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Synthesis of Pyrazolone Derivatives. XXXI.[1] Asynmetric Synthesis of 3a-Alkyl-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-ones

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The reaction of pimelyl dichloride and (−)-menthol gave (−)-(1*R*,2*S*,5*R*)-dimethyl pimelate (I), which was cyclized by the Dieckmann reaction to give (−)-(1*R*,2*S*,5*R*)-menthyl 2-oxocyclohexanecarboxylate (II). Alkylation of II gave (−)-(1*R*,2*S*,5*R*)-menthyl 1-alkyl-2-oxocyclohexanecarboxylates (IIIa—c), which were condensed with hydrazine hydrate in ethanol to give 3a-alkyl-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-ones (Va—c). The compounds (Va,b) were found to be optical active.

The condensation of ethyl 2-oxocyclohexanecarboxylate with (−)-(1*R*,2*S*,5*R*)-methyl carbazate (VII) gave (−)-(1*R*,2*S*,5*R*)-menthyl 3-hydroxy-4,5,6,7-tetrahydro-2*H*-indazole-2-carboxylate (IX), whose reaction with benzyl bromide gave (−)-(1*R*,2*S*,5*R*)-menthyl 1-benzyl-3-oxo-2,3,4,5,6,7-hexahydro-1*H*-indazole-2-carboxylate (X) and (−)-(1*R*,2*S*,5*R*)-menthyl 3a-benzyl-3-oxo-3,3a,4,5,6,7-hexahydro-2*H*-indazole-2-carboxylate (XI). The hydrolysis of XI gave Va. However, the compound Va obtained by this method did not show optical rotation.

Keywords——asynmetric synthesis of pyrazolone derivatives; 3*H*-indazol-3-ones; (−)-dimenthyl pimelate; (−)-menthyl carbazate; (−)-menthyl phenylcarbazate; (−)-menthyl 2-oxocyclohexanecarboxylates; (−)-menthyl 2*H*-indazole-2-carboxylates

In order to search for new analgesic and antipretic agents 1,3-dioxolane indazoles were synthesized previously[3] in our laboratory. As a continuation of the studies of the synthesis of indazole derivatives, this paper deals with the asynmetric synthesis of 3a-alkyl-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-ones(Va—c). Very few works on optically active pyrazoles have been reported except the paper by Dreibelbis, *et al.*[4] Thus it appeared interesting for us to investigate the asynmetric synthesis of Va—c.

The scheme of the synthesis of Va—c was shown as Chart 1. The reaction of pimelyl dichloride[5] and (−)-menthol gave (−)-(1*R*, 2*S*, 5*R*)-dimenthyl pimelate(I), which was cyclized by the Dieckmann condensation reaction to give (−)-(1*R*, 2*S*, 5*R*)-menthyl 2-oxocyclo-hexanecarboxylate (II). Alkylations of II were carried out by the reaction of alkyl halides in the presence of metal sodium in dry ether to give (−)-(1*R*, 2*S*, 5*R*)-menthyl 1-alkyl-2-oxocyclohexanecarboxylate (IIIa—c) in 73—91% yield (Table I). The reaction of IIIa with phenylhydrazine or 2,4-dinitrophenylhydrazine gave (−)-(1*R*, 2*S*, 5*R*)-menthyl 1-benzyl-2-oxocyclohexanecarboxylate phenylhydrazone (IVa) or (−)-(1*R*, 2*S*, 5*R*)-menthyl 1-benzyl-2-oxocyclohexanecarboxylate 2,4-dinitrophenylhydrazone (IVb), while the condensation of IIIa—c with hydrazine hydrate afforded Va—c in 72—89% yield. The infra red (IR) spectra of Va—c revealed amidocarbonyl group at 1690 cm^{-1} and secondary amino group at 3200 cm^{-1}. The compounds (Va and Vb) showed optical rotations (Table II). It appears the cyclization of IIIa,b with hydrazine hydrate gave the chiral compounds (Va,b) on account of the bulky menthyl ester and benzyl or allyl groups. So far as we know this is the first observation that the asynmetric syntheses of Va,b were carried out by this type of the reaction.

1) Part XXX: I. Ito, T. Ueda, and F. Kato, *Chem. Pharm. Bull.* (Tokyo), **25**, 1443 (1977).
2) Location: *3–1, Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan.*
3) I. Ito, N. Oda, H. Kakishima, T. Kato, K. Asano, and T. Sugawara, *Chem. Pharm. Bull.* (Tokyo), **25**, 1124 (1977).
4) R.L. Dreibelbis, H.N. Khatri, and H.M. Walborsky, *J. Org. Chem.*, **40**, 2074 (1975).
5) J. Cason and J. Reist, *J. Org. Chem.*, **23**, 1492 (1958).

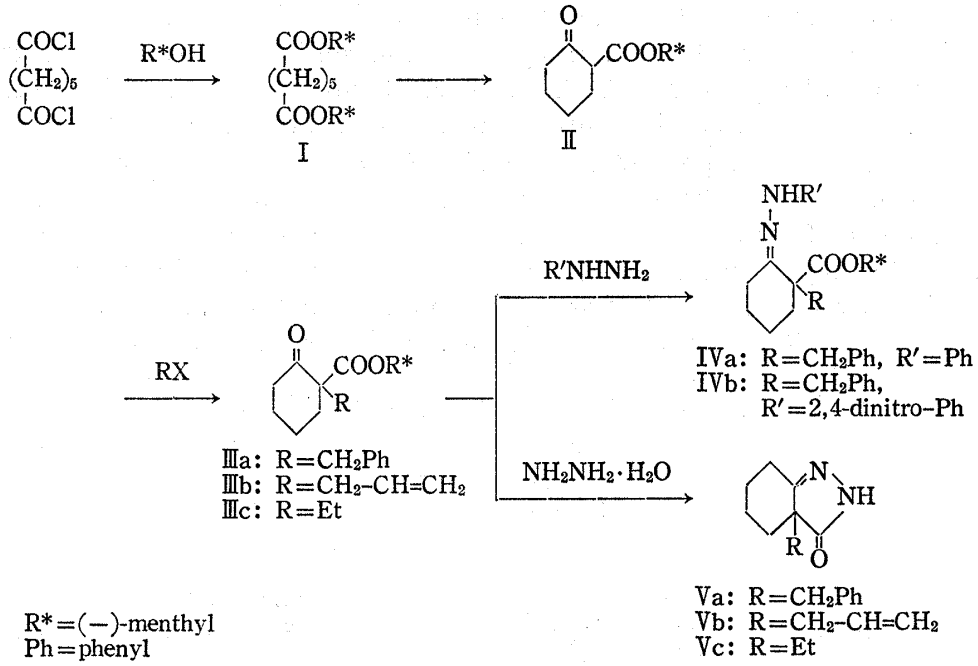
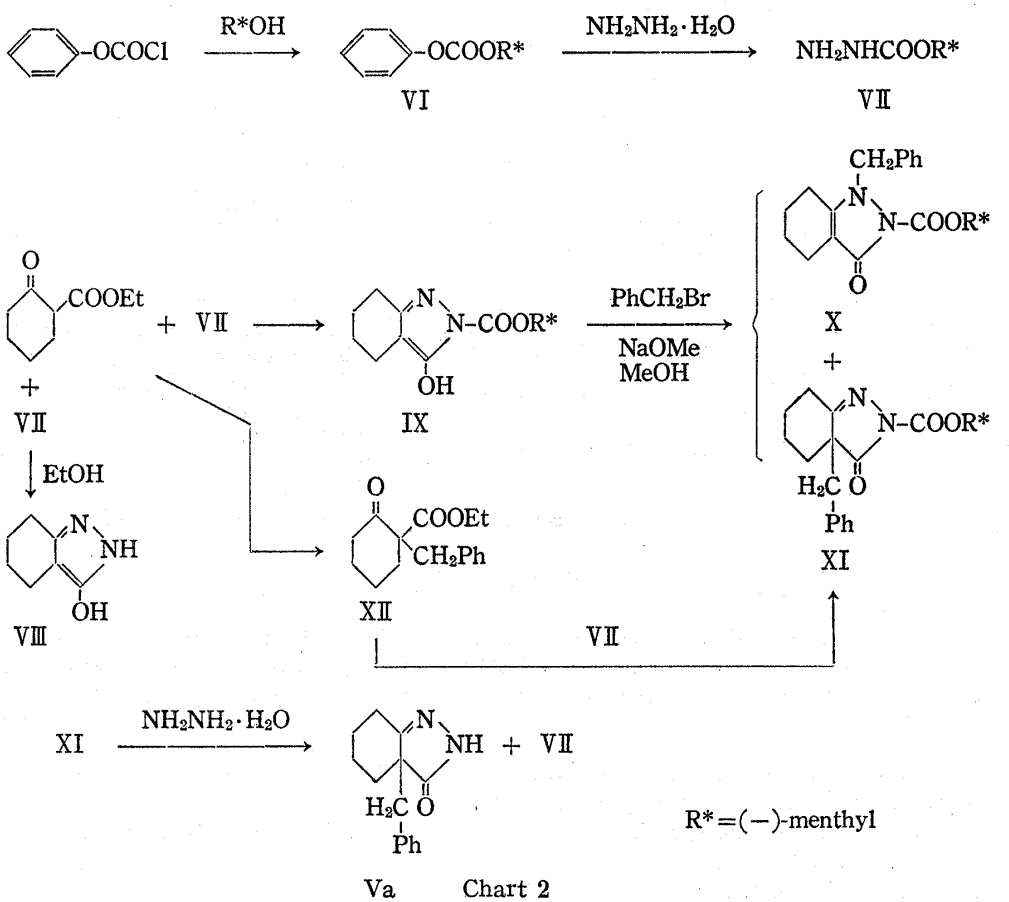


Chart 1

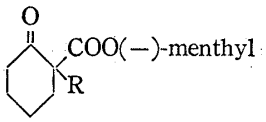
The asynmetric synthesis of Va was also attempted by the hydrolysis of (−)-(1*R*, 2*S*, 5*R*)-menthyl 3a-benzyl-3-oxo-3,3a-4,5,6,7-hexahydro-2*H*-indazole-2-carboxylate (XI) as outlined in Chart 2. (−)-(1*R*, 2*S*, 5*R*)-Menthyl phenylcarbonate (VI) was prepared from phenyl chloroformate and (−)-menthol. The reaction of VI and hydrazine hydrate gave (−)-(1*R*,



Va Chart 2

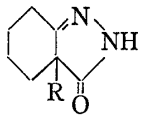
2*S*, 5*R*)-menthylcarbazate (VII). The condensation of ethyl 2-oxocyclohexanecarboxylate[6] with VII in ethanol gave 4,5,6,7-tetrahydro-2*H*-indazol-3-ol[7] (VIII), while the reaction without solvent afforded (−)-(1*R*, 2*S*, 5*R*)-menthyl 3-hydroxy-4,5,6,7-tetrahydro-2*H*-indazole-2-carboxylate (IX), whose treatment with benzyl bromide in the presence of sodium methoxide in methanol produced two products: (−)-(1*R*, 2*S*, 5*R*)-menthyl 1-benzyl-3-oxo-2,3,4,5,6,7-hexahydro-1*H*-indazole-2-carboxylate (X) and XI. The compound (XI) was identical with the sample prepared from the reaction of ethyl 1-benzyl-2-oxocyclohexanecarboxylate[8] (XII) and VII. Removal of menthyl group from XI was performed by refluxing the ethanolic solution of XI in the presence of hydrazine hydrate to give Va in 80% yield. However, the compound (Va) thus obtained in the above experiment did not show optical rotation.

Table I. (−)-(1*R*,2*S*,5*R*)-Menthyl 1-Alkyl-2-oxocyclohexanecarboxylates



Compd. No.	R	bp (°C) (mmHg)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	$[\alpha]_D^{24}$
IIIa	CH_2Ph	188—189 (0.9)	91	$C_{24}H_{34}O_3$	77.80 (77.71)	9.25 (9.08)	−26.1° (*c*=1.9, EtOH)
IIIb	CH_2–CH=CH_2	159—160 (1.0)	88	$C_{20}H_{32}O_3$	74.96 (74.96)	10.07 (9.98)	−42.2° (*c*=3.8, EtOH)
IIIc	Et	158—159 (3.0)	73	$C_{19}H_{32}O_3$	73.98 (73.63)	10.46 (10.56)	−52.7° (*c*=3.3, EtOH)

Table II. 3a-Alkyl-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-ones



Compd. No.	R	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N	$[\alpha]_D^{23}$ *a*)
Va	CH_2–Ph	194.5—195.5	89	MeOH–AcOEt	$C_{14}H_{16}N_2O$	73.66 (73.82)	7.06 (6.88)	12.27 (12.48)	+5.7° (*c*=1.16, EtOH)
Vb	CH_2–CH=CH_2	115—116.5	72	Acetone	$C_{10}H_{14}N_2O$	67.46 (67.46)	7.92 (7.96)	15.72 (15.64)	+4.4° (*c*=0.84, EtOH)
Vc	Et	102—103	75	MeOH	$C_{19}H_{14}N_2O$	65.03 (64.85)	8.49 (8.32)	16.85 (17.04)	0° (*c*=1.60, EtOH)

a) Optical rotations were measured with a Union PM-201 automatic digital polarimeter before recrystallizations.

Experimental

All the melting points were determined on a Yanagimoto Micro Melting Point apparatus and are not corrected. The IR spectra were measured with a Nihon Bunko Spectroscopic Co. Ltd. Model IR-A2. The NMR spectra were measured with a Japan Electron Optics Laboratory Co. Ltd. JNM-MH-100 Spectrometer

6) H.R. Snyder, L.A. Brooks, and S.H. Shapiro, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 531.
7) G. De Stevens, A. Halamandalis, P. Wenk, R.A. Mull, and E. Schlittler, *Arch. Biochem. Biophys.*, **83**, 141 (1959) [*C.A.*, **54**, 1530^a (1960)].
8) J.W. Cook and C.L. Hewett, *J. Chem. Soc.*, **1936**, 62.

using tetramethylsilane as internal standard. Mass spectra were measured with a Hitachi Mass spectrometer, Model M-52. Optical rotations were measured with a Yanagimoto Photo-magnetic Direct Reading Polarimeter, Model OR-10, unless otherwise indicated.

(−)-(1*R*,2*S*,5*R*)-Dimenthyl Pimelate (I)——A mixture of (−)-menthol (28 g), dry pyridine (16 g) and dry benzene (200 ml) was cooled below 10°. Pimelyl dichloride[4] (18 g) was added dropwise into the above mixture under stirring for 1 hr. The mixture was refluxed for 8 hr. After cooling 5% HCl (100 ml) was added to the mixture. Organic layer was separated, washed with water and dried over Na_2SO_4. After the solvent was distilled, the residue was rectified to obtain bp_3 225°. Yield 37 g (93%). *Anal.* Calcd. for $C_{27}H_{48}O_4$: C, 74.26; H, 11.08. Found: C, 74.17; H, 11.21. IR ν_{max}^{film} cm^{-1}: 1730 (C=O). NMR $\delta_{ppm}^{CDCl_3}$: 0.76 (6H, doublet, J=7 Hz, 2× >CH–C<u>H</u>$_3$), 0.93 (12H, doublet, J=6 Hz, 2×–CH<$\underline{CH_3}$ CH_3), 2.28 (4H, triplet, J=7 Hz, 2×–CH_2–COO–), 1.00—2.20 (24H, multiplet, cycloring protons, 2×<u>CH</u><$\underline{CH_3}$ CH_3, and –$(CH_2)_3$–), 4.68 (2H, triplet doublet, J=10 Hz, 4 Hz, 2×–COOCH<). $[\alpha]_D^{24}$ −75.7° (c=1.2, EtOH).

(−)-(1*R*,2*S*,5*R*)-Menthyl 2-Oxocyclohexanecarboxylate (II)——Amixture of I (26 g) and metal sodium (1.4 g) in dry toluene (350 ml) was refluxed for 8 hr under nitrogen gas stream. The reaction mixture was poured into ice (200 g), made acidic with 10% AcOH, and extracted with benzene. The extract was dried over Na_2SO_4. After the solvent was distilled off, the residue was rectified to obtain oil (bp_3 156°). Yield 9.0 g (54%). *Anal.* Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.07. Found: C, 72.70; H, 10.36. IR ν_{max}^{film} cm^{-1}: 1730, 1650 (C=O). $[\alpha]_D^{24}$ −65.5° (c=1.6, EtOH).

(−)-(1*R*,2*S*,5*R*)-Menthyl 1-Alkyl-2-oxocyclohexanecarboxylates (IIIa—c)——A mixture of II (0.01 mol) and metal sodium (0.25 g) in dry ether was stirred for 1 hr. Alkylhalide (0.02 mol) was added and the stirring was continued for 8 hr at room temperature. The mixture was poured into ice (50 g) and made acidic with 10% AcOH. The ether layer was separated and dried over Na_2SO_4. Ether was distilled off and the residue was rectified. Analytical and physical data are summerized in Table I.

(−)-(1*R*,2*S*,5*R*)-Menthyl 1-Benzyl-2-oxocyclohexanecarboxylate 2,4-Dinitrophenylhydrazone (IVb)——IIIa (1 g) and 2,4-dinitrophenylhydrazine (0.54 g) were dissolved in EtOH (50 ml). The mixture was refluxed for 8 hr and the solvent was distilled off. The residue was recrystallized from EtOH to give yellow prisms of mp 129—130°. Yield 1.1 g (74%). *Anal.* Calcd. for $C_{30}H_{38}N_4O_6$: C, 65.44; H, 6.96; N, 10.17. Found: C, 65.42; H, 6.93; N, 9.95. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3300 (–NH–), 1725 (ester C=O), 1505 (–C=N–). MS m/e: 550 (M^+).

3a-Alkyl-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-ones (Va—c)——To a solution of IIIa—c (0.02 mol) in 20 ml of EtOH, 100% hydrazine hydrate (10 g) was added and the mixture was refluxed for 3 hr. Solvent was distilled and the residue was column chromatographed on silica gel (Wako gel C-200). Chloroform eluate was collected and the solvent was distilled off by reduced pressure to give colorless prisms, which were washed with ether and recrystallized from appropriate solvents. Optical rotations were measured before recrystallization. Analytical and physical data are summarized in Table II.

(−)-(1*R*,2*S*,5*R*)-Menthyl Phenylcarbonate (VI)——(−)-Menthol (22 g) and quinoline (18 g) were dissolved in methylene chloride (50 ml). Phenylchloroformate (22 g) was added dropwise to the above solution under cooling with ice. After stirring for 1 hr at room temperature, the mixture was refluxed for 4 hr and poured into 5% HCl (50 ml). The organic layer was separated and dried over Na_2SO_4. Solvent was distilled off and the residue was rectified to give oil ($bp_{0.7}$ 134°). Yield 31 g (79%). *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.87; H, 8.84. $[\alpha]_D^{24}$ −70.3° (c=1.2, EtOH).

(−)-(1*R*,2*S*,5*R*)-Menthyl Carbazate (VII)——A mixture of VI (20 g) and 100% hydrazine hydrate (5 g) was heated at 110° for 20 min. After cooling ether (150 ml) and 20% NaOH (100 ml) were added and the mixture was extracted with ether. The extract was dried over Na_2SO_4 and ether was evaporated to dryness. The residue was recrystallized from MeOH to obtain colorless needles of mp 94—95.5°. Yield 12 g (82%), *Anal.* Calcd. for $C_{11}H_{22}N_2O_2$: C, 61.50; H, 10.35; N, 13.07. Found: C, 61.49; H, 10.62; N, 13.31. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). NMR $\delta_{ppm}^{CDCl_3}$: 3.78 (2H, broad singlet, $-NH_2$), 6.54 (1H, broad singlet, –NH–). $[\alpha]_D^{24}$ −78.4° (c=5.5, $CHCl_3$).

(−)-(1*R*,2*S*,5*R*)-Menthyl 3-Hydroxy-4,5,6,7-tetrahydro-2*H*-indazole-2-carboxylate (IX)——A mixture of ethyl 2-oxocyclohexanecarboxylate[6] (1.7 g) and VII (2 g) was heated at 120° for 3 hr. After cooling the resulting crystals were recrystallized from MeOH to obtain colorless needles of mp 203—204°. $[\alpha]_D^{24}$ −65.0° (c=1.2, EtOH). Yield 1.5 g (47%). *Anal.* Calcd. for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.24; H, 8.91; N, 9.01.

(−)-(1*R*,2*S*,5*R*)-Menthyl 1-Benzyl-3-oxo-2,3,4,5,6,7-hexahydro-1*H*-indazole-2-carboxylate (X) and (−)-(1*R*,2*S*,5*R*)-Menthyl 3a-Benzyl-3-oxo-3,3a,4,5,6,7-hexahydro-2*H*-indazole-2-carboxylate (XI)——Compound (IX) was dissolved in a solution of absolute MeOH (30 ml) containing sodium methoxide (0.42 g). Benzyl bromide (3.1 g) was added dropwise to the above solution under nitrogen gas stream. After stirring for 10 hr solvent was distilled off. The residue was made acidic with 5% HCl and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and the solvent was distilled off. The residue was column chromatographed on silica gel. From $CHCl_3$-eluate compound (XI) was separated. $[\alpha]_D^{24}$ −42.0° (c=2.4, $CHCl_3$). Colorless prisms of mp 206—208° (from MeOH). Yield 0.2 g (3%). *Anal.* Calcd. for $C_{25}H_{34}N_2O_3$: C, 73.14; H, 8.35; N, 6.82. Found: C, 73.12; H, 8.55; N, 6.74. IR ν_{max}^{KBr} cm^{-1}: 1755, 1740 (C=O), 1450 (–C=N–). NMR $\delta_{ppm}^{CDCl_3}$:

3.00, 3.24 (2H, quartet, AB type, $J=14$ Hz, $-CH_2-Ph$), 7.10 (5H, multiplet, -Ph), 4.70 (1H, triplet doublet, $J=10$ Hz, $J=4$ Hz, $-CO_2-CH-$). $[\alpha]_D^{24}$ $-45.1°$ ($c=3.4$, $CHCl_3$).

From the 2% MeOH–$CHCl_3$ eluate compound (X) was separated as an oil. IR ν_{max}^{film} cm^{-1}: 1750, 1680 (C=O). $[\alpha]_D^{24}$ $-42.3°$ ($c=1.8$, $CHCl_3$). The structure of X was confirmed by the conversion of X to the known compound, 1-benzyl-4,5,6,7-tetrahydro-1*H*-indazol-3-ol.[9]

Synthesis of XI from XII and VII——A mixture of ethyl 1-benzyl-2-oxocyclohexanecarboxylate[8] (XII) (2.6 g) and (−)-(1*R*,2*S*,5*R*)-menthylcarbazate (VII) (2.1 g) was heated on an oil-bath (120°) for 3 hr. The resulting crystals were recrystallized from MeOH to give colorless prisms of mp 207—208°. Yield. 3.5 g (85%). $[\alpha]_D^{24}$ $-43.8°$ ($c=2.6$, $CHCl_3$).

1-Benzyl-4,5,6,7-tetrahydro-1*H*-indazol-3-ol (The Reaction of X with Hydrazine Hydrate)——A mixture of 1.0 g of X, 0.5 g of hydrazine hydrate and 20 ml of EtOH was refluxed for 3 hr. Solvent was distilled off. The residue was washed with ether and recrystallized from acetone to give colorless needles of mp 178—179° (Lit.[9] 180—182°). Yield 0.45 g (80%). *Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.59; H, 7.08; N, 12.01. IR ν_{max}^{KBr} cm^{-1}: 3420 (-OH). NMR $\delta_{ppm}^{CDCl_3}$; 4.80 (2H, singlet, $-CH_2-Ph$), 7.18 (5H, singlet, -Ph), 12.20 (1H, broad, -OH). MS *m/e*: 228 (M^+).

Synthesis of Va from XI——A mixture of 1 g of XI, 0.5 g of hydrazine hydrate and 20 ml of EtOH was refluxed for 3 hr. Solvent was distilled off. The residue was column chromatographed on silica gel. Chloroform eluate was collected and the solvent was distilled off by reduced pressure to give colorless prisms, which were washed with ether, mp 191—193°. $[\alpha]_D^{22}$ 0° ($c=1.6$, EtOH). The crystals were recrystallized from acetone, mp 194—195°. Yield 0.32 g (58%). IR spectrum of this compound was identical with that of the compound obtained from IIIa and hydrazine hydrate.

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9) N. Finch and H.W. Gschwend, *Tetrahedron Lett.*, **1969**, 1661.