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The Stereochemistry of Hydrogenation and Hydrogenolysis. XI.[1]
The Stereochemistry of the Reduction of 3-Methyl-4-chromanone*[1]

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3-Methyl-4-chromanone (VIII) was reduced with a metal hydride complex, by the Meerwein-Ponndorf method and by catalytic hydrogenation. When VIII was reduced with a metal hydride complex and the Meerwein-Ponndorf method, *trans*-3-methyl-4-chromanol (IX) was produced as the main product. In the catalytic hydrogenation, VIII gave a *cis*-3-methyl-4-chromanol (X) as the main product over Raney nickel, but over the palladium catalyst the *trnas* isomer was larger than the *cis* isomer. These results indicate that, on Meerwein-Ponndorf and metal hydride reductions, the more stable product was formed as the main product; in the catalytic hydrogenation over the Raney nickel catalyst, VIII seems to be adsorbed mainly on the opposite side of the methyl group of the C-3 position and is hydrogenated to give the *cis* isomer, whereas, over the palladium catalyst, hydrogenation seems to proceed under the effect of "product development control over the catalyst" and the *trans* isomer is produced in a high yield.

In the previous papers of this series, the reductions of 2-phenyl-1-tetralone(I),[2] 2-acetoxy-1-tetralone (II),[3] and 2-methyl-1-tetralone(III)[4] were reported. In the catalytic hydrogenation over the Raney nickel, I and II gave *cis*-2-phenyl-1-tetralol (IV) and *cis*-2-acetoxy-1-tetralol(V) respectively in high yields, whereas III gave a mixture of about equivalent quantities of *cis*-2-methyl-1-tetralol(VI) and *trans*-2-methyl-1-tetralol(VII), but over a palladium catalyst VII was formed in a larger amount than VI, along with hydrocarbons resulting from hydrogenolysis. From these results, it is considered that, on the catalytic hydrogenation, the phenyl or acetoxyl group works as a catalyst hindrance to the adsorption of I or II on a catalyst, while the methyl group does not act as so much a hindrance to the adsorption of III. However, the different behaviour observed in the catalytic hydrogenation of III over Raney nickel and palladium catalysts has not yet been discussed. In the metal hydride reduction of I, II, and III, I and II afforded *cis* isomers as the main products, whereas III gave the *trans* isomer in a larger amount than the *cis* isomer. On the Meerwein-Ponndorf reduction of I and III, if acetone was removed, the *cis* isomer was produced mainly, whereas the *trans* isomer was produced mainly when the reaction mixture was refluxed without removing the acetone. From these results, it can be considered that, in the reduction with metal hydride complex, the phenyl or acetoxyl group sterically hinders the carbonyl carbon atom of I or II from the attack of the hydride ion, but the methyl group of III does not exert any such steric hindrance. On the Meerwein-Ponndorf reduction, if acetone is removed, the reaction may proceed under the effect of steric hindrance. On the other hand, if the reaction mixture is refluxed without removing the acetone, the more stable product is formed as the main product.

In order to obtain further information on the stereochemistry of the reduction of cyclic ketones

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[1] Part X: K. Hanaya, *Nippon Kagaku Zasshi*, **90**, 314 (1969).

*[1] Presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968.

[2] K. Hanaya, *Nippon Kagaku Zasshi*, **87**, 745 (1966).

[3] K. Hanaya, This Bulletin, **40**, 1884 (1967).

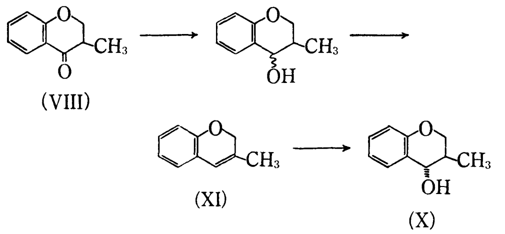
[4] K. Hanaya, *Nippon Kagaku Zasshi*, **87**, 991 (1966).

and on the different behavior of these ketones in catalytic hydrogenation over nickel and palladium catalysts, the reduction of 3-methyl-4-chromanone (VIII) was investigated.

Results and Discussion

The reduction of 3-methyl-4-chromanone (VIII) was carried out by the catalytic, metal hydride complex, and Meerwein-Ponndorf methods. The results of these reductions are shown in Table 1.

The configurations of the product alcohols (IX and X) have been established by the synthesis of *trans*-3-methyl-4-chromanol (X) *via* the hydroboration5) of 3-methyl-3-chromene (XI), which had itself been prepared by the dehydration of 3-methyl-4-chromanol with *p*-toluenesulfonic acid in benzene, and by the examination of the NMR spectra of IX, X, and their acetates. In the NMR spectra of IX, X, and their acetates, the values of the 3,4-coupling constant ($J_{3,4}$=4.8Hz) of X and its acetate are larger than those ($J_{3,4}$=3.4Hz) of IX and its acetate. In view of the Karplus relationship,6) these results indicate that, in X and its acetate, the methyl group is *trans* to the hydroxyl or acetoxyl group, while in IX and its acetate it is *cis*.



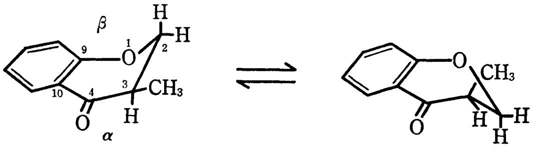
(VIII)

(XI)

(X)

From the experimental results shown above, the stereochemistry of the reduction of VIII can be considered to be as follows.

VIII is considered to have the conformations shown in Fig. 1, which are similar to those of γ-chromanone proposed by Philbin and Wheeler.7)



(A) (B)

Fig. 1. Conformations of VIII.*2

The conformation of the methyl group in the 3-position of VIII may be assumed to be quasi-equatorial, as usual. Therefore, the preferable conformation of VIII will be the A-form of Fig. 1.

The reduction of VIII with the metal hydride complex gave the *trans* isomer as the main product. On the Meerwein-Ponndorf reduction VIII, if the acetone was removed, the *cis* isomer was produced mainly, whereas if the reaction mixture was

Table 1. Products of the reduction of 3-methyl-4-chromanone (VIII)

Expt. No.	Reducing agent or catalyst	Conversion %	Products, % IX	X	XII
1	$LiAlH_4$	100	35	65	—
2	$NaBH_4$	100	46	54	—
3	$Al(OC_3H_7)_3$a)	100	73	27	—
4	$Al(OC_3H_7)_3$b)	91	37	63	—
5	Raney Ni	96	52	37	11
6	Raney Nic)	91	64	36	—
7	5% Pd-C-B (2 hr)	53	35	58	7
8	5% Pd-C-B (4 hr)	84	33	60	7
9	5% Pd-C-B (6 hr)	98	29	61	10
10	5% Pd-C-A	44	27	49	24
11	5% $Pd-CaCO_3$	92	33	49	18
12	5% $Pd-BaSO_4$	94	23	52	25

a) Acetone was removed.
b) The reaction mixture was refluxed without removing acetone for 4 hr.
c) 1/2000 mol of NaOH was added.

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5) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 247 (1959); H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961); E. L. Allred, J. Sonnenberg and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960).

6) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

7) E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.*, **1958**, 167.

[*2] Philbin and Wheeler have been proposed that five atoms in the heterocyclic, O_1, C_3, C_4, C_9, and C_{10}, are coplanar. However, the present author has considered that C_2, C_3, and the 4-keto group are not coplanar with the adjacent benzene nucleus.8) A study of the conformations of γ-chromanone derivatives is now in progress.

8) K. Hanaya and K. Furuse, *Nippon Kagaku Zasshi*, **89**, 1002 (1968); K. Hanaya, *ibid.*, **90**, 314 (1969).

refluxed without removing the acetone, the *trans* isomer was produced mainly. These results parallel the findings on III. On reduction with the metal hydride complex, the steric structure near the carbonyl group influences the stereochemical course of the reaction, rather than the whole steric structure of the molecule. When a hydride ion attacks the carbonyl carbon atom, the methyl group of the 3-position of VIII does not seem to exert any steric hindrance; this reaction proceeds under the effect of "product development control." On the Meerwein-Ponndorf reduction of VIII, a consideration of its reaction mechanism[9] suggests that the reaction will proceed under the effect of steric hindrance if the acetone is removed. On the other hand, if the reaction mixture is refluxed without removing the acetone, the reaction mixture will easily reach an equilibrium in which the *trans* isomer predominates.

In the case of the catalytic hydrogenation over the Raney nickel catalyst, VIII afforded the *cis* isomer as the main product, while over the palladium catalyst, VIII gave the *trans* isomer as the main product. In the catalytic hydrogenation of VIII over the palladium-charcoal-B, the *trans* isomer was obtained preferably, even at the initial stage of hydrogenation (Expts. 7, 8, and 9). Therefore, it is considered that the predominant formation of the *trans* isomer was not due to the isomerization of the *cis* isomer.

Generally, the course of the hydrogenation of ketones can be represented as involving three steps, as is shown in Fig. 2: Step 1, the formation of a first adsorbed intermediate; Step 2, the formation of a half-hydrogenated intermediate, and Step 3, the formation and desorption of the product.

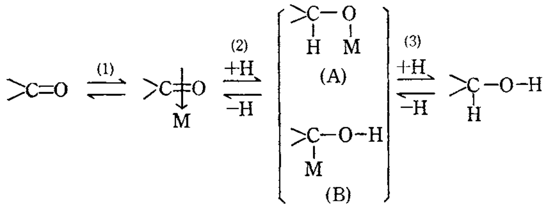

Fig. 2

When the molecule of VIII shown as in Fig. 1-A adsorbs over a catalyst, the adsorption seems to be hindered more at the β-face of the molecule than at the α-face. It is considered that the predominant production of the *cis* isomer in the Raney nickel catalyst hydrogenation of VIII is caused by this catalyst hindrance. The nickel catalyst is considered to have a larger affinity for the oxygen atom than the palladium catalyst.[10] Therefore, on the catalytic hydrogenation of VIII over the Raney nickel catalyst the molecule does not desorb easily, but it will be hydrogenated rapidly when the carbonyl group is strongly adsorbed. That is, on the Raney nickel catalyst, the stereochemistry of hydrogenation may be controlled mainly by the first adsorption step of the molecule and, therefore, by the steric interaction between the molecule and the catalyst surface. On the other hand, since the palladium catalyst does not have a strong affinity for the oxygen atom, the products are not determined by the step of adsorption of the molecule, but, rather, by the step of the transfer of hydrogen from the catalyst surface to the molecule. That is, in the catalytic hydrogenation of VIII over the palladium catalyst, a large contribution of the second or third process will give a stable isomer predominantly. There are two possible states, (A) and (B), to be considered for the half-hydrogenated state, as is shown in Fig. 2. Bent and Keevil[11] reported that the free energy of the addition of sodium to a carbonyl group is at least 5 kcal more negative in the case of the oxygen atom. This fact indicates that sodium is much more firmly attached to oxygen than to carbon. In view of this fact, the oxygen-metal bond may be formed more easily than the carbon-metal bond, and the hydrogenation of ketones may proceed mainly *via* the (A)-type half-hydrogenated state. Besides, in the case of the hydrogenation of VIII, the (B)-type may be expected to be less stable than the (A)-type because of a more severe nonbonded interaction between the quasi-equatorial carbon-metal bond and the hydrogen atom at the peri-position than between the quasi-equatorial oxygen-metal bond and the hydrogen atom in the peri-position. The palladium-catalyzed hydrogenation of VIII will proceed *via* the half-hydrogenated state, as is shown in Fig. 3, and will give the *trans* isomer predominantly.

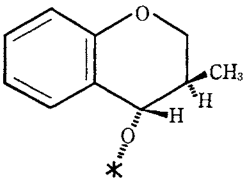

Fig. 3

On the basis of the previous works and the present work, the catalytic hydrogenation of 1-tetralone and 4-chromanone derivatives having the substituent at the α-position of carbonyl group may be summarized as follows. When the substituent is sterically bulky, as in the case of the phenyl or

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[9] R. B. Woodward, N. L. Wendler and F. J. Brutschy, *J. Amer. Chem. Soc.*, **67**, 1425 (1945); W. E. Doering and R. W. Young, *ibid.*, **72**, 631 (1950); E. D. Williams, K. A. Krieger and A. R. Day, *ibid.*, **75**, 2404 (1953); W. N. Moulton, *J. Org. Chem.*, **26**, 290 (1961).

[10] S. Mitsui, Y. Senda and H. Saito, This Bulletin, **39**, 694 (1966).

[11] H. E. Bent and N. B. Keevil, *J. Amer. Chem. Soc.*, **58**, 1367 (1936).

acetoxyl group, the molecule is hydrogenated in the adsorbed state on the catalyst surface at the opposite side to the substituent, not dependent on the sort of catalyst. On the other hand, when the substituent is relatively small, as in the case of the methyl group, the catalyst hindrance has the largest influence with nickel catalyst, while the hydrogenation over the palladium catalyst is not influenced by the catalyst hindrance, but will give thermodynamically more stable products predominantly because of the large influence of the reaction process of the transfer of hydrogen from the catalyst surface to the molecule.

Experimental

3-Methyl-4-chromanone (VIII). VIII was prepared by the catalytic hydrogenation of 3-methyl-4-chromone[12] over Raney nickel in ethanol. Bp 125—128°C/11 mmHg; The oxime, mp 154—156°C(lit,[13] mp 156°C). IR(liquid film): 1680(C=O) cm^{-1}. NMR(CCl_4): 1.15 (3H, doublet, J=6.9 Hz, CH_3), 2.75 (1H, multiplet, methine at the 3-position), 4.2(2H, multiplet, methylene at the 2-position), and 7.25 ppm(4H, multiplet, benzene-ring protons).

The Catalytic Hydrogenation of VIII. Two hundredths of a mole of VIII, 40 m*l* of ethanol or 10 m*l* of acetic acid, and the catalyst (0.5 g of Raney nickel, 0.2 g of 5% Pd-C-B, 0.1 g 5% Pd-C-A, 0.2 g of 5% Pd-$CaCO_3$ or 0.2 g of 5% Pd-$BaSO_4$) were shaken under hydrogen at an ordinary temperature and pressure. After the theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and the ethanol or acetic acid was distilled off. The products were analyzed by gas chromatography.

Reduction of VIII with $NaBH_4$. A solution of VIII(5.0 g) in ethanol (100 m*l*) was added over a 30-min period to a well-stirred mixture of sodium borohydride (2.4 g) in ethanol (100 m*l*) at 0°C. After the mixture had then been allowed to stand for 24 hr at room temperature, water (50 m*l*) was added and the ethanol was removed under reduced pressure. The residue was acidified with dilute hydrocholric acid, the solution was extracted with ether, and the ether solution was washed with a sodium bicarbonate solution and then with water, and dried over anhydrous sodium sulfate. After the evaporation of the ether, the residue were analyzed by gas chromatography. The oily residue was dissolved in hot ligroin and then cooled in an ice bath. *trans*-Rich crystals of 3-methyl-4-chromanol were thus obtained. The recrystallization of them from ligroin gave the pure *trans*-chromanol (X) (mp 97—98.5°C) (1.5 g). NMR ($CDCl_3$): 0.97(3H, doublet, J=6.9 Hz, CH_3), 2.01(1H, multiplet, methine at the 3-position), 2.17(1H, singlet, OH), 4.0(2H, multiplet, methylene at the 2-position), 4.3(1H, doublet, J=4.8 Hz, methine at the 4-position), and 7.0 ppm(4H, multiplet, benzene-ring protons).

Found: C, 73.44; H, 7.46%. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37%.

Reduction of VIII with $LiAlH_4$. To a well-stirred suspension of lithium aluminum hydride (0.3 g) in dry ether (50 m*l*), VIII (0.8 g) dissolved in dry ether (50 m*l*) was added over a 30-min period at 0°C; the mixture was then stirred at room temperature for 12 hr. Water (10 m*l*) and 20% sulfuric acid (5 m*l*) were then added, and the ether layer was separated. The aqueous solution was extracted with ether, and the combined ether extracts were washed with a sodium bicarbonate solution and then with water and dried over anhydrous sodium sulfate, and the ether was removed. The products were analyzed by gas chromatography.

Meerwein-Ponndorf Reduction of VIII. *Method A (The acetone was removed).* The ketone (0.02 mol) was mixed with an aluminum isopropoxide solution (prepared from 2.24 g of aluminum and 80 m*l* of dry isopropyl alcohol) and isopropyl alcohol (20 m*l*), and was then distilled slowly until acetone was no longer detectable in the distillate. The isopropyl alcohol was then removed by vacuum distillation, the residue mixed with water, and diluted hydrochloric acid was added until all the precipitated solid had dissolved. The solution was extracted with ether, and the extract was washed with a 5% sodium carbonate solution and with water, and dried over anhydrous sodium sulfate. After the evaporation of the ether, the residue was analyzed by gas chromatography. The residue oil was then distilled under reduced pressure to give 2.0g of *cis*-chromanol (IX) (bp 140—142°C/12 mmHg). The identity of IX was ascertained by a study of its IR spectrum, by gas chromatography, and by a study of its NMR spectrum. NMR ($CDCl_3$): 1.05(3H, doublet, J=6.9 Hz, CH_3), 2.0(1H, singlet, OH), *ca.* 2.2(1H, multiplet, methine at the 3-position), 4.05(2H, multiplet, methylene at the 2-position), 4.53(1H, doublet, J=3.4 Hz, methine at the 4-position), and 7.0 ppm(4H, multiplet, benzene-ring protons).

Method B (The acetone was not removed but refluxed). A solution of VIII (0.01 mol) and an aluminum isopropoxide solution (prepared from 1.12 g of aluminum and 40 m*l* of dry isopropyl alcohol) and isopropyl alcohol (10 m*l*) were refluxed for 4 hr. The reaction products were then treated as above. The residue was analyzed by gas chromatography.

3-Methyl-3-chromene (XI). 3-Methyl-4-chromanol (2.0 g) was heated with 0.2 g of *p*-toluenesulfonic acid in 200 m*l* of benzene for 10 hr. The water was successively removed by azeotropic distillation; the benzene layer was washed with a sodium bicarbonate solution and water, and the benzene was distilled off under reduced pressure. 1.5 g of XI was thus obtained. This compound was checked by a study of its IR spectrum and by gas chromatography.

The Hydroboration of XI. To a solution of 0.4g of sodium borohydride in 10 m*l* of diglyme containing 1g of XI, there was added 0.85 m*l* of boron trifluoride etherate under cooling with ice. The mixture was stirred for 3 hr at room temperature before the excess hydride was decomposed with water. The organoborane was oxidized at room temperature by the addition of 5 m*l* of a 3N solution of sodium hydroxide, followed by the drop-by-drop addition of 6 m*l* of 30% hydrogen peroxide. The reaction mixture was then extracted with ether, and the extract was washed five times with equal volumes of a saturated salt solution in order to remove the diglyme. The extract was then dried over

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[12] A. Schonberg and A. Sina, *J. Chem. Soc.*, **1950**, 3344.

[13] J. Colonge and A. Guyot, *Bull. Soc. Chim. Fr.*, **1958**, 325.

anhydrous sodium sulfate, and the solvent was removed. The residue was recrystallized from ligroin to give *trans*-chromanol (X) (mp 97—98°C) (0.8g).

3-Methylchroman (XII). The mixture of 2g of VIII, 0.2g of the 5% Pd-C-A catalyst, and 50 m*l* of ethanol was shaken under hydrogen at an ordinary temperature and pressure. After 2 mol of the hydrogen had been absorbed, the catalyst was filtered off and the residue were distilled under reduced pressure to give 1.2g of XII (bp 94.5—96°C/9 mmHg). This compound was checked by a study of its IR spectrum, by gas chromatography, and by a study of its NMR spectrum. NMR(CCl_4): 1.03 (3H, doublet, $J=6.9$ Hz, CH_3), 1.9—2.9 (3H, multiplet, methine at the 3-position and methylene at the 4-position), 3.8(2H, multiplet, methylene at the 2-position) and 6.9 ppm (4H, multiplet, benzene-ring protons).

***cis*-3-Methyl-4-acetoxychroman (XIII) and *trans*-3-Methyl-4-acetoxychroman (XIV).** XIII and XIV were prepared by the acetylation of IX and X by means of the acetic anhydride-pyridine method at room temperature overnight. These products were checked by a study of their IR spectra, by gas chromatography, and by a study of their NMR spectra. IR (liquid film): XIII, 1725, 1225 (-O-CO-CH_3) cm^{-1}; XIV, 1735, 1230(-O-CO-CH_3) cm^{-1}. NMR($CDCl_3$): XIII, 0.98(3H, doublet, $J=6.9$ Hz, CH_3), 2.08(3H, singlet, -O-CO-CH_3), *ca.* 2.4(1H, multiplet, methine at the 3-position), 4.0(2H, multiplet, methylene at the 2-position), 5.98(1H, doublet, $J=3.4$ Hz, methine at the 4-position), and 7.1(4H, multiplet, benzene-ring protons); XIV, 1.0(3H, doublet, $J=6.9$ Hz, CH_3), 2.08(3H, singlet, –O–CO–CH_3), *ca.* 2.3(1H, multiplet, methine at the 3-position), 4.14(2H, multiplet, methylene at the 2-position), 5.65(1H, doublet, $J=4.8$ Hz, methine at the 4-position), and 7.05(4H, multiplet, benzene-ring protons).

Instrumentation. The gas chromatographic analysis of the reduction products were carried out with a Hitachi Model K-53 apparatus, fitted with a 45-m Golay column coated with PEG 4000 and equipped with a flame-ionization detector. The nitrogen carrier-gas inlet pressure was 1.5 kg/cm^2, and the column temperature was 180°C. The NMR spectra were measured on a Hitachi H-60 high-resolution nuclear spectrometer. The sample was dissolved in $CDCl_3$ or CCl_4, containing TMS as the internal reference. The IR spectra were measured with a Hitachi EPI-S infrared spectrometer.

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