[Chem. Pharm. Bull. 19(10)2166—2172(1971)]

UDC 547.833.3.04 : 546.31.04

Studies on Tetrahydroisoquinolines. V.[1] Synthesis of 4-Alkyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines

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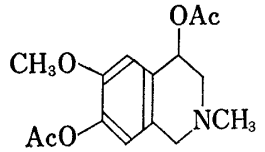
(Received April 30, 1971)

4-Cyano- or 4-alkyl-7-hydroxy tetrahydroisoquinolines (V or VI—X, XII, XVIII) were obtained by reaction of 4,7-diacetate (I) with potassium cyanide or nitromethane–K_2CO_3 in aqueous solution or with active methylene compounds (malononitrile, acetophenone, cyclohexanone, cyclopentanone, diethyl malonate or dimethylsulfoxide(DMSO) in anhydrous solution (*tert*-BuOH–KO-*tert*-Bu, C_6H_6–NaH or DMSO–NaH).

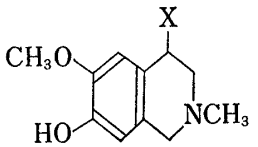
While a diastereoisomeric mixture of IX or XVIII was obtained in the case of cyclohexanone or DMSO, two kinds of diastereoisomer, Xa and Xb (also formed by reaction of I with 2-cyclopentylidene cyclopentanone), could be isolated in the case of cyclopentanone. With respect to diethyl malonate, the reaction afforded 7-acetoxy- and 7-hydroxy-4-alkyl compound (XI and XII).

Furthermore, the reaction pathway on formation of XI was inferred.

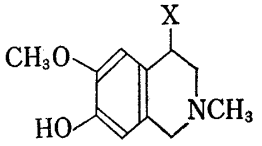
Previously, a facile reaction of 4,7-diacetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (I) with alcohols, alkyl(phenyl)mercaptans or amines in the presence of base at room temperature has been shown to give the corresponding 4-alkoxy,[3] alkyl(phenyl)mercapto[3] or alkyl(phenyl)amino[1] compounds (II, III or IV). The finding has proved that 4-acetoxy group in I can be replaced easily by nucleophiles such as alcohols, alkyl(phenyl)-mercaptans or amines under mild condition and tetrahydroisoquinolines having hetero atoms (oxygen, sulfur, or nitrogen) at 4-position are readily synthesized.



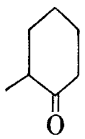
I

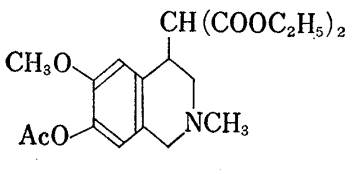


II : X=O-alkyl
III : X=S-alkyl (phenyl)
IV : X=N-alkyl
H (alkyl)

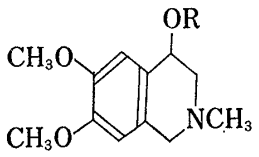


V : X=CN
VI : X=CH_2NO_2
VII : X=$CH(CN)_2$
VIII : X=$CH_2COC_6H_5$
IX : X=

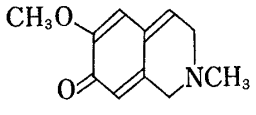




XI

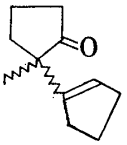


XIII : R=Ac
XIV : R=H



XVI

X a, b : X=



XII : X=$CH_2(COOC_2H_5)_2$
XVIII : X=CH_2SCH_3
O

Chart 1

1) Part IV: O. Hoshino, Y. Yamanashi and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2161 (1971).
2) Location: *12, Ichigayafunagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
3) B. Umezawa, O. Hoshino and Y. Yamanashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2154 (1971).

Then, it was quite natural to consider that active methylene compounds could be employed as nucleophiles to form the corresponding 4-alkyl derivatives. Moreover, synthesis of 4-alkyl compounds under basic condition was not yet encounterd so far. Therefore, the present reaction was extensively investigated under aqueous or anhydrous solution and the result was summarized in Table I.

Table I. Yield, Melting Point and Elemantal Analysis of V—XII and XVIII

Compound	Yield (%)	Melting point (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
V	70	159—160	$C_{12}H_{14}O_2N_2$	66.03	6.47	12.84	65.78	6.58	12.73
VI	51	154—155	$C_{12}H_{16}O_4N_2$	57.13	6.39	11.11	57.02	6.46	11.02
VII	75	136—137.5	$C_{14}H_{15}O_2N_3$	65.35	5.88	16.33	65.52	5.78	16.40
VIII	70	176—178	$C_{19}H_{21}O_3N$	73.29	6.80	4.50	73.24	6.85	4.40
IX[a]	48	157—159	$C_{17}H_{23}O_3N$	70.56	8.01	4.84	70.45	8.04	4.86
Xa	14	155—157	$C_{16}H_{21}O_3N$	73.87	7.97	4.10	73.37	8.11	3.95
Xb	19	200.5—202					73.88	7.94	3.89
XI	9	185—186	$C_{26}H_{30}O_{14}N$[b]	50.15	4.98	9.00	49.83	4.67	9.28
XII	43	88—89.5	$C_{18}H_{25}O_6N \cdot H_2O$	60.00	7.22	3.89	59.99	6.98	4.05
XVIII[a]	32	171—172	$C_{13}H_{19}O_3NS$	57.98	7.11	5.20	58.37	7.10	5.39

a) a diastereoisomeric mixture *b*) picrate

Reaction in Aqueous Solution

First, potassium cyanide (KCN) was employed as a nucleophile for formation of carbon-carbon bond. A solution of I in aqueous KCN was stirred for 1 hr at room temperature. Usual treatment of the reaction mixture gave colorless prisms of V, mp 159—160°, in 70% yield. Its infrared (IR) spectrum displayed a characteristic absorption band at 2200 cm^{-1} for cyano group and nuclear magnetic resonance (NMR) spectrum of V showed a one proton broad triplet at τ 5.93 for C-4 hydrogen.

Thereupon, it was assumed on the basis of the above spectral data and elemental analysis that structure of V was 4-cyano-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.

Next, nitromethane was chosen as an active methylene compound, because its reactivity appeared to be comparable to that of compounds having two activating groups such as carbonyl, ester or cyano group. In this case, however, employment of alcohols as solvent and strong bases must be avoided, since an unfavorable replacement[3] of 4-acetoxy with alkoxy group or hydroxide ion may take place. With this in mind, the reaction of I in aqueous nitromethane solution containing potassium carbonate was undertaken to afford colorless plates of VI, mp 146—147°, in 51% yield, whose structure was confirmed by means of NMR spectrum and elemental analysis to be 7-hydroxy-6-methoxy-2-methyl-4-nitromethyl-1,2,3,-4-tetrahydroisoquinoline.

Thus formation of a carbon-carbon bond at 4-position was also accomplished in the case of nitromethane as well as in that of KCN. However, acetonitrile did not react under the above condition.

Reaction in Anhydrous Solution

In general, the reaction in aqueous solution had the advantage of being easily carried out. Considering reactivity or structure of nucleophiles employed, however, the reaction in aqueous solution was not always favorable. Furthermore, in order to explore the scope of the present reaction, establishment of suitable condition was required. So, anhydrous condition was chosen. As reported previously, the reaction in alcohols (except neopentyl- or *tert*-butyl alcohol) containing strong base has been found to give the corresponding 4-alkoxy

derivatives[3] (III). Therefore, if alcohols were necessarily used as solvent, *tert*-butyl alcohol (*tert*-BuOH) was the most adequate. Then, the reaction in anhydrous *tert*-BuOH and potassium *tert*-butoxide (KO-*tert*-Bu) was examined.

a) In *tert*-BuOH and KO-*tert*-Bu——A solution of I and malononitrile in *tert*-BuOH containing KO-*tert*-Bu was stirred for 30 min at room temperature. Usual work-up of the reaction mixture followed by chromatographic separation (silicic acid, Mallinckrodt) gave colorless feathery crystals of VII, mp 136—137.5°, in 75% yield. Structure of VII was confirmed to be 4-dicyanomethyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline by inspection of its IR and NMR spectral data as well as by elemental analysis.

Thus the reaction with malononitrile was found smoothly to form the corresponding 4-dicyanomethyl compound. Based on this fact, with carbonyl compounds[4] such as acetophenone, cyclohexanone or cyclopentanone the similar reaction was performed. In the case of acetophenone, the corresponding 4-phenacyl derivative (VIII) was formed in 70% yield and with cyclohexanone a diastereoisomeric mixture of 4-(2′-oxocyclohexyl) compound (IX), mp 157—159°, was obtained in 48% yield. Evidence on structure of the latter was provided by its NMR spectrum. In the case of cyclopentanone, the following fact that I reacted not with cyclopentanone but its dimer, 2-cyclopentylidene cyclopentanone[5] (see experimental), was found. Namely, chromatography of the reaction mixture gave two kinds of diastereoisomeric product (Xa), mp 155—157°, and (Xb), mp 200.5—202°, in 1: 1.3 ratio and each structure was supposed to be 4-(1′-cyclopenten-1″-yl-2′-oxo-cyclopentyl) compound (X) by inspection of NMR spectrum [Xa: τ 4.20 (1H, broad singlet, olefinic proton) and Xb: τ 4.18 (1H, broad singlet, olefinic proton)] and by elemental analysis, though conformationally ambiguous. The same products (Xa and Xb) were also formed in approximately 1: 2 ratio by the similar reaction of I with 2-cyclopentylidene cyclopentanone.[6] It was thus proved that 4-acetoxy group was undoubtedly replaced not with cyclopentanone but 2-cyclopentylidene cyclopentanone.

b) In Anhydrous Benzene and Sodium Hydride (NaH)——With respect to active methylene compounds as noted above, the reaction in *tert*-BuOH containing KO-*tert*-Bu was succesful. With diethyl malonate, however, the similar treatment was repeatedly carried out to be fruitless.

Thereupon, in this case the reaction in anhydrous benzene containing NaH was undertaken nicely to afford 7-acetoxy- and 7-hydroxy-4-diethoxycarbonylmethyl-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline [(XI) (oil, picrate, mp 185—186°) and (XII) (mp 88—89.5°)] in 9% and 43% yield, respectively.

Structure of XI and XII were secured by means of NMR and IR spectral data as well as elemental analysis and the former was identical with 7-acetoxy compound prepared by acetylation of the latter with acetic anhydride and pyridine.

The finding that XI was formed without apparent hydrolysis of 7-acetoxy group was surprising, because similar reaction of 4-acetoxy-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[7] (XIII) with diethyl malonate under the above condition was found to furnish the corresponding 4-hydroxy compound[7] (XIV) as a sole product. However, formation

4) Similar treatment with ethyl acetoacetate or methyl ethyl ketone gave the corresponding 4-alkyl product (each as oil), in 37% or 44% yield. Structure of each product was supported to be 4-(1′-ethoxycarbonyl-1′-acetylmethyl- or (1′-acetylethyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline from each NMR spectrum. All efforts to crystallize either the product or its derivative were unsuccessful.

5) G. Hess and M. Maurer, *Ann.*, **658**, 21 (1962).

6) Ethylation of 2-cyclopentylidene cyclopentanone with diethylsulfate is already reported to give 2-ethyl-2-(1′-cyclopenten-1′-yl)cyclopentanone (Z.-M. Conia, *Bull. Soc. Chim. France*, **1954**, 943). Our finding would also be another instance on reaction of 2-cyclopentylidene cyclopentanone with such a bulky alkylating reagent as I.

7) B. Umezawa, O. Hoshino, Y. Terayama, K. Ohyama, Y. Yamanashi, T. Inoue and T. Toshioka, *Chem. Pharm. Bull.* (Tokyo), **19**, 2138 (1971).

of XI would be well understood by considering the reaction pathway as pictured in Chart 2. Namely, addition of hydride ion to positively charged carbon atom of carbonyl in 7-acetoxy group followed by elimination of acetaldehyde and acetoxyl anion would give an intermediate (XVI). Successively, concerted addition of acetaldehyde generated above and diethylmalonate carbanion to XVI would take place. Finally hydride ion from XVII would be eliminated to result in XI.

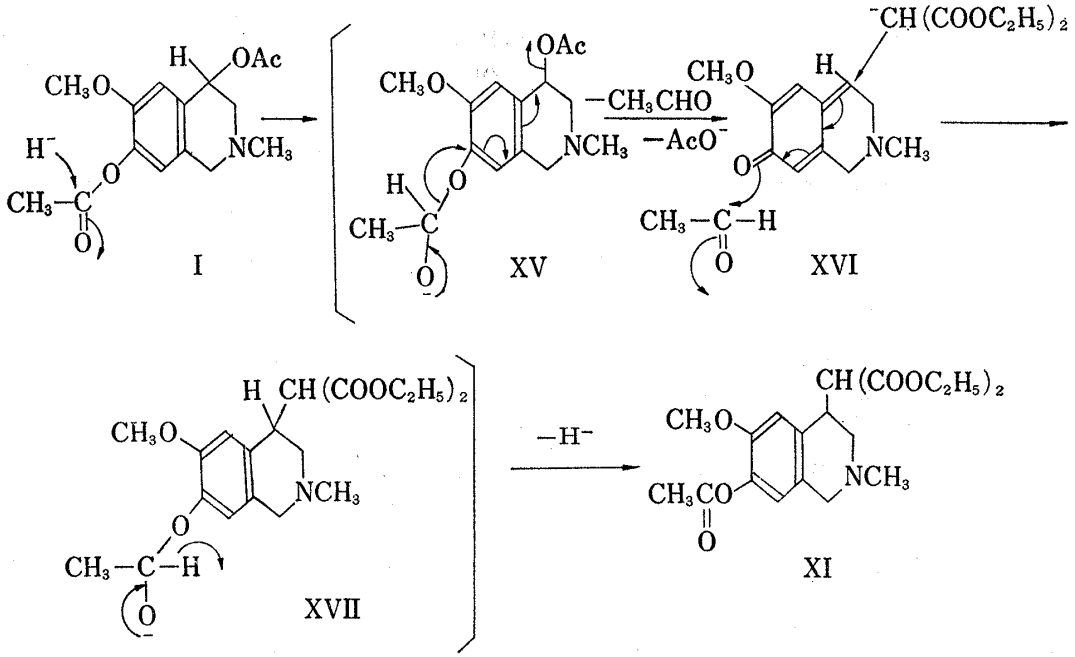


Chart 2

As to other nucleophiles such as Grignard reagent, phenyllithium, phenylacetylene, anisole or dimethylaniline, attempted reaction under the above condition was unsuccessful.

c) Dimethylsulfoxide (DMSO) and NaH——DMSO[8] is widely known not only to be an excellent solvent but to function as active methyl compound.

Therefore, reaction of I with methylsulfinyl carbanion,[9] which was prepared from DMSO and NaH, was carried out under stirring at room temperature. Usual work-up of the reaction mixture followed by column chromatography afforded colorless prisms of XVIII, mp 171—172°, in 32% yieid. Its NMR spectrum showed a three proton singlet at τ 7.35 for methylsulfinyl group, each singlet of three protons (1: 2 ratio of peak area) at τ 6.12 and 6.09 for aromatic methoxy groups and three singlets of two protons (3: 2: 1 ratio of peak area) at τ 3.35, 3.25 and 3.10 for aromatic ring protons.

From the above spectral datum and elemental analysis, structure of XVIII was supposed to be a diastereoisomeric mixture[10,11] of 7-hydroxy-6-methoxy-2-methyl-4-methylsulfinylmethyl-1,2,3,4-tetrahydroisoquinoline.

8) T. Durst, "Advances in Organic Chemistry, Methods and Results," Vol. 6, ed. by E. C. Taylor and H. Wynberg, Interscience Publishers, Inc., New York, 1969, p. 285.
9) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).
10) Recently, similar reaction was found by T. Natsume, M. Takahashi, S. Kumadaki, M. Wada, I. Utsunomiya and K. Kiuchi (Abstracts of 3rd Symposium on the Chemistry of Heterocyclic Compounds, Tokyo, 1970, p. 104): treatment of 4-cyanoisoquinoline with methylsulfinyl carbanion in DMSO followed by tosylation or benzoylation afforded each diastereoisomeric mixture of the corresponding 2-tosyl- or benzoyl-1-methylsulfinylmethyl-4-cyano-1,2-dihydroisoquinoline.
11) This was supported by the fact that NMR spectrum of a deoxygenated product of XV ($LiAlH_4$ reduction) indicated a three proton singlet at τ 6.82 for methylmercapto group, a three proton singlet at τ 6.10 for aromatic methoxy group, and each one proton singlet at τ 3.41 and 3.28 for C-8 and C-5 H.

In conclusion, it was clearly proved that reaction of I with active methylene compounds gave the corresponding 4-alkyl products in a moderate yield, if suitable condition was chosen. Finally, with respect to the reaction mechanism the present reaction was reasonably inferred to proceed through *p*-quinone methide[12] (XVI) as noted in reaction of I with alcohols,[3] alkyl-(phenyl)mercaptans,[3] or amines[1] in the presence of base.

Experimental[13]

Reaction in Aqueous Solution——a) Potassium Cyanide (KCN): To a stirred solution of KCN (141 mg) in H_2O (4 ml), I (200 mg) was added and the whole was stirred for 1 hr at room temperature. The reaction mixture was carefully acidified with 10% HCl and HCN gas generated was removed under reduced pressure. The acidic solution was basified with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried. Removal of the solvent gave an oil (175 mg), whose treatment with *n*-hexane afforded a crystalline mass of V (105 mg, 70 %), mp 132—135°. Recrystallization from *n*-hexane furnished colorless prisms of V, mp 159—160°. NMR τ: 7.52 (3H, s, NCH_3), 6.46 (2H, s, C-1 H_2), 6.10 (3H, s, OCH_3), 5.92 (1H, m, C-4 H), 3.38, 3.15 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 3470 (OH), 2200 (CN).

b) Nitromethane ($MeNO_2$): To a stirred solution of $MeNO_2$ (0.4 ml) and K_2CO_3 (400 mg) in H_2O (4 ml), I (200 mg) was added and the reaction mixture was stirred for 1.75 hr at room temperature. After completion of the reaction, the product was taken up in $CHCl_3$. The same treatment of the $CHCl_3$ extract as noted above a solid of VI (88 mg, 51%), mp 133—134°, recrystallization of which from MeOH–H_2O afforded colorless plates of VI, mp 154—155°. NMR: τ 7.58 (3H, s, NCH_3), 6.79, 6.24 (2H, AB q, J=15 Hz, C-1 H_2), 6.12 (3H, s, OCH_3), 3.37 (2H, s, aromatic ring protons).

General Procedure for Reaction in *tert*-BuOH and KO-*tert*-Bu——To an ice-cooled, stirred KO-*tret*-Bu–*tert*-BuOH solution (*tert*-BuOH, 10 ml and K, 330 mg) of freshly distilled active methylene compound, a solution of I (400 mg) in *tert*-BuOH (4 ml) was added and the whole was stirred at room temperature. To a residue obtained on removal of the solvent under reduced pressure, H_2O was added and the aqueous solution was acidified with 10% HCl. The acidic solution was basified with K_2CO_4 (powder). The product was taken up in $CHCl_3$. The same treatment of the $CHCl_3$ extract as noted above gave a solid or an oil which was subjected to column chromatography.

a) Malononitrile: Malononitrile (180 mg) was employed and the reaction mixture was stirred for 30 min. Chromatography of a crystalline residue (325 mg, mp 123—132°) gave a solid of VII (263 mg, 75%), mp 133—136°, from an eluate with $CHCl_3$. Recrystallization from C_6H_6 afforded colorless feathery crystal of VII, mp 136—137.5°. NMR τ: 7.52 (3H, s, NCH_3), 6.71, 6.15 (2H, AB q, J=15 Hz, C-1 H_2), 6.06 (3H,s, OCH_3), 5.48 [1H, d, J=10 Hz, ArC<u>H</u>-C<u>H</u>$(CN)_2$], 3.33, 3.10 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 2170 (CN).

b) Acetophenone : Acetophenone (327 mg) was employed and the reaction mixture was stirred for 10 min. Chromatography of a solid residue (301 mg, mp 112—140°) gave a crystalline mass of VIII (298 mg, 70%), mp 173—176°, from an eluate with $CHCl_3$–MeOH (100:1). Recrystallization from C_6H_6 yielded colorless fine prisms of VIII, mp 176—178°. NMR τ: 7.60 (3H, s, NCH_3), 6.18 (3H, s, OCH_3), 3.38, 3.31 each 1H, s, C-8 and C-5 H), 2.58—2.38 (3H, m, aromatic ring protons), 1.95 (2H, d d, J=10 Hz, C-2′ and C-6′ H). IR[14] $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1680 (COC_6H_5), 1600 (C=C).

c) Cyclohexanone: The reaction mixture with cyclohexanone (264 mg) was stirred for 1 hr. Chromatography of a solid residue (306 mg, mp 126—134°) yielded a crystalline substance of IX (208 mg, 48%), mp 150—157°, from an eluate with $CHCl_3$–MeOH (100: 1)—(100: 2). Recrystallization from C_6H_6 afforded colorless prisms of IX, 157—159°. NMR τ : 7.53, 7.51 (3H, each s, 1: 2 ratio of peak area, NCH_3), 6.16, 6.13 (3H, each s, 1: 2 ratio of peak area, OCH_3), 3.45, 3.41, 3.29 (2H, three s, 2: 3: 1 ratio of peak area, C-8 and C-5 H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1705 (C=O).

d) Cyclopentanone: The reaction mixture with cyclopentanone (230 mg) was stirred for 10 min. Chromatography of an oil (409 mg) afforded a solid of Xa (66 mg, 14%), mp 148—151°, and subsequently that of Xb (88 mg, 19%), mp 191—200°, from an eluate with $CHCl_3$–MeOH (100: 1). The former was recrystallized from *n*-hexane to yield colorless prisms of Xa, mp 155—157°. NMR τ : 7.71 (3H, s, NCH_3), 6.85, 6.30 (2H, AB q, J=15 Hz, C-1 H_2), 6.45 (1H, t, J=3 Hz, C-4 H), 6.22 (3H, s, OCH_3), 4.43 (1H, b s, OH), 4.18

12) *cf.* A.B. Turner, *Quart. Revs.*, **18**, 347 (1964).

13) All melting points were uncorrected and measured with a Yanagimoto micro melting point measuring apparatus. NMR spectra were taken with Japan Electron Optics Lab. Model JNR-4H-100 spectrometer in $CDCl_3$ solution (5—10%) by using $(CH_3)_4Si$ as internal standard and following abbreviations were used: s, singlet; b s, broad singlet; d, doublet; d d, double doublet; t, triplet; AB q, AB quartet; m, multiplet. IR spectroscopy was carried out on a Hitachi EPI-S_2 infrared spectrometer. Column chromatography was run over silicic acid (Mallinckrodt) and the organic phase was dried over K_2CO_3.

(1H, b s, >C=CHCH$_2$–), 3.41, 3.40 (each 1H, s, aromatic ring proton). IR[14] $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1720 (C=O), 1620 1600, 1510 (C=C). Recrystallization of the latter from *n*-hexane–C_6H_6 furnished colorless prisms of Xb, mp 200.5—202°. NMR τ: 7.65 (3H, s, NCH_3), 6.53 (2H, b s, C-1 H_2), 6.24 (3H, s, OCH_3), 4.20 (1H, b s, >C=CH–CH_2–), 4.07 (1H, b s, OH), 3.45, 3.28 (each 1H, s, C-8 and C-5 H). IR[14] $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1720 (C=O), 1630, 1600, 1510 (C=C).

2-Cyclopentylidene Cyclopentanone——To an ice-cooled, stirred KO-*tert*-Bu-*tert*-BuOH solution (*tert*-BuOH, 110 ml and K, 4.3 g) freshly distilled cyclopentanone (8.4 g) was added during 5 min and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture displayed dark brown color. After completion of the reaction, removal of the solvent under reduced pressure gave an oily residue, to which H_2O was added and the aqueous solution was acidified with 10% HCl. The product was taken up in $CHCl_3$. Fractional distillation of the residue obtained on usual treatment of the $CHCl_3$ extract gave an oil of 2-cyclopentylidene cyclopentanone (3.6 g, 47%), bp 138—140° (32 mm Hg)[lit.,[5] bp 139—142° (20 mm Hg)]; oxime, mp 124—127° (EtOH–H_2O) (lit.,[5] mp 123—124°).

Reaction of I with 2-Cyclopentylidene Cyclopentanone——To an ice-cooled, stirred KO-*tert*-Bu-*tert*-BuOH solution (*tert*-BuOH, 30 ml and K, 1.0 g) of 2-cyclopentylidene cyclopentanone (0.7 g) prepared as noted above, a solution of I (1.1 g) in *tert*-BuOH (12 ml) was added during 12 min. The same treatment as noted above afforded an oil (1.16 g), whose chromatography yielded a solid of compound A (170 mg) from an eluate with $CHCl_3$–MeOH (200:1)—(100:1) and that of compound B (193 mg) from an eluate with $CHCl_3$–MeOH (100:1)—(50:1). Recrystallization of compound A or B from *n*-hexane–C_6H_5 gave colorless prisms of Xa (45 mg, mp 149—151°) or Xb (93 mg, mp 190—192°). Each was identical with product (Xa) or (Xb) obtained in (d) by comparison of NMR and IR spectral data and by mixed fusion.

Reaction of I with Diethyl Malonate in Anhydrous Benzene and NaH——To a mixture of NaH [prepared by washing 50% NaH in oil (1.2 g) with anhydrous C_6H_6] in anhydrous C_6H_6, diethyl malonate (1.1 g) was added and the mixture was stirred for 30 min at room temperature. To the ice-cooled, stirred mixture, a solution of I (1.1 g) in anhydrous C_6H_6 (30 ml) was added and the whole was stirred for 15 hr at room temperature. The reaction mixture was neutralized with AcOH. To the whole H_2O was added and then the C_6H_6 layer was separated. After basification of the aqueous solution with K_2CO_3 (powder), the basic solution was extracted with $CHCl_3$. The $CHCl_3$ extract was combined to the above C_6H_6 layer. Usual treatment of the combined extract gave an oil (1.8 g) which was chromatographed. Elution with CH_2Cl_2–MeOH (100:0.5) yielded an oil of XI (125 mg, 9%). NMR τ: 8.89, 8.76 (each 3H, t, J=7.5 Hz, $OCH_2CH_3\times2$), 7.72 (3H, s, OAc), 7.62 (3H, s, NCH_3), 6.21 (3H, s, OCH_3), 6.00, 5.70 [5H, m, $OCH_2CH_3\times2$ and $CH(COOC_2H_5)_2$], 3.28, 3.20 (each 1H, s, aromatic ring proton). IR ν_{max}^{KBr} cm^{-1}: 1760 (OAc), 1750, 1730 $(COOEt)_2$, 1620 (C=C); picrate, mp 185—186° (MeOH). Elution with CH_2Cl_2–MeOH (100:0.5)–MeOH furnished a solid of XII (568 mg, 43%), mp 83—85°, whose recrystallization from *n*-hexane yielded colorless prisms of XII, mp 88 89.5°. NMR τ: 8.87, 8.78 (each 3H, t, J=7.5 Hz, $OCH_2CH_3\times2$), 7.63 (3H, s, NCH_3), 6.19 (3H, s, OCH_3), 6.02—5.70 [5H, m, $OCH_2CH_3\times2$ and $-CH(COOC_2H_5)_2$], 3.44, 3.32 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 1750, 1730 $(COOEt)_2$, 1605, 1530 (C=C).

Acetylation of XII——A solution of XII (100 mg) and Ac_2O (1 ml) in pyridine (1 ml) was allowed to stand for 12 hr at room temperature. To the reaction mixture, crashed ice was added and the solution was basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. Usual treatment of the reaction mixture gave an oil (110 mg), which was converted into its picrate, mp 185—186° (MeOH). This was identical with XI by comparison of each IR spectrum (picrate) and by mixed fusion (picrate).

Reaction of XIII with Diethyl Malonate in Anhydrous Benzene and NaH——A mixture of diethyl malonate (187 mg) and NaH [prepared by the same treatment of 50% NaH in oil (110 mg) as noted above] in anhydrous C_6H_6 (10 ml) was stirred for 30 min at room temperature. To the ice-cooled, stirred solution, a solution of XIII[7] (150 mg) in anhydrous C_6H_6 (3 ml) was added and the whole was stirred for 4 days at room temperature. The same treatment of the reaction mixture as described above gave XIV (65 mg, 52%), mp 126—127° (ether), which was identical with an authentic specimen[7] (mp 127—128°) by mixed fusion.

Reaction of I in DMSO and NaH——According to the method[9] of E.J. Corey and M. Chaykovsky, sodium methylsulfinyl carbanion was prepared. A mixture of anhydrous DMSO (distilled twice from CaH_2) (10 ml) and 50% NaH in oil (394 mg) was stirred for 45 min under N_2 at 65—70°. To the cooled, stirred mixture, a solution of I (400 mg) in anhydrous DMSO (4 ml) was added and the reaction mixture was stirred for 45 min under N_2 at room temperature. To the oily residue obtained on careful removal of the solvent under reduced pressure, H_2O was added under ice-cooling, excess of DMSO was washed with $CHCl_3$ and the aqueous solution was acidified with conc. HCl. The acidic solution was washed with $CHCl_3$, basified with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oil (250 mg), which was chromatographed. Elution with $CHCl_3$–MeOH (100:3) afforded a solid of XVIII (316 mg, 32%), mp 166—170°, whose recrystallization from C_6H_6–*n*-hexane yielded colorless prisms of XVIII, mp 171—172°. NMR τ: 7.52, 7.35 (each 3H, s, NCH_3 and SCH_3), 6.12, 6.09 (3H, each s, 1:2 ratio of peak area, OCH_3), 3.35, 3.25, 3.10 (2H, three s, 3:2:1 ratio of peak area, aromatic ring protons).

14) This spectrum was recorded with a Hitachi 215 grafting infrared spectrometer.

Acknowledgement The authors wish to express their sincere thanks to Dr. I. Iwai of Sankyo Co., Ltd. and Prof. M. Hamana of Kyushu University for their unfailing encouragements. They are indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind supply of the starting material. Thanks are also due to Dr. Y. Kishida and Dr. H. Mishima of Central Research Laboratories of Sankyo Co., Ltd. for elemental analyses, and to Dr. A. Tahara of Rikagaku Kenkyusho (the Institute of Physical and Chemical Research) and to Miss T. Kawana of this Faculty for NMR spectral measurements.