[Chem. Pharm. Bull. 33(7)2705—2711(1985)]

Studies on Tetrahydroisoquinolines. XXIV.[1] A Synthesis of Dibenzo[*c,f*]-1-azabicyclo[3.3.1]nonanes and Dibenzo[*d,g*]-1-azabicyclo[4.3.1]decanes[2]

HIROSHI HARA, OSAMU HOSHINO, and BUNSUKE UMEZAWA*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, 12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

(Received October 2, 1984)

Treatment of the *N*-benzyl *p*-quinol acetates **2a** and **2b** with trifluoroacetic acid gave dibenzo[*c,f*]-1-azabicyclo[3.3.1]nonanes (**3a** and **3b**) in good yields. The homologs **3c**, **3d**, and **3e** were similarly prepared from the *N*-phenethyl *p*-quinol acetates **2c**, **2d**, and **2e**, respectively. On the other hand, the *o*-quinol acetate (**17**), obtained from the tetrahydroisoquinolin-6-ol (**9**) by lead tetraacetate oxidation, was rearranged to the 4-acetoxy derivative (**18**). Acid treatment of **18** induced cyclization to construct the same skeleton as that of **3a**.

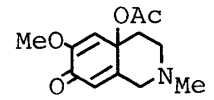
Keywords——lead tetraacetate oxidation; *p*-quinol acetate; *o*-quinol acetate; trifluoroacetic acid; dibenzo[*c,f*]-1-azabicyclo[3.3.1]nonane; dibenzo[*d,g*]-1-azabicyclo[4.3.1]decane; cyclization

Up to the present, nucleophilic substitution of the so-called *p*-quinol acetates (**1**) at the 8-, 4-, or 4a-position has been reported.[3] As a part of our program of studies on the nucleophilic reactions of **1**, we investigated the acid treatment of *N*-benzyl (**2a**, **b**) and *N*-phenethyl (**2c**—**e**) *p*-quinol acetates. In general, ease of ring formation among 6- to 8-membered rings is considered to decrease with increase of ring size, *i.e.* preference in the formation of 6-, 7-, and 8-membered rings would be in the order of $6>7>8$. Therefore, the title bicyclic heterocycles (**3**) were anticipated to be obtainable from *N*-benzyl (**2a**, **b**) and *N*-phenethyl (**2c**—**e**) *p*-quinol acetates. In other words, nucleophilic attack would occur mostly at the 4-position rather than at the 4a- or 8-position because of the intervention of the *p*-quinione methides (**4**).

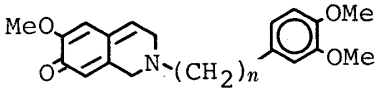
The starting phenols (**5a**, **b**) were prepared by the known method[4] as follows. Namely, Schiff bases (**6a**, **b**) prepared from aryl aldehydes (**7a**, **b**) and phenethylamine (**8**) were subjected to a sequence of reactions ($NaBH_4$ reduction, Pictet–Spengler reaction, and debenzylation), giving **5a** and **5b**. Through the same route, the 6-hydroxy congener (**9**) was prepared from **7a** and **10**. On the other hand, the tetrahydroisoquinoline (**11**) was converted to phenylacetamides (**12**), which were reduced with $LiAlH_4$ followed by debenzylation to give the N-phenethyl derivatives (**5c**—**e**).

The *p*-quinol acetate (**2a**) (see Table I), which was obtained quantitatively by $Pb(OAc)_4$ oxidation of **5a**, was treated with trifluoroacetic acid (TFA) in CH_2Cl_2[3] to give **3a**, as expected, in 38% yield. In spite of numerous attempts under a variety of conditions (Lewis acids, solvents, and/or various reaction temperatures), no heterocycles incorporating a 7-membered ring were detected.

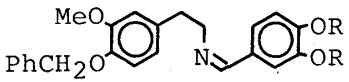
The structure of **3a** was supported by both infrared (IR) and nuclear magnetic resonance (NMR) spectral data [IR: 3530 cm^{-1} and NMR (δ): 6.39, 6.41, 6.56, 6.58 (each 1H, s)] and conversion of **3a** to the known tetramethly ether (**13a**).[5] Since we have already prepared isopavine (**14**) by acid treatment of the 4-acetoxy derivative (**15**), which was readily obtainable from the 6-phenolic tetrahydroisoquinoline (**16**),[6] we applied the same methodology to obtain an authentic sample of **13a**. Thus, the *o*-quinol acetate (**17**)[1] obtained from **9**



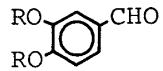
1



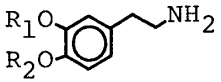
4



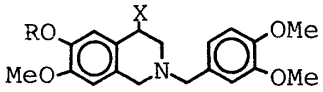
6a : R=Me
6b : R+R=CH_2



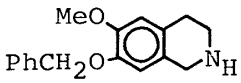
7a : R=Me
7b : R+R=CH_2



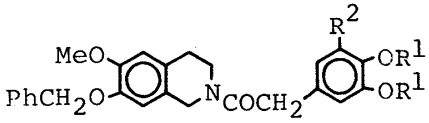
8 : R_1=Me, R_2=CH_2Ph
10 : R_1=CH_2Ph, R_2=Me



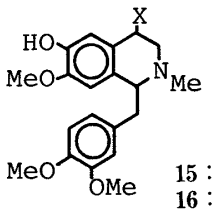
9 : R=X=H
18 : R=H, X=OAc
27 : R=CH_2Ph, X=H



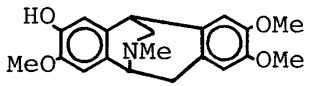
11



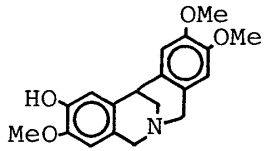
12c : R^1=Me, R^2=H
12d : R^1+R^1=CH_2, R^2=H
12e : R^1=Me, R^2=OMe



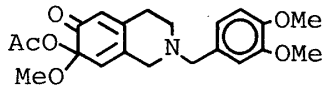
15 : X=OAc
16 : X=H



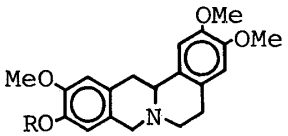
14



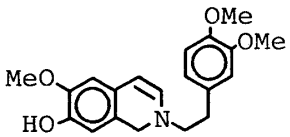
19



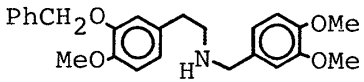
17



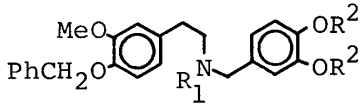
20 : R=H
22 : R=Me



21



26



23a : R^1=H, R^2=Me
23b : R^1=H, R^2+R^2=CH_2
25a : R^1=R^2=Me
25b : R^1=Me, R^2+R^2=CH_2

Fig. 1

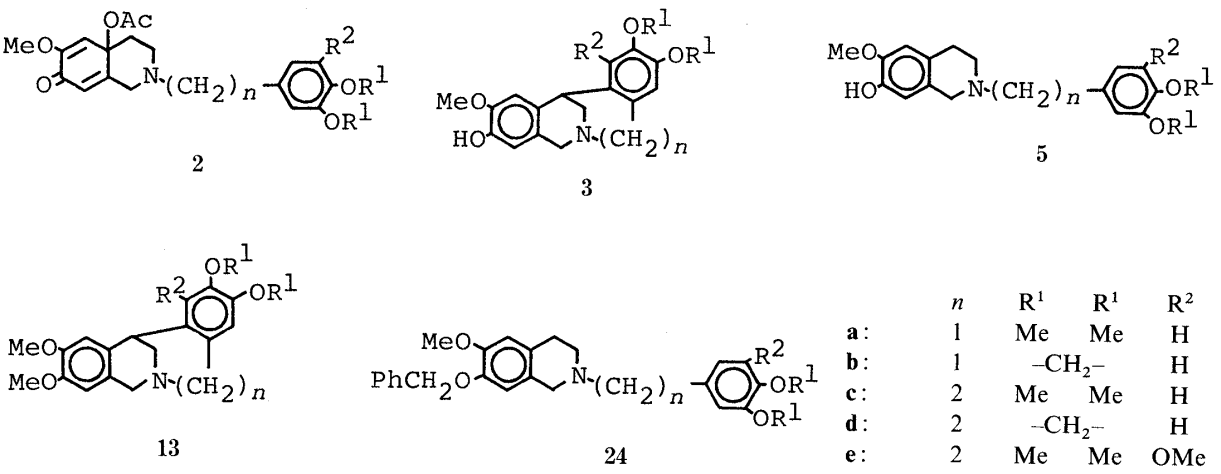


Fig. 2

TABLE I. IR and NMR Spectral Data for the Quinol Acetates

Compound	IR (cm^{-1})				NMR (δ)			
	OAc	Dienone			OAc	OMe	OCH_2O	Olefinic H
2a	1735	1670	1650	1625	2.03	3.86 (9H)	—	5.81, 6.06
2b	1745	1680	1655	1630	2.02	3.60	5.82	5.75, 6.01
2c	1740	1675	1645	1625	2.05	3.65, 3.80 (6H)	—	5.80, 6.13
2d	1750	1685	1660	1635	2.00	3.60	5.78	5.73, 6.05
2e	1750	1680	1660	1635	2.02	3.60, 3.73, 3.76 (6H)	—	5.75, 6.05
17	1740	1685			2.03	3.36, 3.77 (6H)	—	5.73, 5.79

quantitatively gave the 4-acetoxy derivative (**18**),[1] treatment of which with TFA gave the cyclized product (**19**) in 80% yield. The methyl ether of **19** was identical with **13a**. Similarly, **3b** was prepared from **5b** *via* **2b** in 50% yield. The methyl ether of **3b**, *i.e.* **13b** was shown to be identical with an authentic sample[7] by mixed melting point determination.

By a simple analogy, the *N*-phenethyl *p*-quinol acetate (**2c**) was expected to be cyclized at the 4-position, giving a dibenzo[*d*, *g*]-1-azabicyclo[4.3.1]decane (**3c**) which incorporated a 7-membered ring. However, another possible mode of cyclization leading to the 10-hydroxytetrahydroprotoberberine (**20**) seemed to intervene *via* the intermediacy of the 1,2-dihydroisoquinoline (**21**). Eventually, treatment of **2c** with TFA in CH_2Cl_2 gave the dibenzoazabicyclodecane (**3c**) in 48% yield; this product was different (mp, NMR, and thin-layer chlomatography (TLC) behavior) from an authentic sample of **20**,[8] confirming that no formation of the latter has occurred. Accordingly, the structure of **3c** was unequivocally determined as 3-hydroxy-2,10,11-trimethoxydibenzo[*d*, *g*]-1-azabicyclo[4.3.1]decane. In addition, the methyl ether of **3c**, *i.e.* **13c** [mp 152—153 °C (lit.[9] 154—155 °C)] was not identical with **22**.[10] Thus, it was realized that the *p*-quinone methide (**4**) was reactive enough to be attacked preferentially and the isomerization of **4** to **21** was a time-consuming process, at least under the reaction conditions employed.

Similarly, *p*-quinol acetates (**2d**, **e**) gave dibenzoazabicyclodecanes (**3d**, **e**) in 43% and 49% yields, respectively. Their methyl ethers (**13d**, **e**) were also prepared readily.

Thus, we have developed a new route to dibenzo[*c*,*f*]-1-azabicyclo[3.3.1]nonanes and -[*d*, *g*]-1-azabicyclo[4.3.1]decanes by use of the so-called *p*-quinol acetates.

TABLE II. Microanalytical or High-Resolution Mass Spectral Data for New Compounds

Compound	Formula	Molecular weight	Analysis (%) Calcd (Found)		
			C	H	N
3a	$C_{19}H_{21}NO_4$	327.37	69.70	6.47	4.28
			(69.53	6.45	4.42)
3b	$C_{18}H_{17}NO_4 \cdot 1/4\,H_2O$	315.824	68.44	5.58	4.44
			(68.54	5.58	4.33)
3c	$C_{20}H_{23}NO_4$	341.39	70.36	6.79	4.10
			(70.27	6.86	4.29)
3d	$C_{19}H_{19}NO_4 \cdot 1/3\,C_6H_6$	377.422	73.18	6.14	3.71
			(73.24	6.44	3.86)
3e	$C_{21}H_{25}NO_5$	371.422	67.90	6.78	3.77
			(67.93	6.84	3.89)
5a	$C_{19}H_{23}NO_4$	329.38	69.28	7.04	4.25
			(68.91	7.05	4.39)
5b	$C_{18}H_{19}NO_4$	313.34	68.99	6.11	4.47
			(69.02	6.11	4.27)
5c	$C_{20}H_{25}NO_4$	343.41	69.95	7.33	4.08
			(69.96	7.28	3.95)
5d	$C_{19}H_{21}NO_4 \cdot 1/6\,C_6H_6$	340.388	70.56	6.51	4.12
			(70.42	6.53	4.07)
5e	$C_{21}H_{27}NO_5$	373.43	67.54	7.29	3.75
			(67.73	7.28	3.74)
6a	$C_{25}H_{27}NO_4$	405.47	74.05	6.71	3.45
			(74.12	6.74	3.60)
6b	$C_{24}H_{23}NO_4$	389.43	74.02	5.95	3.60
			(74.03	5.93	3.44)
9	$C_{19}H_{23}NO_4$	329.38	69.28	7.04	4.25
			(69.09	7.19	4.30)
13c	$C_{21}H_{25}NO_4$	355.1781	(355.1780[a])		
13d	$C_{20}H_{21}NO_4$	339.1468	(339.1464[a])		
13e	$C_{22}H_{27}NO_5$	385.1888	(385.1893[a])		
19[b]	$C_{19}H_{22}ClNO_4$	363.835	62.72	6.10	3.85
			(62.34	5.98	3.83)
23a	$C_{25}H_{29}NO_4$	407.49	73.68	7.17	3.44
			(73.63	7.17	3.57)
24a	$C_{26}H_{29}NO_4$	419.50	74.44	6.97	3.34
			(74.41	6.98	3.50)
24b	$C_{25}H_{25}NO_4$	403.46	74.42	6.25	3.47
			(74.22	6.24	3.22)
24c	$C_{27}H_{31}NO_4$	433.53	74.80	7.21	3.23
			(74.78	7.24	3.42)
25a	$C_{26}H_{31}NO_4$	421.52	74.08	7.41	3.32
			(74.07	7.43	3.47)
25b	$C_{25}H_{27}NO_4$	405.47	74.05	6.71	3.45
			(73.84	6.68	3.12)
27	$C_{26}H_{29}NO_4$	419.50	74.44	6.97	3.34
			(74.22	6.99	3.45)

a) High-resolution mass spectral data. *b*) Hydrochloride.

Experimental

All melting points were measured on a Büchi melting point apparatus, and are uncorrected. NMR spectra were taken with a JEOL model JNM-FX100 (100 MHz) or a Hitachi model R-24 (60 MHz) instrument in $CDCl_3$ solution

Table III. NMR Spectral Data for the Dibenzoazabicyclo Derivatives and Tetrahydroprotoberberines

Compound	Chemical shift (δ)		
	OMe	OCH_2O	ArH
3a	3.73, 3.81 (6H)	—	6.39, 6.41, 6.56, 6.58
3b	3.82	5.73 (m[a])	6.33, 6.41, 6.54, 6.58
3c	3.73, 3.80, 3.93	—	6.38, 6.46, 6.56, 6.78
3d[b]	3.75	5.88	6.38, 6.42, 6.56, 6.75
3e	3.72, 3.79, 3.89, 3.96	—	6.27, 6.42, 6.53
13a	3.76 (6H), 3.85 (6H)	—	6.44 (2H), 6.66 (2H)
13b	3.78, 3.86	5.81 (m[a])	6.40, 6.44, 6.63, 6.66
13c	3.73, 3.80, 3.84, 3.93	—	6.40, 6.45, 6.50, 6.78
13d	3.75, 3.84	5.88	6.41, 6.42, 6.49, 6.76
13e	3.72, 3.78, 3.84, 3.88, 3.96	—	6.26, 6.44, 6.48
14	3.77, 3.79, 3.86	—	6.43 (2H), 6.64, 6.74
20	3.77, 3.83, 3.86	—	6.54, 6.60 (2H), 6.73
22	3.86, 3.87, 3.88, 3.89	—	6.56, 6.58, 6.63, 6.70

a) Multiplet. *b*) The signal due to protons (2H) of benzene incorporated into the crystals appeared at δ 7.32.

Table IV. NMR Spectral Data for Other New Compounds

Compound	Chemical shift (δ)				
	OMe	OCH_2O	NCH_2Ar	OCH_2Ph	Others
5a	3.78, 3.82 (6H)	—	3.47, 3.57	—	
5b	3.77	5.75	3.45, 3.52	—	
5c	3.84, 3.86, 3.88	—	3.60	—	
5d	3.84	5.90	3.59	—	7.32 (1H)[a]
5e	3.82, 3.85 (9H)	—	3.60	—	
6a	3.74, 3.84, 3.89	—	—	5.04	7.94 (CH=N)
6b	3.74	5.86	—	5.01	7.82 (CH=N)
9	3.71, 3.80 (6H)	—	3.45, 3.53	—	
23a	3.83 (9H)	—	3.63	5.03	
23b	3.78	5.77	3.61	5.00	
24a	3.78, 3.82 (6H)	—	3.43, 3.52	4.98	
24b	3.79	5.83	3.42, 3.50	4.99	
25a	3.78 (9H)	—	3.47	5.00	2.25 (NMe)
25b	3.80	5.82	3.39	5.03	2.22 (NMe)
26	3.75 (9H)	—	3.60	4.98	
27	3.70, 3.77 (6H)	—	3.43, 3.50	4.95	

a) The signal of protons (2H) of benzene incorporated into the crystals.

with Me_4Si as an internal standard. IR spectra were run on a Hitachi model 215 spectrometer in $CHCl_3$ solution. Preparative TLC was performed on Silica gel HF_{254} (Merck). Microanalytical data for all new, crystalline compounds are listed in Table II. EtOH denotes 99% aq. EtOH.

1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-dimethoxybenzyl)- (5a), 1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-methylenedioxybenzyl)- (5b), and 1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-2-(3,4-dimethoxybenzyl)isoquinoline (9): Typical Procedure——A stirred solution of **8** (6.7 g) and **7b** (3.91 g) in benzene (200 ml) was refluxed for 2.5 h. Evaporation of the solvent under reduced pressure gave the Schiff base **6b** (7.4 g; 70%), mp 80—82 °C (EtOH). $NaBH_4$ (1.31 g) was added portionwise to a solution of **6b** (7 g) in MeOH (100 ml) and the whole was stirred for 30 min at room temperature. Usual work-up of the reaction mixture gave oily **23b** (7.05 g; 100%). A mixture of **23b** (7 g), 87% formic acid (10 ml), and 37% formalin (10 ml) was heated on a boiling water bath for 3 h.

After condensation followed by basification (sat. aq. $NaHCO_3$ solution) of the reaction mixture, the product was extracted with CH_2Cl_2. Usual work-up of the extract and subsequent chromatographic purification on silica gel gave the 1,2,3,4-tetrahydroisoquinoline (**24b**) (4.29 g; 59%), mp 99—100 °C (EtOH) and the *N*-methylamine (**25b**) (2.26 g; 31%), mp 80.5—81.5 °C (iso-PrOH). A solution of **24b** (2 g) in a mixture of EtOH (20 ml) and conc. HCl (20 ml) was refluxed for 3 h. The reaction mixture was diluted with water and the whole was washed with ether. After basification of the aqueous layer with sat. aq. $NaHCO_3$ solution, the product was extracted with $CHCl_3$. Usual work-up of the extract gave the phenolic base (**5b**) (1.5 g; 96%), mp 166—167 °C (MeOH). **6a**: 80.5%, mp 103—104 °C (iso-PrOH). **23a**: 85.9%, mp 52—54 °C (ether). **26**: 98%, oil. **25a**: 10.6%, mp 58—60 °C (ether). **24a**: 66.5%, mp 106—107 °C (EtOH). **5a**: 50.8%, mp 169—171 °C (EtOH).

The Pictet–Spengler reaction of **26** gave none of the *N*-methylamine. Thus, treatment of **26** (140 mg) with 37% formalin (0.5 ml) in MeOH (5 ml) for 30 min at room temperature and subsequent treatment with conc. HCl (0.5 ml) for 2 h at room temperature gave exclusively the 1,2,3,4-tetrahydroisoquinoline (**27**) (141 mg; 98%), mp 108.5—109.5 °C (EtOH). **9**: 100%, mp 149—150 °C (MeOH).

1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-dimethoxyphenethyl)- (5c), 1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-methylenedioxyphenethyl)- (5d), and 1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4,5-trimethoxyphenethyl)isoquinoline (5e): Typical Procedure——Heating of a mixture of **11**[4] and 3,4-dimethoxyphenylacetic acid (19.3 g) at 160 °C (bath temperature) for 4 h gave the amide (**12c**) (11.8 g; 96%) as a pale yellow oil. $LiAlH_4$ reduction of **12c** (200 mg) in a mixture of tetrahydrofuran (THF) and ether gave the 2-phenethyl-1,2,3,4-tetrahydroisoquinoline (**24c**) (176 mg; 91%), colorless needles, mp 102—103 °C (benzene–*n*-hexane). Hydrogenolysis of **24c** (4.7 g) with 13.7% Pd–C (1.74 g) for 2 h and usual work-up of the reaction mixture gave the phenolic 1,2,3,4-tetrahydroisoquinoline (**5c**) (3.52 g; 94.6%), colorless needles, mp 145—147 °C ($CHCl_3$). **12d**: 84.7%, oil. **12e**: 90.2%, oil. **24d**: 100%, oil. **24e**: 100%, oil. **5d**: 57.9%, colorless needles, mp 168—169 °C (benzene–*n*-hexane). **5e**: 62.1%, colorless needles, mp 157—158 °C (benzene–*n*-hexane).

3-Hydroxy-2,9,10-trimethoxy- (3a) and 3-Hydroxy-2-methoxy-9,10-methylenedioxydibenzoazabicyclononane (3b) and 3-Hydroxy-2,10,11-trimethoxy- (3c), 3-Hydroxy-2-methoxy-10,11-methylenedioxy- (3d), and (±)-3-Hydroxy-2,10,11,12-tetramethoxydibenzoazabicyclodecane (3e): Typical Procedure——A solution of **5c** (100 mg) in AcOH (1 ml) was oxidized as usual[3] to give the *p*-quinol acetate (116.6 mg), which was treated with CF_3CO_2H (1 ml) in CH_2Cl_2 (10 ml) for 1 h at room temperature to give **3c** (47.8 mg; 48%), mp 211—212 °C (dec.) (benzene–*n*-hexane). Non-identity of **3c** with 10-hydroxy-2,3,11-trimethoxytetrahydroprotoberberine (**20**), mp 201—204 °C[10] (acetone) was confirmed by comparison of their IR and NMR spectrum. **3a**: 24.9%, mp 213—215 °C (EtOH). **3b**: 50%, mp 203.5—205.5 °C (dec.) (EtOH), **3d**: 43%, mp 198—199 °C (benzene–*n*-hexane). **3e**: 49%, mp 222—225 °C (dec.) (benzene–*n*-hexane).

2-Hydroxy-3,9,10-trimethoxydibenzoazabicyclononane (19)——A solution of **9** (50 mg) in CH_2Cl_2 (10 ml) was oxidized as usual[1] to give the *o*-quinol acetate (**17**); on standing at room temperature for 15 h, this product gave the 4-acetoxy compound (**18**). Treatment of **18** with CF_3CO_2H as above followed by purification by preparative TLC ($CHCl_3$: MeOH = 10 : 1) gave an amorphous mass of **19** (40 mg; 80%). Hydrochloride: mp 238—240 °C (MeOH).

2,3,9,10-Tetramethoxy- (13a) and 2,3-Dimethoxy-9,10-methylenedioxydibenzoazabicyclononane (13b) and 2,3,10,11-Tetramethoxy- (13c), 2,3-Dimethoxy-10,11-methylenedioxy- (13d), and 2,3,10,11,12-Pentamethoxydibenzoazabicyclodecane (13e)——A solution of the starting phenolic base in MeOH was methylated with diazomethane by a conventional procedure. **13a**: 47% from **3a**, 59% from **19**; hydrochloride, mp 278—279 °C (EtOH) (lit.[5] 280—282 °C). **13b**: 47%; hydrochloride, 268—270 °C (dec.) (MeOH). **13c**: 46%, mp 152—153 °C (EtOH) (lit.[9] 154—155 °C). **13d**: 57%, mp 219—220 °C (EtOH–ether). **13e**: 62%, mp 145—146 °C (EtOH–ether).

Acknowledgement The authors gratefully acknowledge the financial support of this work by a Grant-in-Aid for Scientific Research (No. 58570890) from the Ministry of Education, Science and Culture, Japan. They are indebted to Prof. J. M. Bobbitt (University of Connecticut) and Prof. H. Takayama (Teikyo University) for providing NMR charts and an authentic sample of **13b**, and to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for providing the starting vanillin. Thanks are also due to Mr. Y. Takemasa for this technical assistance and to Miss N. Sawabe and Mrs. F. Hasegawa of this Faculty for NMR and mass spectral measurements.

References and Notes

1) Part XXIII: O. Hoshino, M. Ohtani, B. Umezawa, and Y. Iitaka, *Chem. Pharm. Bull.*, **32**, 4873 (1984).
2) A preliminary communication has appeared: H. Hara, O. Hoshino, and B. Umezawa, *Heterocycles*, **15**, 907 (1981).
3) H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **24**, 262 (1976); H. Hara, O. Hoshino, B. Umezawa, and Y. Iitaka, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2657; H. Hara, O. Hoshino, and B. Umezawa, *Nippon Kagaku Kaishi*, **1981**, 813.
4) T. Kametani and K. Ohkubo, *Chem. Pharm. Bull.*, **15**, 608 (1967).
5) J. M. Bobbitt and S. Shibuya, *J. Org. Chem.*, **35**, 1181 (1970).

6) O. Hoshino, M. Taga, and B. Umezawa, *Heterocycles*, **1**, 223 (1973).
7) H. Takayama, T. Nomoto, T. Suzuki, M. Takamoto, and T. Okamoto, *Heterocycles*, **9**, 1545 (1978).
8) H. Hara, M. Hosaka, O. Hoshino, and B. Umezawa, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1169.
9) M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron*, **25**, 1881 (1969).
10) Methylation followed by trituration with *n*-hexane gave crude crystals of **22**, mp 152—157 °C (lit.[11] 157—158 °C); this product was distinguishable from **13c** by comparison of the TLC (benzene : MeOH : ethyl acetate = 10 : 1 : 1) behavior and NMR spectra.
11) A. R. Battersby, D. J. Le Count, S. Garratt, and R. I. Thrift, *Tetrahedron*, **14**, 46 (1961).