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Studies on Tetrahydroisoquinolines. IV.[1] Synthesis of 4-Alkyl(phenyl)amino-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines[2]

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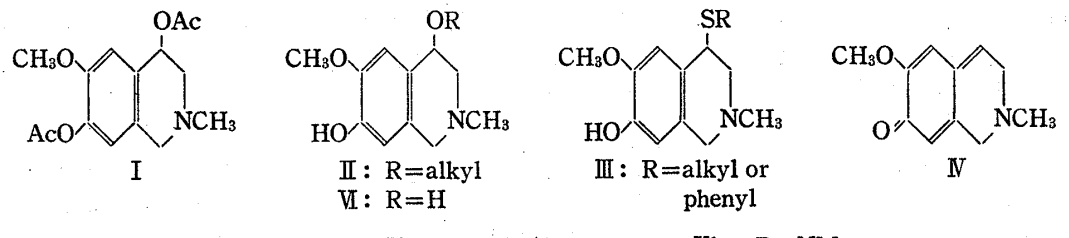
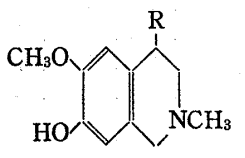
Reaction of 4,7-diacetate (I) in a variety of aqueous amine solution was found to give the corresponding 4-alkylamino derivatives (Va—e or Vg—l) in good yield. In the case of aniline, however, the presence of potassium hydroxide was always required. Similar reaction with aqueous semicarbazide or thiosemicarbazide solution containing potassium carbonate or hydroxide afforded the corresponding 4-hydrazino derivatives (Vm or Vn) in good yield.

In a preceeding paper,[1] treatment of 4,7-diacetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4,7-diacetate) (I) with alcohols or alkyl(phenyl)mercaptans in the presence of potassium hydroxide (KOH) or carbonate (K_2CO_3) at room temperature has been shown to afford smoothly the corresponding 4-alkoxy or alkyl(phenyl)mercapto derivatives [(II) or (III)] through an intermediate (*p*-quinone methide[4]) (IV), which is formed by hydrolysis of 7-acetoxy group accompanied with concerted detouch of acetic acid. Taking account of the finding that the reaction is initiated by hydrolysis of 7-acetoxy group, reaction of I with amine which is more basic than alcohol or alkyl(phenyl)mercaptan was expected to give readily the corresponding 4-alkylamino product even in the absence of KOH or K_2CO_3. Moreover, the reaction with amine appeared to be possible in an aqueous solution by considering the fact that the above reaction occurs in an aqueous methanol solution, since amine is more reactive nucleophile than alcohol. Then treatment of I with aqueous amine solution was carried out and the present result was obtained.



I II: R=alkyl VI: R=H III: R=alkyl or phenyl IV



Va : R=NH_2 Vb : R=NHMe Vc : R=NHEt Vd : R=$NHCH_2C_6H_5$ Ve : R=$NHCH_2CH_2C_6H_5$ Vf : R=NHC_6H_5 Vg : R=$NHCHMe_2$ Vh : R=NMe_2 Vi : R=NC_4H_8 Vj : R=NC_5H_{10} Vk : R=NC_4H_8O Vl : R=NC_4H_8N-Bu-*n* Vm: R=$NHNHCONH_2$ Vn : R=$NHNHCSNH_2$

Chart 1

A solution of I in 28% aqueous ammonia solution was stirred for 15 min at room temperature. Usual work-up of the residue obtained on removal of ammonia under reduced pres-

1) Part III: B. Umezawa, O. Hoshino and Y. Yamanashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2154 (1971).
2) The preliminary communication of this work appeared in, O. Hoshino, Y. Yamanashi, B. Umezawa, *Tetrahedron Letters*, **1969**, 937.
3) Location: *12, Ichigayafunagawaramachi, Shinjuku-ku, Tokyo, 162, Japan.*
4) *cf.* A.B. Turner, *Quart. Revs.*, **18**, 347 (1964).

sure led to colorless prisms of Va, mp 142—143.5°, in 55% yield. Its nuclear magnetic resonance (NMR) spectrum showed two three proton singlets at τ 7.57 (N-methyl group) and τ 6.16 (aromatic methoxy group) and a defused triplet at τ 6.09 (C-4 hydrogen).

Structure of Va was thus assumed to be 4-amino-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline by means of the NMR spectrum as well as elemental analysis and on the analogy with the result that alcoholysis[1] or hydrolysis[5] of I in the presence of KOH gives rise to the corresponding 4-alkoxy or hydroxy compound [(II) or (VI)].

On the basis of the finding, similar reaction in aqueous primary or secondary amine solution was undertaken. In the case of methyl-,[6] ethyl-,[6] benzyl-, β-phenethyl- or isopropylamine, the corresponding 4-alkylamino compounds (Vb—e, g) were obtained in 58, 82, 70, 84 or 71% yield and their structures were confirmed by inspection of the NMR spectrum and by elemental analysis. As for dimethylamine, pyrrolidine, piperidine, morpholine or N-*n*-butylpiperazine,[7] the corresponding 4-dimethylamino, pyrrolidino, piperidino, morpholino[8] or N-*n*-butylpiperazino product (Vh—l) was formed in 70, 69, 55, 55 or 79% yield. Characterization of their structures was performed by means of the NMR spectrum and elemental analysis.

Thus the finding proved that acetoxy group at 4-position in I could be readily replaced with ammonia or aliphatic primary or secondary amines. In the case of aniline, however, the similar reaction as noted above did not take place and I was recovered unchanged. This

Table I. Reaction Time, Yield, Melting Point and Elemental Analysis of V

Compd.	Solvent	Reaction time (min)	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Va	28% NH_3–H_2O	15	78	142—143.5	$C_{11}H_{16}O_2N_2$	63.44	7.74	13.45	63.48	7.79	13.23
Vb	30% $MeNH_2$	15	58	142—143 (decomp.)	$C_{12}H_{18}O_2N_2$	64.84	8.16	12.60	65.23	8.27	12.37
Vc	50% $EtNH_2$	15	82	92—93	$C_{13}H_{20}O_2N_2 \cdot \frac{1}{4}H_2O$	64.79	8.53	11.63	65.20	8.69	11.50
Vd	50% $C_6H_5CH_2NH_2$	15	70	95—96	$C_{18}H_{22}O_2N_2$	72.45	7.43	9.39	72.38	7.54	9.63
Ve	50% $C_6H_5CH_2CH_2NH_2$	15	84	145—146	$C_{19}H_{24}O_2N_2$	73.04	7.74	8.94	72.71	7.85	8.71
Vf	$C_6H_5NH_2$–H_2O	30[a]	66	166—167	$C_{17}H_{20}O_2N_2$	71.80	7.09	9.85	71.93	7.27	10.18
Vg	50% Me_2CHNH_2	15	71	141.5—142.5 (decomp.)	$C_{14}H_{22}O_2N_2$	67.17	8.86	11.19	66.96	8.91	11.33
Vh	30% Me_2NH	15	70	118—120	$C_{13}H_{20}O_2N_2$	66.07	8.53	11.86	66.01	8.58	12.12
Vi	50% pyrrolidine	15	69	111—112.5	$C_{15}H_{22}O_2N_2$	68.67	8.45	10.68	68.82	8.60	10.93
Vj	50% piperidine	15	55	134—136	$C_{16}H_{24}O_2N_2$	69.53	8.75	10.14	69.78	8.73	10.09
Vk	50% morphorine	15	55	139—140	$C_{15}H_{22}O_3N_2$	64.72	7.97	10.07	65.03	8.05	10.13
Vl	50% N-*n*-bu-piperazine	30	91	148—150	$C_{19}H_{31}O_2N_3$	68.43	9.37	12.66	68.35	9.48	12.36
Vm	$NH_2CONHNH_2 \cdot HCl$ H_2O	240[b] 420[c]	45 62	132—133.5	$C_{12}H_{18}O_3N_3 \cdot H_2O$	50.69	5.09	19.71	50.57	7.20	19.83
Vn	$NH_2CSNHNH_2$ H_2O	15[b] 120[c]	73 41	200—202	$C_{12}H_{18}O_3N_3S$	51.05	6.43	19.85	50.76	6.54	20.48

a) KOH and dioxane as co-solvent were used. *b*) KOH was used. *c*) K_2CO_3 was used.

5) B. Umezawa, O. Hoshino, Y. Terayama, K. Ohyama, Y. Yamanashi, T. Inoue and T. Toshioka, *Chem. Pharm. Bull.* (Tokyo), **19**, 2138 (1971).
6) Similar reaction of I in 30% aqueous methylamine or 70% aqueous ethylamine solution containing KOH gave Vb or Vc in 50 or 68% yield, respectively.
7) Y. Ikeda, Y. Nitta and K. Yamada, *Yakugaku Zasshi*, **89**, 669 (1969).
8) Reflux of a solution of I and morpholine in chloroform furnished Vk in 58% yield. Therefore, the reaction with amine except methyl- or ethylamine would result in the same product as in the case of aqueous solution.

meant that 7-acetoxy group could not be hydrolyzed by aniline, since its hydrolysis was the important prerequisite to the reaction. Thereupon, the reaction with aniline was carried out in the presence of KOH. A solution of I, aniline and KOH in aqueous dioxane was stirred for 30 min at room temperature. Usual work-up of the reaction mixture gave colorless prisms of Vf, mp 166—167°, in 66% yield and the structure was confirmed by means of the NMR, infrared (IR) spectrum and elemental analysis.

Thus, in the case of amine, such as aniline, whose basicity is lower than that of aliphatic amine, employment of KOH was found to be always required.

Analogous treatment of I with semicarbazide or thiosemicarbazide was performed. In this case, the presence of KOH (or K_2CO_3) would also be necessary. Actually, the reaction proceeded in the presence of K_2CO_3 giving the same product (Vm), (mp 132—133.5°) or (Vn) (mp 200—202°) as that in the presence of KOH. The result was summarized in Table I.

As expected, the reaction with amines was proved to give the corresponding 4-alkyl-(phenyl)amino derivatives (Va—n). However, the reaction with diethyl amine was unsuccessful. When compared with the result that treatment with dimethylamine or heterocyclic secondary amines gave the corresponding 4-alkylamino product, the above result pointed out that the reaction with secondary amines (except dimethylamine or heterocyclic amines) would be interfered by the steric effect of alkyl group.

In conclusion, it was found that acetoxy group at 4-position in I could be easily substituted with amines in the absence of KOH or K_2CO_3 (except in the case of aniline, semicarbazide or thiosemicarbazide) and that the reaction was applicable to synthesis of 4-alkylamino-tetrahydroisoquinolines. Moreover, existence of *p*-quinone methide (IV) as an intermediate was further supported by the result that KOH was required in the case of aniline. Therefore, the same reaction pathway[1] as noted in the case of alcohols or alkyl(phenyl) mercaptans would be inferable.

Experimental[9]

General Procedure for Reaction of I with Amines——A solution of I in aqueous amine was stirred at room temperature. In the case of ammonia, methyl-, ethyl-, iso-propyl- or dimethylamine, excess of amine was removed under reduced pressure and the product was taken up in $CHCl_3$. In the case of benzyl- or *β*-phenethylamine, pyrrolidine, morpholine or piperidine, KOH and H_2O were added to the reaction mixture and excess of amine was washed with ether. The aqueous solution was acidified with 10% HCl and made basic with K_2CO_3 (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over K_2CO_3. Removal of the solvent gave an oil or a crystalline mass.

1) Ammonia: I (200 mg) and 28% NH_3 (4 ml) were used. A crystalline mass (Va), mp 130—137°, (78 mg, 55%) was obtained. Recrystallization gave colorless prisms of Va, mp 142—143.5°. NMR τ: 7.53 (3H, s, NCH_3), 6.16 (3H, s, OCH_3), 6.72, 6.40 (2H, AB q, J=15 Hz, C-1 H_2), 6.09 (1H, d t, C-4 H), 3.47, 3.13 (each 1H, s, C-8 and C-5 H).

2) Methylamine: I (200 mg) and 30% $MeNH_2$ (4 ml) were used. Treatment of an oil (124 mg) with *n*-hexane afforded a solid (Vb), mp 137—142°, (88 mg, 58%), which was recrystallized to colorless prisms of Vb, mp 142—143°. NMR τ: 7.57, 7.51 (each 3H, s, NCH_3 and $NHCH_3$), 6.80, 6.37 (2H, AB q, J=15 Hz, C-1 H_2), 6.46 (1H, d t, C-4 H), 6.21 (3H, s, OCH_3), 3.51, 3.18 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 3450, 3300, 3050 (OH, NH), 1620, 1595 (C=C).

3) Ethylamine: I (200 mg) and 50% $EtNH_2$ (4 ml) were used. Treatment of an oil (155 mg) with *n*-hexane gave a solid (Vc), mp 86—91°, (125 mg, 82%), which was recrystallized to colorless prisms of Vc, mp 92—93°. NMR τ: 8.84 (3H, t, J=7.5 Hz, $NHCH_2\underline{CH_3}$), 7.57 (3H, s, NCH_3), 6.78, 6.35 (2H, AB q, J

9) All melting points were determined on a Yanagimoto micro melting point measuring apparatus and uncorrected. NMR spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in $CDCl_3$ solution (5—10%) by using Me_4Si as internal standard, unless otherwise noted. Following abbreviations were used: s, singlet; b s, broad singlet; d, doublet; t, triplet; d t, defused triplet; AB q, AB quartet; m, multiplet. IR spectra were run on a Hitachi infrared spectrometer Model EPI-S_2. Recrystallization was carried out from *n*-hexane, unless otherwise stated.

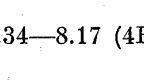
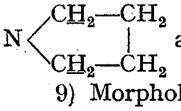
=15 Hz, C-1 H_2), 6.31 (1H, t, J=2.5 Hz, C-4 H), 6.20 (3H, s, OCH_3), 3.50, 3.18 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 3350, 3250, 3050 (OH, NH), 1625, 1595 (C=C).

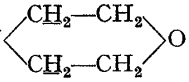
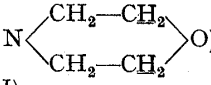
4) Benzylamine: I (200 mg) and 50% $C_6H_5CH_2NH_2$ (4 ml) were used. Treatment of an oil (200 mg) with *n*-hexane afforded a solid (Vd), mp 90—93°, (140 mg, 70%), which was recrystallized to colorless prisms of Vd, mp 95—96°. NMR τ: 7.57 (3H, s, NCH_3), 7.46, 7.10 (2H, octet, J=12.5 Hz, J=3.8 Hz, C-3 H_2), 6.76, 6.36 (2H, AB q, J=15 Hz, C-1 H_2), 6.29 (1H, d t, C-4 H), 6.18 (3H, s, OCH_3), 6.08 (2H, b s, $OC\underline{H}_2C_6H_5$), 3.47, 3.21 (each 1H, s, C-8 and C-5 H), 2.70—2.55 (5H, m, $OCH_2C_6\underline{H}_5$).

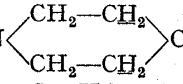
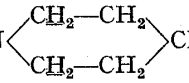
5) β-Phenethylamine: I (200 mg) and 50% $C_6H_5CH_2CH_2NH_2$ (4 ml) were used. Treatment of an oil (220 mg) with *n*-hexane furnished a solid (Ve), mp 145—147.5°, (178 mg, 84%), whose recrystallization afforded colorless prisms of Ve, mp 145—146°. NMR τ: 7.60 (3H, s, NCH_3), 7.20—6.90 (4H, m, $NHC\underline{H}_2C\underline{H}_2C_6H_5$), 6.77, 6.40 (2H, AB q, J=15 Hz, C-1 H_2), 6.29 (1H, d t, C-4 H), 6.23 (3H, s, OCH_3), 3.47, 3.26 (each 1H, s, C-8 and C-5 H), 2.83 (5H, s, $NHCH_2CH_2C_6\underline{H}_5$).

6) iso-Propylamine: I (200 mg) and 50% iso-$PrNH_2$ (4 ml) were used. Treatment of an oil (210 mg) with *n*-hexane yielded a solid (Vg), mp 141—143° (decomp.), (111 mg, 71%), which was recrystallized to colorless plate of Vg, mp 141.5—142.5° (decomp.). NMR τ: 8.88 [6H, d, J=6.3 Hz, $NHCH(C\underline{H}_3)_2$], 7.59 (3H, s, NCH_3), 6.80, 6.37 (2H, AB q, J=15 Hz, C-1 H_2), 6.27 (1H, d t, C-4 H), 6.22 (3H, s, OCH_3), 3.52, 3.19 (each 1H, s, C-8 and C-5 H).

7) Dimethylamine: I (200 mg) and 30% Me_2NH (4 ml) were used. Treatment of an oil (193 mg) with *n*-hexane furnished a solid (Vh), mp 116—118°, (112 mg, 70%), which was recrystallized from C_6H_6 to colorless prisms of Vh, mp 118—120°. NMR τ: 7.66 [6H, s, $N(CH_3)_2$], 7.60 (3H, s, NCH_3), 6.61 (2H, b s, C-1 H_2), 6.17 (3H, s, OCH_3), 6.06 (1H, d t, C-4 H), 3.50, 2.93 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 3400, 3100 (OH), 1620, 1595 (C=C).

8) Pyrrolidine: I (200 mg) and 50% pyrrolidine (4 ml) were used. Treatment of an oil (193 mg) with *n*-hexane gave a solid (Vi), mp 85—100°, (123 mg, 69%). Recrystallization yielded colorless prisms of Vi, mp 111—112.5°. NMR τ: 8.34—8.17 (4H, m, ), 7.60 (3H, s, NCH_3), 7.40—7.20 (6H, m,  and C-3 H_2), 6.09 (1H, t, J=5 Hz, C-4 H), 3.50, 3.02 (each 1H, s, C-8 and C-5 H).

9) Morpholine: I (200 mg) and 50% morpholine (4 ml) were used. Treatment of an oil (250 mg) with *n*-hexane afforded a solid (Vj), mp 139—140°, (104 mg, 55%), which was recrystallized to colorless prisms of Vj, mp 139—140°. NMR τ: 7.61 (3H, s, NCH_3), 7.45—7.25 (6H, m,  O and C-3 H_2), 6.61 (2H, b s, C-1 H_2), 6.35—6.22 (4H, m,  O), 6.15 (3H, s, OCH_3), 6.07 (1H, t, J=5 Hz, C-4 H), 3.49, 2.87 (each 1H, s, C-8 and C-5 H).

10) Piperidine: I (200 mg) and 50% piperidine (4 ml) were used. A solid (Vj), mp 127—131°, (104 mg, 55%) was obtained. Recrystallization furnished colorless prisms of Vj, mp 134—136°. NMR τ: 8.51 (6H, b s, ), 7.61 (3H, s, NCH_3), 7.45 (4H, b s, ), 6.75, 6.50 (2H, AB q, J=15 Hz, C-1 H_2), 6.14 (3H, s, OCH_3), 6.10—5.98 (1H, m, C-4 H), 3.48, 2.82 (each 1H, s, C-8 and C-5 H).

Reaction with N-*n*-Butylpiperazine——A solution of I (100 mg) in 50% N-*n*-butylpiperazine (prepared according to the method[6] of K. Ikeda, Y. Nitta and K. Yamada) (4 ml) was stirred for 30 min at room temperature. As the reaction proceeded, a crystalline mass was precipitated. The precipitate was collected, washed with H_2O and dried. A solid (86 mg), mp 145—148°, was obtained. The filtrate was basified with KOH (100 mg) and excess of N-*n*-butylpiperazine was washed with ether. The aqueous solution was acidified with 20% HCl and the acidic solution was basified with K_2CO_3 (powder). The product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave an oil (30 mg), whose treatment with *n*-hexane yielded a solid (17 mg), mp 144—147°. Total weight of Ve was 103 mg (91%). Recrystallization from MeOH–H_2O gave colorless prisms of Ve, mp 149—150°. NMR τ: 9.10 (3H, t, J=7.5 Hz, $NCH_2CH_2CH_2C\underline{H}_3$), 7.62 (3H, s, NCH_3), 6.75, 6.55 (2H, AB q, J=15 Hz, C-1 H_2), 6.25 (3H, s, OCH_3), 6.08 (1H, t, J=7.5 Hz, C-4 H), 3.52, 2.88 (each 1H, s, C-8 and C-5 H).

Reaction with Aniline——A solution of I (200 mg) in a mixture of aniline (1 ml), H_2O (1 ml), dioxane (2 ml) and KOH (150 mg) was stirred for 30 min at room temperature. To a residue obtained on removal of the solvent under reduced pressure, H_2O was added and excess of aniline was washed with C_6H_6. The aqueous solution was acidified with 10% HCl and the acidic solution was basified with K_2CO_3 (powder). The product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave a solid (Vf), mp 150—163°, (106 mg, 66%), which was recrystallized from EtOH–H_2O to colorless prisms of Vf, mp 166—167°. NMR τ (DMSO-d_6): 7.68 (3H, s, NCH_3), 6.31 (3H, s, OCH_3), 3.48, 3.13 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH, NH), 1620, 1600 (C=C).

Reaction with Semicarbazide——1) To a solution of $NH_2CONHNH_2 \cdot HCl$ (115 mg) and KOH (120 mg) in H_2O (4 ml), I (100 mg) was added and the whole was stirred for 240 min at room temperature. A crystalline mass was precipitated. To the reaction mixture, NH_4Cl was added. The precipitate was collected, washed with H_2O and dried. Vm, mp 125—127°, (44 mg, 45%), was obtained. Recrystallization from MeOH–H_2O furnished colorless prisms of Vm, mp 132—133.5°. NMR τ (D_2O–NaOD)[10]: 7.66 (3H, s, NCH_3), 6.82, 6.42 (2H, AB q, J=15 Hz, C-1 H_2), 6.22 (3H, s, OCH_3), 6.17 (1H, d t, C-4 H), 3.61, 3.15 (each 1H, s, C-8 and C-5 H).

2) To a solution of $NH_2CONHNH_2 \cdot HCl$ (2 g) and K_2CO_3 (1.7 g) in H_2O (4 ml), I (200 mg) was added and the whole was stirred for 420 min. A crystalline substance was precipitated. The precipitate was collected, washed with H_2O and dried. Vm, mp 124—126°, (113 mg, 62%), was obtained. Recrystallization from MeOH–H_2O afforded colorless prisms of Vm, mp 132—133.5°. This was identical with a product obtained above in all respects.

Reaction with Thiosemicarbazide——1) To a solution of $NH_2CSNHNH_2$ (127 mg) and KOH (75 mg) in H_2O (4 ml), I (100 mg) was added and the whole was stirred for 15 min at room temperature. The same treatment as noted in the case of $NH_2CONHNH_2 \cdot HCl$ and KOH gave a solid (Vn), mp 195—198°, (70 mg, 73%), which was recrystallized from MeOH to colorless prisms of Vn, mp 200—202°. NMR τ (D_2O–NaOD)[10]: 7.65 (3H, s, NCH_3), 6.74, 6.53 (2H, AB q, J=15 Hz, C-1 H_2), 6.23 (3H, s, OCH_3), 5.90 (1H, d t, C-4 H), 3.66, 3.03 (each 1H, s, C-8 and C-5 H),

2) To a solution of $NH_2CSNHNH_2$ (124 mg) and K_2CO_3 (400 mg) in H_2O (4 ml), I (200 mg) was added and the whole was stirred for 120 min at room temperature. A solid was precipitated. The precipitate was collected, washed with H_2O and dried. Vn, mp 188—190°, (80 mg, 41%) was obtained. Recrystallization from MeOH furnished colorless prisms of Vn, mp 200—202°. This was identical with a product obtained above in all respects.

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10) DSS was used as internal standard.