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Diterpenoids. XXXI. Reaction of Methyl Dehydroabietate Derivatives with Aluminum Chloride under Effect of Electron-withdrawing Group. Synthesis of Methyl Deisopropyldehydroabietate Series[1]

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Reaction of 12-acetyl ester (**5**) with aluminum chloride gave predominant *trans*-isomer (**6**) in company with the *cis* (**7**). *trans*-Isomer had not been observed as major product in the reactions of methyl dehydroabietate having electron-donating group at aromatic ring as described previously. In the other cases of reactions of methyl dehydroabietate derivatives having electron-withdrawing group, 7-oxo ester (**20**) did not react even under the drastic condition. But 7-oxo ester having a hydroxyl or a methoxyl group at 12- or 14-position was deisopropylated to give only the respective *trans* deisopropyl isomer.

In our preceding work,[1] effect of electron-donating groups (hydroxyl and methoxyl groups) in the aromatic ring to the reaction of methyl dehydroabietate derivatives (*e.g.*, **1** and **2**) with aluminum chloride was described in detail. As a result, isomerisation of 10-methyl group and deisopropylation were found to occur competitively and tendency of the reaction varied according to the substituent. In equilibrium of the reaction, two kinds of isomeric deisopropyl ester having *cis*- and *trans*-A/B-ring juncture are only detected and *cis* one is always predominant.

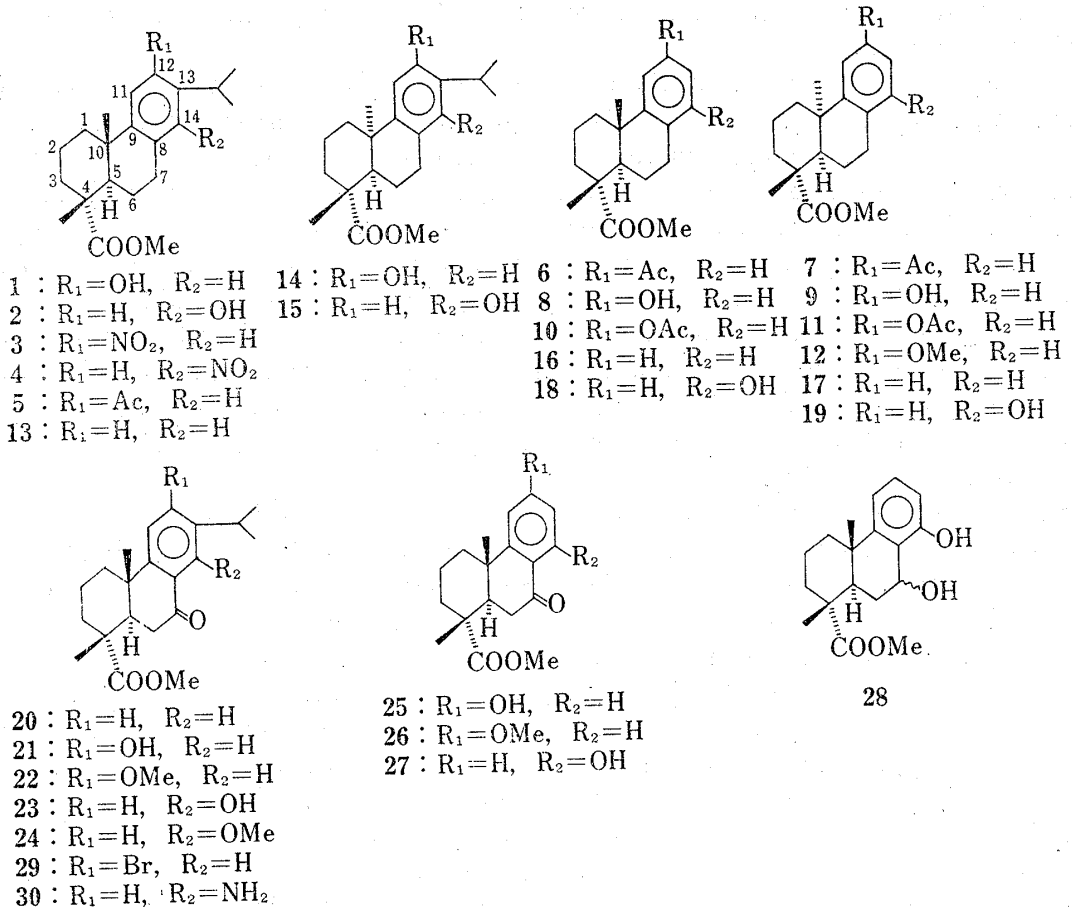
In continuation of this study, the effect of electron-withdrawing group having the opposite property to the reaction aroused our interest.

As the first example of an electron-withdrawing group, nitro group was examined. Reaction of 12-nitro (**3**) and 14-nitro ester (**4**) did not proceeded even under the more drastic condition ($AlCl_3$; 53.9 mol. eq., room temp. 20 hr) than that of the previous case.[1] However, 12-acetyl ester (**5**) reacted ($AlCl_3$; 53.5 mol. eq., room temp. 24 hr) to give an inseparable mixture consisting of two isomers, *trans*-(**6**) and *cis*-deisopropyl ester (**7**). For the separation, the mixture (**6**+**7**) was converted to the corresponding *trans*[1] (**8**: 42% yield) and *cis* 12-hydroxy ester[1] (**9**: 25% yield) *via* acetoxy esters (**10** and **11**) by oxidation and then hydrolysis.[3]

This observation is worth notice for the priority of *trans* isomer (**6**) over the *cis* (**7**) unlike in the previous case[4] and the fact is also supported by gas-liquid chromatographic analysis (Table I). In comparison with unsubstituted (**13**), 12-hydroxy (**1**), and 14-hydroxy ester (**2**), it became clear that the reaction of 12-acetyl ester (**5**) is the slowest among those of the other esters (Table II).

As described in the preceding paper,[1] cis-deisopropyl ester was always predominant in the reaction equilibrium of methyl dehydroabietate derivatives, unsubstituted and substituted with an electron-donating group (*e.g.*, **13**, **1**, and **2**). Method available for the preparation of *trans*-deisopropyl ester derivative is little known with the exception of the reaction of 12-acetyl ester (**5**). In order to improve the yield of *trans*-deisopropyl ester, the effect of other electron-withdrawing groups was examined. The reactions of methyl dehydroabietate

1) Part XXX: A. Tahara and H. Akita, *Chem. Pharm. Bull.* (Tokyo), **23**, 1976, (1975).
2) Location: *Wako-shi, Saitama-ken, 351, Japan.*
3) *cf.* E. Wenkert and B.G. Jackson, *J. Amer. Chem. Soc.*, **80**, 217 (1958).
4) *a*) M. Ohta and L. Ohmori, *Chem. Pharm. Bull.* (Tokyo), **5**, 91 (1957); *b*) E. Wenkert and B.G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).



1 : R_1=OH, R_2=H
2 : R_1=H, R_2=OH
3 : R_1=NO_2, R_2=H
4 : R_1=H, R_2=NO_2
5 : R_1=Ac, R_2=H
13 : R_1=H, R_2=H

14 : R_1=OH, R_2=H
15 : R_1=H, R_2=OH

6 : R_1=Ac, R_2=H
8 : R_1=OH, R_2=H
10 : R_1=OAc, R_2=H
16 : R_1=H, R_2=H
18 : R_1=H, R_2=OH

7 : R_1=Ac, R_2=H
9 : R_1=OH, R_2=H
11 : R_1=OAc, R_2=H
12 : R_1=OMe, R_2=H
17 : R_1=H, R_2=H
19 : R_1=H, R_2=OH

20 : R_1=H, R_2=H
21 : R_1=OH, R_2=H
22 : R_1=OMe, R_2=H
23 : R_1=H, R_2=OH
24 : R_1=H, R_2=OMe
29 : R_1=Br, R_2=H
30 : R_1=H, R_2=NH_2

25 : R_1=OH, R_2=H
26 : R_1=OMe, R_2=H
27 : R_1=H, R_2=OH

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Chart 1

TABLE I. Relation between Ratio of Products and Amount of Aluminum Chloride in the Reaction of Methyl 12-Acetyl Dehydroabietate (**5**)[a)]

Amount of $AlCl_3$ (g, mol. eq.)	Product (%)		
	5	*trans* Deisopropyl (**6**)	*cis* Deisopropyl (**7**)
2 (5.35)	100	0	0
10 (26.8)	0	72	28
20 (53.5)	0	67	33

a) general procedure: A solution of the ester (1 g) in ab. benzene (100 ml) was stirred at room temp. for 24 hr with $AlCl_3$ and the reaction mixture was treated usually as in the experimental part.
Ratio (%) of the resulting components was measured by their peak area (height × width of half height) in gas-liquid chromatogram (260—280°).

TABLE II. Comparison of the Yield of 12-Acetyl Ester (**5**) with Unsubstituted (**13**), 12-Hydroxy (**1**), and 14-Hydroxy Ester (**2**) in the Reaction[a)]

Compound (100 mg) ($AlCl_3$: mol. eq.)	Product (%)			
	Starting material	*cis* Isopropyl	*trans* Deisopropyl	*cis* Deisopropyl
13 (4.72)	**13** (0)		**16** (27)	**17** (73)
1 (4.96)	**1** (19)	**14** (35)	**8** (32)	**9** (14)
1 (49.6)	**1** (0)	**14** (0)	**8** (38)	**9** (62)
2 (4.96)	**2** (60)	**15** (0)	**18** (40)	**19** (0)
2 (49.6)	**2** (0)	**15** (0)	**18** (32)	**19** (68)

a) general procedure: A solution of the ester (100 mg) in ab.benzene (10 ml) was stirred at room temp. for 2 hr with $AlCl_3$ and the reaction mixture was treated usually as in the experimental part.
Ratio (%) of the resulting components was measured by their peak area (height × width of half height) in gas-liquid chromatogram (260—280°).

series having 7-oxo group were taken up and the selective preparation of *trans*-deisopropyl ester will be described.

Reaction of 7-oxo ester (**20**) itself did not proceed even under the drastic condition ($AlCl_3$; 49.3 mol. eq., reflux, 24 hr). However, 7-oxo ester having a hydroxyl or a methoxyl group at 12- or 14-position was deisopropylated. 12-Hydroxy-7-oxo ester (**21**) hardly reacted under a similar condition ($AlCl_3$; 25.8 mol. eq., room temp., 12 hr) as 12-acetyl ester (**5**), 12-hydroxy (**1**), and 14-hydroxy ester (**2**) mentioned before,[1] but reaction of **21** and the corresponding methoxy ester (**22**) smoothly proceeded under a more drastic condition ($AlCl_3$; 51.6—53.8 mol. eq., reflux, 8 hr). The reaction mixture (**25** and **21**) obtained from **21** and **22** was converted to the corresponding methoxy compounds and *trans*-12-methoxy-deisopropyl ester (**26**: 77% yield from **21** and 61% yield from **22**), bp 150° (bath temp)/3×10^{-2} Torr, was obtained together with **22** (22% yield from **21** and 30% yield from **22**). *trans* 12-Hydroxy-deisopropyl ester (**25**: 58% yield from **21** and 70% yield from **22**), oil, was easily isolated by alkaline extraction of the mixture (**25** and **21**).

The structures of the resulting 12-hydroxy-7-oxo ester (**25**) and the corresponding methoxy ester (**26**) were confirmed by nuclear magnetic resonance (NMR) analysis. NMR signal due to the isopropyl group disappeared in the both compounds and the pattern of 1,3,4-substituted benzene type (δ 6.68—6.85 (m), 7.92 (d, J=9.6 Hz) for **25** and δ 6.68—6.84 (m), 7.99 (d, J= 9.6 Hz) for **26**) was shown. Chemical proof for the structure was provided by the conversion of **25** into the known deoxo ester (**8**) having a definite *trans*-A/B ring juncture.

In contrast, 14-hydroxy- (**23**) and 14-methoxy-7-oxo ester (**24**) more easily reacted ($AlCl_3$; 25.8—26.9 mol. eq., room temp., 12 hr) to give only the *trans*-deisopropyl ester (**27**) (95% yield from **23** and 76% yield from **24**), bp 150° (bath temp.)/10^{-2} Torr. A difference in the reaction of 14-hydroxy ester (**23**) from that of 12-hydroxy ester (**21**) would be due to the interrelation between 7-oxo and 14-hydroxyl group located closer in **23** (infrated (IR) (KBr): 1635). Reaction of the corresponding methoxy ester (**24**) showed the same tendency that **24** is easily deisopropylated and simultaneously demethylated to give **27**. Structure of the product (**27**) was confirmed by the chemical relation of **27** to the known 14-hydroxy ester (**18**) *via* 7,14-dihydroxy ester (**28**) ($NaBH_4$–MeOH and then, H_2–10% Pd-C, AcOH–conc.H_2SO_4).

In other analogus compounds, deisopropylation of 12-bromo-(**29**) and 14-amino-7-oxo ester (**30**) was unsuccessful even under a drastic condition ($AlCl_3$; 61.0 mol. eq. for **29** and 51.5 mol. eq. for **30**, reflux, 24 hr).

Deisopropylation of 7-oxo ester series (*e.g.* **21** and **23**) is notable for the sole formation of *trans*-deisopropyl ester (*e.g.* **25** and **27**, respectively). As the oxo group of *trans*-esters (*e.g.* **25** and **27**) was easily eliminated, this synthesis is the most useful method for methyl deisopropyl-dehydroabietate derivatives (*e.g.* **8** and **18**), which are regarded as the useful intermediates for our study on the chemical conversion of pine rosin to biologically active compounds.

Experimental

All melting points were measured on the Kofler block and were uncorrected. NMR spectra were measured (δ) at 60 MHz in $CDCl_3$ *vs.* Me_4Si as internal reference. Infrared (IR) data (CCl_4) indicated maximum absorption in cm^{-1}. Gas-liquid chromatography (GLC) values were measured with a column conditon (2 m×4 mm, 1.5% OV-17 on Shimalite W (80—100 mesh)).

Reaction of Methyl 12-Acetyl-dehydroabietate (5) with Aluminum Chloride to 6 and 7 (Identification as the Corresponding Hydroxy Esters (8 and 9))——12-Acetyl ester [5] (**5**) (1 g) was reacted in ab. benzene (100 ml) with $AlCl_3$ (20 g) (53.5 mol. eq.) at room temperature for 24 hr. After H_2O was added, the reaction mixture was extracted with ether. The extract was washed with 5% Na_2CO_3aq., sat. NaClaq. and dried over Na_2SO_4. Removal of the solvent gave the oily product (964 mg), which was oxidized in CH_2Cl_2 (5.5 ml) with AcO_2H (prepared from AcOH (3.5 g), conc. H_2SO_4 (0.04 ml), and 90% H_2O_2aq. (3.22 g)) at room temperature for 40

5) R.C. Cambie and R.A. Franich, *Aust. J. Chem.*, **24**, 117 (1971).

hr. After H_2O was added, the reaction mixture (**10**+**11**) was extracted with ether and then, the extract was washed with sat. $NaHCO_3$aq., sat. NaClaq. and dried over Na_2SO_4. Removal of the solvent gave oily product (807 mg), which was hydrolyzed in conc. H_2SO_4 (2 drops)–H_2O (0.5 ml)–MeOH (100 ml) under reflux for 2 hr. The residue resulted by removal of MeOH, was extracted with ether and the extract was washed with 5% Na_2CO_3aq., sat. NaClaq. and dried over Na_2SO_4. The resulting oily product was chromatographed on silica gel (80 g) to give two fraction in petr. ether–ether (4: 1) elution, successively.

i) The first fraction (341 mg; 42% yield) was recrystallized from ether–*n*–hexane to give colorless plates (243 mg), mp 186—189°, which was identical (mixed mp, IR, NMR, and GLC) with 10β-12-hydroxy-deisopropyl ester [1] (**8**).

ii) The second fraction (204 mg, 25% yield) was identified (GLC) with 10α-12-hydroxy-deisopropyl ester[1] (**9**) and the fraction was methylated by the usual method (Me_2SO_4–K_2CO_3). The resulting plates (40 mg), mp 103—104°, was identical (mixed mp, IR, NMR, and GLC) with 10α-12-methoxy-deisopropyl ester[1] (**12**).

Reaction of Methyl 12-Hydroxy-7-oxo-dehydroabietate (21) with Aluminum Chloride——i) Methyl 12-Hydroxy-7-oxo-deisopropyl-dehydroabietate (**25**): 12-Hydroxy-7-oxo ester [6] (**21**) (300 mg) in ab. benzene (60 ml) was refluxed with $AlCl_3$ (6 g; 51.6 mol. eq.) for 8 hr. After H_2O was added, the reaction mixture was extracted with ether and then, the extract was washed with 5% Na_2CO_3aq. The alkaline extract was acidified with 10% HClaq. and then, extracted with ether. The extract was washed with sat. NaClaq. and dried over Na_2SO_4. Removal of the solvent gave an oily product (**25**) (154 mg; 58% yield). Mass. Calcd. for $C_{18}H_{22}O_4$: 302.1518. Found: 302.1533. IR: 3625, 1730, 1680, 1660. NMR: 1.23, 1.33 (s, 3H each; 4- and 10-Me), 3.66 (s, 3H; COOMe), 6.68—6.85 (m, 2H; 11- and 13-H), 7.92 (d, 2H; J=9.6 Hz; 14-H).

ii) Mixture of **25** and the Starting Material (**21**) (Identified as the Corresponding Methoxy Esters (**26** and **22**)): 12-Hydroxy-7-oxo ester (**21**) (500 mg) in ab. benzene (40 ml) was refluxed with $AlCl_3$ (10 g; 51.6 mol. eq.) for 6 hr. After H_2O was added, the reaction mixture was extracted with ether. The extract was washed with sat. NaClaq. and dried over Na_2SO_4. The resulting oily product (**21**+**25**) was methylated in acetone (40 ml) with Me_2SO_4 (2 ml)–K_2CO_3 (10 g) under reflux for 12 hr. After the reaction mixture was condensed and H_2O was added, it was extracted with ether and the extract was washed with sat. NaClaq., dried over Na_2SO_4. The oily product obtained (623 mg) was chromatographed on silica-gel (30 g) to afford oily compounds (**22**, identified by GLC and NMR) (115 mg; 22% yield) in petr. ether–ether (4: 1) elution and (**26**) (354 mg; 77% yield), bp 150° (bath temp)/0.03 Torr., in petr. ether–ether (4: 1—2: 1). *Anal.* Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.08; H, 7.70. IR: 1730, 1690. NMR: 1.24, 1.32 (s, 3H each; 4- and 10-Me), 3.62 (s, 3H; COOMe), 3.83 (s, 3H; OMe), 6.68—6.84 (m, 2H; 11- and 13-H), 7.99 (d, 1H, J=9.6 Hz; 14-H).

Reduction of Methyl 12-Hydroxy-7-oxo-deisopropyl-dehydroabietate (25) to 8——12-Hydroxy-7-oxo ester (**25**) (349 mg) in diethylene glycol (12 ml) was heated (160°) with NH_2NH_2–H_2O (1.6 ml)–KOH (1.6 g) for 2 hr and then, refluxed (220—230°) for 2 hr after KOH (1.6 g) was added. After H_2O was added and the reaction mixture was washed with ether, the aqueous layer was acidified with 10% HClaq. and extracted with ether. The extract was washed with sat.NaClaq., dried over Na_2SO_4 and was evaporated. The resulting oil was methylated (CH_2N_2) and the residue (146 mg) obtained was chromatographed on silica gel (15 g) to give crystals (34 mg) in petr. ether–ether (4: 1) elution. They were recrystallized from ether–*n*–hexane to give colorless scales (16 mg), mp 186—189°, which were identical (mixed mp, IR, NMR, and GLC) with the authentic sample [1] (**8**).

Reaction of Methyl 12-Methoxy-7-oxo-dehydroabietate (22) with Aluminum Chloride——i) Methyl 12-Hydroxy-7-oxo-deisopropyl-dehydroabietate (**25**): 12-Methoxy-7-oxo ester[6] (**22**) (300 mg) in ab. benzene (20 ml) was reacted with $AlCl_3$ (6 g; 53.8 mol. eq.) as the case of **21** (i). The resulting oil (177 mg; 70% yield) was identical (IR and NMR) with the 12-hydroxy deisopropyl ester (**25**).

ii) Mixture of **25** and **21** (Identified as the Corresponding Methoxy Esters (**26** and **22**)): 12-Methoxy-7-oxo ester (**22**) (200 mg) in ab. benzene (15 ml) was refluxed with $AlCl_3$ (4 g; 53.8 mol. eq.) for 2 hr. The reaction mixture was treated and the resulting oil (306 mg) was methylated as the case of **21** (ii). The oily product obtained was chromatographed on silica-gel (40 g) to separate **22** (identified by NMR and GLC) (60 mg; 30% yield) in petr. ether–ether (9: 1—2: 1) elution and **26** (identified by IR, NMR, and GLC) (108 mg; 61% yield) in petr. ether–ether (2: 1) elution.

Reaction of Methyl 14-Hydroxy-7-oxo-dehydroabietate (23) with Aluminum Chloride to 27——14-Hydroxy-7-oxo ester [6] (**23**) (500 mg) in ab. benzene (20 ml) was stirred with $AlCl_3$ (5 g; 25.8 mol. eq.) at room temperature for 12 hr. The reaction mixture was treated as the case of **5**. The resulting oil (467 mg) was chromatographed on Florisil (20 g) to give an oily fraction (**27**) (417 mg; 95% yield), bp 150° (bath temp.)/10^{-2} Torr. *Anal.* Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.48; H, 7.50. IR: 1730, 1640. NMR: 1.20, 1.30 (s, 3H each; 4- and 10-Me), 3.63 (s, 3H; COOMe), 6.67—6.84 (m, 2H; 11- and 13-H), 7.20—7.54 (m, 1H; 12-H).

Reduction of Methyl 14-Hydroxy-7-oxo-deisopropyl-dehydroabietate (27) to 18——The crude oily product (**27**) (615 mg) was reduced in MeOH (20 ml) with $NaBH_4$ (2 g) for 2 hr under ice cooling. The reaction mixture

6) A. Tahara, H. Akita, and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **22**, 1547 (1974).

was condensed and was extracted with ether after H_2O addition. The extract was washed with sat.NaClaq. and then dried over Na_2SO_4. The resulting oily product (**28**), IR: 3620, 3410, was catalytically hydrogenolysed in AcOH (10 ml)–conc. H_2SO_4 (1 drop) in the presence of 10% Pd-C (500 mg) under H_2-atomosphere (3 kg/cm^2). After the filtrate was evaporated and H_2O was added, the residue was extracted with ether and the extract was washed with 5% Na_2CO_3aq., sat.NaClaq., then dried over Na_2SO_4. Removal of the solvent gave oily product (323 mg), which was chromatographed on silica-gel (30 g) to give an oil (203 mg) in petr. ether–ether (4: 1) elution. They are crystallized from MeOH to give colorless prisms (120 mg), mp 146—147.5°, which were identical (mixed mp, IR, NMR, and GLC) with 14-hydroxy-deisopropyl ester[1] (**18**).

Reaction of Methyl 14-Methoxy-7-oxo-dehydroabietate (24) with Aluminum Chloride to 27——14-Methoxy-7-oxo ester[1] (**24**) (500 mg) in ab. benzene (20 ml) was reacted with $AlCl_3$ (5 g; 26.9 mol. eq.) as the case of **5**. The resulting oil (438 mg) was chromatographed on Florisil (20 g) to give colorless oil (322 mg; 76% yield) in petr. ether–ether (9: 1) elution, which was identical (IR, NMR, and GLC) with 14-hydroxy-7-oxo-deisopropyl ester (**27**).

Attempted Reaction of Methyl 12-Nitro-dehydroabietate (3), Methyl 14-Nitro-dehydroabietate (4), Methyl 7-Oxo-dehydroabietate (20), Methyl 12-Bromo-7-oxo-dehydroabietate (29), and Methyl 14-Amino-7-oxo-dehydroabietate (30) with Aluminum Chloride (Recovery of the Starting Material)——12-Nitro[7] (**3**) and 14-nitro ester[7] (**4**) (650 mg, $AlCl_3$ (13 g; 53.9 mol. eq.), benzene (30 ml)) were stirred at room temperature for 20 hr. 7-Oxo ester (**20**) (1.42 g, $AlCl_3$ (28.32 g; 49.3 mol. eq.), benzene (60 ml)), 12-bromo-7-oxo ester[6] (**29**) (500 mg, $AlCl_3$ (10 g; 61.0 mol. eq.), benzene (30 ml)), 14-amino-7-oxo ester[6] (**30**) (100 mg, $AlCl_3$ (2 g; 51.5 mol. eq.), benzene (10 ml)) were refluxed for 24 hr. After these reactions were treated as the case of **5**, the starting materials were only recovered, respectively.

7) E. Ochiai and M. Ohta, *Yakugaku Zasshi*, **74**, 203 (1954).