_3O_6N_3$: C, 60.45; H, 4.82; N, 10.58. Found: C, 60.65; H, 4.97; N, 10.27.

4-Isopropyl-6,10-dimethylbicyclo[5,3,0]decan-4-ol (XII)——The Grignard reagent prepared from isopropyl bromide (1.65 g.) and magnesium (300 mg.) was applied to the ketone (V, 413 mg.) in ether solution and treated in the usual manner to give an oily product (424 mg.), which gave colorless needles,*4 m.p. 162~163° (25.5 mg.) and a pale yellow oil (396 mg.) by crystallization from ether. This oil was chromatographed on Al_2O_3 to give V (210 mg.), XII (109 mg.) and a mixture of these compounds (ca. 1:3, 70 mg.).

*3 Ultraviolet and visible spectra were taken in hexane.

*4 This compound, ν_{max}^{Nujol} 3545 and 1687 cm^{-1}, was quantitatively recovered to the starting material (V) by Al_2O_3 chromatography. *Anal.* Calcd. for $(C_{12}H_{20}O)_n$: C, 79.94; H, 11.18. Found: C, 79.83; H, 11.03.

8) K. Takeda, H. Minato, M. Ishikawa: Chem. Commun., **1965**, 79.
9) K. Takeda, H. Minato, M. Ishikawa, M. Miyawaki: Tetrahedron, **20**, 2655 (1964).

Since compound (XII) was an unstable oil on heating and turned into a resin, crude (XII) was used to afford (XIV).

6-Isopropyl-1,4-dimethylazulene (XIV) (Entry No. 11 in Table I)——A mixture of XII (150 mg.) and thionyl chloride (0.1 ml.) in pyridine (1 ml.) was left for 2 hr. at room temperature and treated under the same manner as IX. The residue was chromatographed on Al_2O_3 to give a colorless oil (XIII, 124 mg.). A mixture of XIII (27.2 mg.) and 10% Pd-C (20 mg.) was heated at 320~322° for 1 min. in a nitrogen atmosphere and treated as described above to give an oily blue-violet azulene (XIV, 3.0 mg., 11.0% yield), UV λ_{max} mμ (log ε): 242.5 (4.27), 285 (4.69), 291 (4.69), 343 (3.51), 351 (3.59) and 368 (3.30), and Visible Spectrum λ_{max} mμ(ε): 539(216), 563 (257), 585 (286), 613 (245), 638 (219), 675 (107) and 706 (72), IR $\nu_{max}^{CS_2}$ cm^{-1}: 1330, 1287, 1198, 1040, 1020, 880, 865, 826, 775 and 713. 2,4,6-Trinitrobenzene adduct: Dark purple prisms, m.p. 149.5~150.5° (from EtOH). *Anal.* Calcd. for $C_{15}H_{18}\cdot C_6H_3O_6N_3$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.27; H, 5.21; N, 10.06. This azulene (XIV) was identical with 6-isopropyl-1,4-dimethylazulene synthesized by Plattner[7] by comparison of infrared and visible spectra.

Summary

A microtechnique for dehydrogenation of some perhydroazulene and -naphthalene derivatives was developed, and the optimum reaction conditions were discussed.

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96. Kyosuke Tsuda*1, Yoshihiro Sato,*1 Nobuo Ikekawa,*2 Sayoko Tanaka,*1 Hideaki Higashikuze,*1 and Ryuzaburo Ohsawa*3 : Studies on Bile Acids and Bile Alcohols. II.*4 Separation of Bile Acids by Gas Liquid Chromatography.

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Gas liquid chromatography has already been recognized to be a powerful tool for the qualitative and quantitative analysis of steroids. Horning and his co-workers[1] were the first to report the separation of bile acids by this technique and the application of such separation in the analysis of acetate, trifluoroacetate or trimethylsilyl ether of bile acids have since been demonstrated by several workers.[2]

In view of its potential use in the field of bile acids, a systematic program was undertaken in this laboratory to explore the conditions under which favorable separa-

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*4 This paper constituted Part XLIX of a series "Steriod Studies." Reported at the 83rd Annual Meeting of Pharm. Soc. of Japan, Nov., 2, 1963 (Tokyo).

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