Notes

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Chemistry of Salicylic Acid and Anthranilic Acid. I. Reduction of Methyl Salicylate, Methyl Anthranilate and Their Derivatives with Sodium Borohydride[1]

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The ester derivatives of salicylic acid and some kinds of anthranilic acid were reduced to corresponding alcohols with sodium borohydride. The reduction behavior of 4-oxo-1,3-benzodioxanes (IXa—b), 1,2-dihydro-4-oxo-3,1-benzoxazines (XIIa—c,e,k) and 4-oxo-3,1-benzoxazines (XVd—j) were also investigated. These results may be explained in terms of the contribution of the electronic structure of carbonyl group or the neighbouring participation of hydroxyl or amino group.

Keywords——methyl salicylate; methyl anthranilate; reduction of ester with sodium borohydride; 4-oxo-4H-3,1-benzoxazine; 4-oxo-1,3-benzodioxane

To reduce an ester group to an alcohol, lithium aluminum hydride is most often used, while lithium or calcium borohydride can also be used.[3,4] Sodium borohydride (SBH), which is a more convenient agent to handle especially in large-scale manufacturing, can not be used for the reduction of esters because of its weaker activity, except when an electronegative substituent, such as OH, NH_2 or halogen is at the α-position to the ester group in question, and the ester which is susceptible to the reduction with SBH is aliphatic.[5,6]

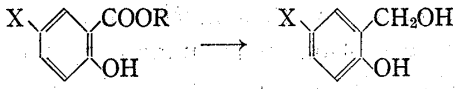
In our study of the application of salicylic acid or anthranilic acid derivatives to drug research, we investigated the reduction of the ester group in the derivatives with SBH.

I. Reduction of Methyl Salicylate and Its Derivatives with SBH

Reduction of methyl salicylate (Ia) with 0.5—3.0 mol equivalents of SBH was attempted in various solvents, and the results are summarized in Table I. In methanol, Ia resisted reduction at room temperature even when treated for 16 hr (No. 1). However Ia was reduced to salicyl alcohol in a good yield in polar aprotic solvents such as tetrahydrofuran (THF), dioxane, diglyme, dimethylsulfoxide and ethyl acetate (No. 2—6). The yields were rather poor in solvents such as dimethylformamide and sulfolane (No. 7, 8). In non polar solvents such as benzene or dichloroethane, reduction did not occur, probably because of the low solubility of SBH in them (No. 9, 10).

1) Presented at the 93 rd Annual Meeting of Pharmaceutical Society of Japan, April, 1973, Tokyo.
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) *a*) V.I. Mikkeeva and E.M. Tedneva, *Dokl. Akad. Nauk SSSR*, **101**, 99 (1955); *b*) L. Berlinguet, *Can. J. Chem.*, **33**, 1119 (1955); *c*) P.H.S. Portophese and A.A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966).
4) *a*) H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 4106 (1959); *b*) Z. Földi, *Acta Chim. Acad. Sci. Hung.*, **11**, 205 (1959) [*C.A.*, **54**, 2326 (1960)]; *c*) A. Hajos and O. Fuchs, *ibid.*, **24**, 411 (1960) [*C.A.*, **55**, 11350 (1961)]; *d*) G. Winters, G. Nathauschu and E. Testa, *Gazz. Chim. Ital.*, **94**, 1419 (1964); J. Kollenitsch, *Nature* (London), **175**, 346 (1955).
5) For example, *a*) E. Schenker, *Angew. Chem.*, **73**, 81 (1961); *b*) H. Seki, K. Koga and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 1948 (1967).
6) M.S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963). Rapoport observed that the treatment of methyl benzoate with large excess of SBH in methanol gave benzylalcohol.

TABLE I. Reduction of Salicylic Acid Esters with $NaBH_4$



Ia—g IIa—d

Exp. No.	Ester: Comp. No.	Ester: Kind (R)	Ester: Substituent (X)	Reduction condition: Solvent	Molar ratio	Time (hr)	Temp.[a]	Yield (%)
1	Ia	CH_3	H	MeOH	2.0	16	RT	8
2	Ia	CH_3	H	THF	2.0	16	RT	80
3	Ia	CH_3	H	Dioxane	2.0	16	RT	60
4	Ia	CH_3	H	Diglyme	2.0	16	RT	89
5	Ia	CH_3	H	DMSO	2.0	16	RT	75
6	Ia	CH_3	H	AcOEt	2.0	16	RT	80
7	Ia	CH_3	H	DMF	2.0	16	RT	20
8	Ia	CH_3	H	Sulfolane	2.0	16	RT	5
9	Ia	CH_3	H	Benzene	2.0	16	RT	—
10	Ia	CH_3	H	$ClCH_2CH_2Cl$	2.0	16	RT	—
11	Ia	CH_3	H	THF	0.5	16	RT	—
12	Ia	CH_3	H	THF	1.0	16	RT	58
13	Ia	CH_3	H	THF	1.0	2	BP	97
14	Ia	CH_3	H	THF	1.5	7	RT	80
15	Ia	CH_3	H	THF	2.0	7	RT	80
16	Ia	CH_3	H	THF	3.0	16	RT	88
17	Ib	CH_3	5-Cl	THF	1.0	2	BP	99
18	Ic	CH_3	5-*n*Bu	THF	1.5	8	BP	80
19	Id	CH_3	5-NO_2	DMSO	2.0	16	RT	65
20	Ie	C_2H_5	H	AcOEt	1.0	2	BP	83
21	If	$PhCH_2$	H	DMSO	2.0	16	RT	75
22	Ig	Ph	H	THF	2.0	16	RT	83

a) RT: room temperature, BP: boiling point.

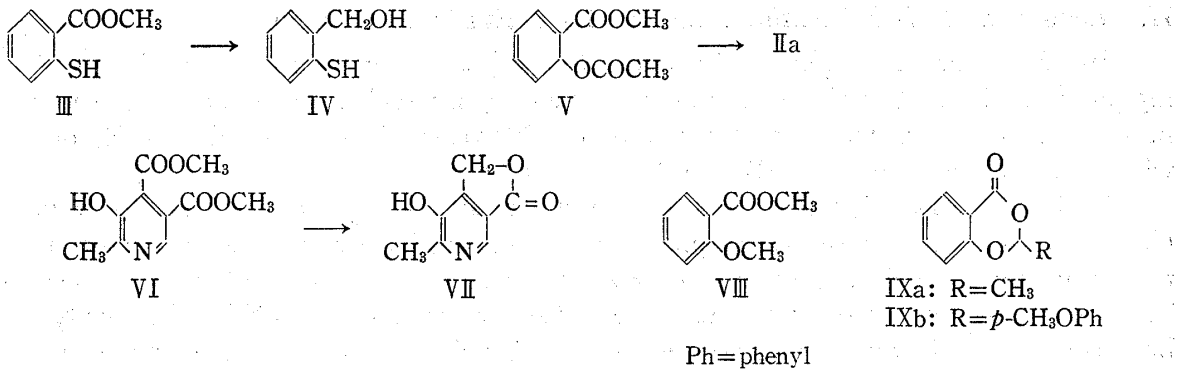


Chart 1

In regard to the molar ratio of SBH to Ia, more than a mole equivalent of SBH was required (No. 11—16), with 2 mol equivalents of SBH being practical. Methyl salicylates with a ring substituent, for example, electron withdrawing Cl or NO_2 or electron donating *n*-butyl at position 5, were similarly reduced with SBH in a suitable solvent (No. 17—19). Reducibility seems to be independent of the kind of alcoholic residue in the ester, since ethyl, benzyl and phenyl esters of salicylic acid were all reduced with SBH in comparable yields.

Methyl thiosalicylate (III), methyl acetylsalicylate(V) and 3-hydroxy-4,5-bismethoxycarbonyl-2-methylpyridine (VI) were also reduced in good yields with SBH to afford their corresponding alcohols (Chart 1). The acetoxy group of V underwent reductive elimination simultaneously. In the case of compound VI, only the ester group located *ortho* to the hy-

droxyl substituent was reduced to afford lactone (VII). Methyl derivative VIII of Ia, in which the hydroxyl substituent was masked with a methyl radical, resisted reduction.

Differing from the methyl ester, 4-oxobenzodioxanes (IXa, IXb), cyclic esters of salicylic acid, were easily reduced to afford IIa, although the ortho hydroxy group of IXa or IXb was involved in the ring.

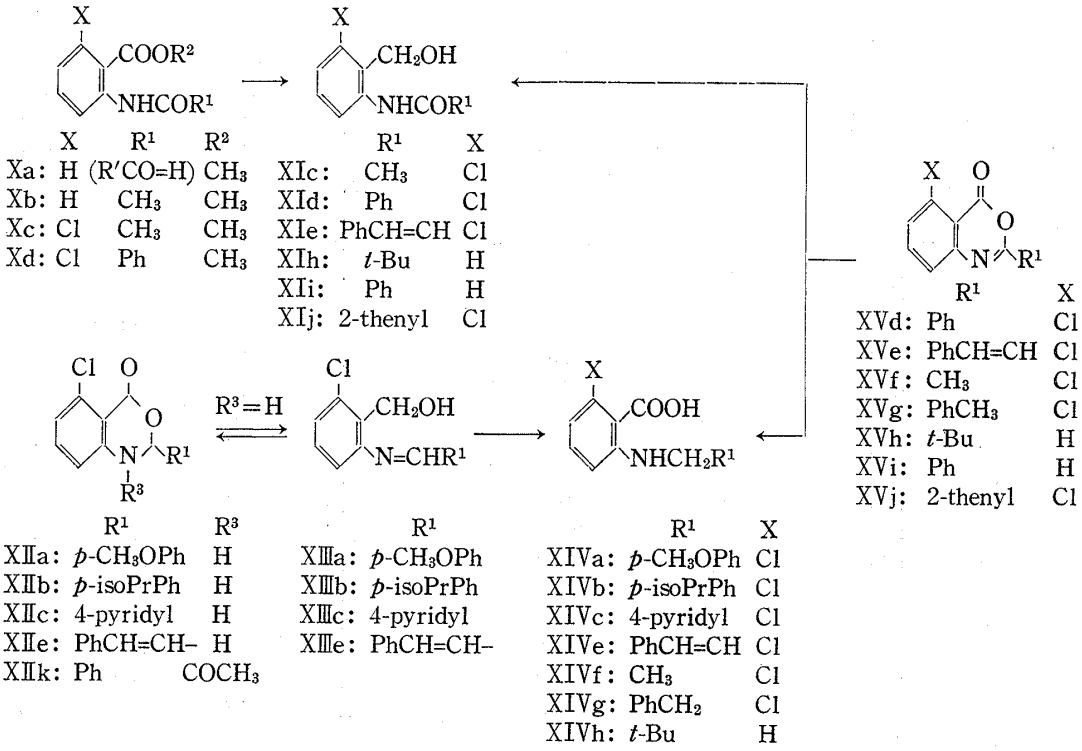


Chart 2

II. Reduction of Methyl Anthranilate and Its Derivatives with SBH

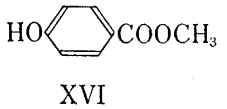
Methyl anthranilate (Xa) and its acetate (Xb) were not reduced with SBH at the boiling point of THF. But the 6-chloro derivative (Xc) and its benzoyl analog (Xd) were reduced in fairly good yields to afford 2-acylamino-6-chlorobenzyl alcohols (XIc, XId) on boiling with two mol equivalents of SBH in THF (Chart 2).

Cyclic analogs of anthranilates, 2-substituted-1,2-dihydro-4-oxo-4H-3,1-benzoxazines (XIIa—c,e) are known to exist in equilibrium with Schiff base structures (XIIIa—c,e) and the reduction may take place either at the C=O bond of XIIa—c,e or the C=N bond of XIIIa—c,e. The present experiment showed that the reduction occurred at the C=N bond not only in THF but also in alcohol, which could not be used in the reduction of salicylates or their cyclic derivatives, and afforded N-alkyl-anthranilic acid derivatives (XIVa—c,e). However, 1-acetyl-1,2-dihydro-4H-4-oxo-3,1-benzoxazine (XIIk), which can not take the Schiff base structure, was reduced at the C=O bond to afford XId. In the case of 2-substituted-4-oxo-4H-3,1-benzoxazines (XVd—j), having both C=O and C=N bonds in the same molecule, rather complex behavior was observed in the reduction with SBH. 2-Methyl- and 2-benzyl-benzoxazines (XVf, g) were reduced at the C=N bond in ethanol to afford the N-alkylanthranilic acid derivatives (XIVf,g). In THF, the reduction of XVf took place both at the C=O and C=N bonds to afford a mixture of XIVf and XIc. 2-Arylbenzoxazines (XVd,e,i,j), in which C=N bond is conjugated to the substituent at the position 2, were reduced at the C=O bond to afford 2-acyl-aminobenzyl alcohol derivatives (XId,e,i,j, respectively). 2-*t*-Butylbenzoxazine (XVh), having a sterically hindered C=N bond, was mainly reduced at the C=O bond to afford XIh along with the minor product XIVh.

Thus, 4-oxo-2-phenyl-4H-3,1-benzoxazine (XVd or XVi) was the most suitable derivative of anthranilic acid, for reduction of the carboxyl group of anthranilic acid with SBH.

Discussion

Wheeler *et al.*[7] showed that SBH exhibited stronger reducing activity in methanol than in a non-hydroxylic solvent, due to its conversion into a more powerful reducing reagent, sodium trimethoxyborohydride, in methanol. In our case, methyl salicylate (Ia) resisted reduction in methanol, but not in THF. Also, a hydroxy or mercapto group located otrho to the ester group was needed for the reduction. This ortho effect was supported by the failure of the SBH reduction of methyl *p*-hydroxybenzoate (XVI) in THF or methanol. The reduction of VI to VII may be another illustration of this effect. The mechanism of such a reduction with SBH can be pictured as involving a complex formation between the hydroxy group of Ia and SBH, and subsequent hydride transfer to the neighbouring methoxycarbonyl function (Chart 3).[8] In alcohol, the Ia-SBH complex probably is difficult to form. The ability for complex formation of methyl N-acylanthranilate (Xa) with SBH seemed to be less than that of Ia, and only in the case of methyl N-acylanthranilate which has an electronegative Cl atom at the position 6, did the reduction of the methoxycarbonyl function proceed. In 4-oxobenzodioxanes (IXa, b), the electronegativity at the oxygen atom of carbonyl seemed to be delocalized by the strong electronegative oxygen atom at the position 1, as the infrared spectrum shows ($\nu_{C=O}$: 1760 cm^{-1}), which may have facilitated the reduction with SBH.



XVI

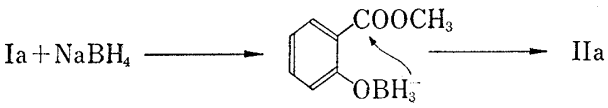


Chart 3

Among the compounds XIIa—c,e, XIIa and XIIb had the 1,2-dihydro-4-oxo-4H-3,1-benzoxazine structure at least in the solid state, as their infrared spectra showed the presence of the NH group. However, the reduction took place preferentially at the C=N bond of the equilibrium Schiff base structure rather than at the C=O bond of benzoxazine, even when an electronegative Cl atom was at the position 5.

The C=O bonds of 4-oxo-4H-3,1-benzoxazine (XVd-j), as the infrared spectra showed ($\nu_{C=O}$: 1760 cm^{-1}), seemed to be susceptible to the SBH reduction and the reaction behavior, as to whether the reduction took place at the C=O or C=N bond, depended on the electronic or steric factors of the substituents at the position 2. 2-Arylbenzoxazines (XVd,e,i,j), in which the substituents at the position 2 made the C=N bond less polarized preventing the attack of SBH, were reduced at the C=O bond almost exclusively. In the case of 2-alkylbenzoxazine (XVf,g), the reduction took place at the C=N bond and 2-*t*-butylbenzoxazine (XVh), in which the C=N bond was sterically hindered, was reduced mainly at the C=O bond and partially at the C=N bond.

Experimental

All melting points are uncorrected. IR spectra were obtained with a Hitachi 215 spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane (TMS) as an internal standard.

7) E.C. Pesterfield and D.M.S. Wheeler, *J. Org. Chem.*, 30, 1513 (1965).
8) The neighbouring effects due to hydroxyl or amino group were observed in the case of the reduction of aliphatic hydroxy or amino acid esters with SBH. See reference 5).

Materials——4-Oxo-1,3-benzodioxane derivatives (IXa, IXb) were prepared according to literature.[9] 6-Chloro-N-acyl-anthranilic acid was prepared from 2-methyl-3-chloroaniline according to Piper *et al.*,[10] and its N-acyl derivatived were obtatiined by the Schotten-Baumann method using corresponding acid chlorides or acid anhydrides. 1,2-Dihydro-4-oxo-3,1-benzoxazine (XIIa—c,e,k) and, 4-oxo-3,1-benzoxazine (XVd—j) were prepared in the similar manner to Synder *et al.*[11a] and Zentmeyer *et al.*,[11b,c] respectively. The new compounds among them were showed in Table II and III.

Table II. 1,2-Dihydro-4-oxo-3,1-benzoxazines (XIIa—c,e,k)

Comp. No.	Formula	mp (°C)	IR (cm^{-1})		Analysis (%)					
					Calcd.			Found		
			$\nu_{C=O}$	ν_{NH}	C	H	N	C	H	N
XIIa	$C_{15}H_{12}ClNO_3$	117—118	1700	3375	62.18	4.17	4.83	61.99	3.85	4.89
XIIb	$C_{17}H_{16}ClNO_2$	154—155	1700	3260	67.67	5.34	4.64	67.73	5.29	4.59
XIIc	$C_{13}H_9ClN_2O_2$	172—173	1700	—	59.90	3.48	10.75	59.92	3.35	10.75
XIIe	$C_{16}H_{12}ClNO_2$	168—169	1720	—	67.26	4.23	4.90	67.26	4.01	4.81
XIIk	$C_{16}H_{12}ClNO_3$	157—159	1750 1700	—	63.69	4.01	4.63	63.91	3.93	4.67

Table III. 4-Oxo-3,1-benzoxazines

Comp. No.	Formula	mp (°C)	IR (cm^{-1})	Analysis (%)					
				Calcd.			Found		
			$\nu_{C=O}$	C	H	N	C	H	N
XVd	$C_{14}H_8ClNO_2$	151—152	1760	65.26	3.12	5.44	65.37	2.90	5.20
XVe	$C_{16}H_{10}ClNO_2$	156—157	1760	67.74	3.55	4.94	67.95	3.31	4.90
XVg	$C_{15}H_{10}ClNO_2$	126—128	1760	66.31	3.71	5.16	66.20	3.81	4.98
XVh[a]	$C_{12}H_{13}NO_2$	—	1760	—	—	—	—	—	—
XVj	$C_{12}H_6ClNO_2S$	180—181	1760	54.66	2.29	5.31	54.93	2.20	5.27

a) Crude substance was used for reduction with $NaBH_4$ without purification.

General Procedures for the Reductions of Salicylic Acid Esters with SBH——Ester (0.01 mol) was dissolved in 10 ml of solvent and $NaBH_4$ (0.005—0.03 mol) was added portionwise to this solution. The mixture was stirred at room temperature for 2—16 hr in most cases or refluxed for 2—8 hr, concentrated to remove solvent, added 10% HCl an extracted with ether or ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, concentrated to remove the solvent and the residue was recrystallized from proper solvent. The structure of the products were confirmed by the comparison of their melting points and IR spectra with those of the authentic samples.[12]

1,3-Dihydro-7-hydroxy-6-methyl-3-oxofuro[3,4-*c*]pyridine (VII) Hydrochloride[13]——To a solution of VI (2.5 g, 0.02 mol) was added $NaBH_4$ (0.8 g, 0.02 mol). After stirring the mixture for 24 hr at room temperature, 10% HCl was added and concentrated under reduced pressure. The residue was triturated with ethanol and recrystallized from ethanol to give 1 g (50%) of white needle. mp 224°. IR ν_{max}^{KBr} cm^{-1}: 1780 (C=O). NMR (in D_2O) δ, ppm: 2.90 (3H, CH_3, s), 5.80 (2H, CH_2, s), 8.90 (1H, arom H, s). *Anal.* Calcd. for $C_8H_7NO_2 \cdot HCl \cdot 1/2H_2O$: C, 45.60; H, 4.27; N, 6.65. Found: C, 45.86; H, 3.83; N, 6.64.

2-Acetamido-6-chlorobenzyl Alcohol (XIc)——To a solution of Xc (3.4 g, 0.015 mol)in THF (15 ml) was added $NaBH_4$ (1.2 g, 0.03 mol). The mixture was refluxed for 2 hr and treated as described above in

9) D.T. Mowry, *J. Am. Chem. Soc.*, **69**, 2362 (1947).
10) J.R. Piper and F.J. Stevens, *J. Org. Chem.*, **27**, 3134 (1962).
11) *a*) H.R. Synder, R.H. Levin and P.F. Wiley, *J. Am. Chem. Soc.*, **60**, 2025 (1938); *b*) D.T. Zentmeyer and E.C. Wagner, *J. Org. Chem.*, **17**, 967 (1949); *c*) S. Somasekhara, V. S. Dighe and S.L. Mukherjee, *Curr. Sci.*, **35**, 594 (1966).
12) *a*) A. Russert and Karl Crämer, *Chem. Ber.*, **61**, 2555 (1928); *b*) J. Arct, Z. Eckstein and H. Krywicka, *Prezemysl. Chem.*, **43**, 87 (1964) [*C.A.*, **61**, 3000*g* (1964)].
13) S.A. Harris, D. Heyl and K. Folkers, *J. Am. Chem. Soc.*, **66**, 2088 (1944).

the case of salicylates to give 1.8 g (60%) of XIc. mp 148—149°. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1660 (C=O). *Anal.* Calcd. for $C_9H_{10}ClNO_2$: C, 54.13; H, 5.01; N, 7.01. Found: C, 53.86; H, 5.04; N, 6.98.

2-Benzamido-6-chloro-benzylalcohol (XId)——In the similar manner to XIc, XId was obtained in 57% yield from Xd. mp 140—142°. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1640 (C=O). *Anal.* Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.33; H, 4.52; N, 5.49.

Reduction of 4-oxo-1,3-benzodioxanes (IXa, b) with $NaBH_4$——To a solution of 4-oxo-1,3-benzodioxane (0.05 mol) in THF (100 ml) was added $NaBH_4$ (3.8 g, 0.1 mol) and the mixture was stirred at room temperature for 24 hr and extracted with ether after addition of 10% HCl (50 ml). The ether layer was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (Mallincrodt). Thus, salicyl alcohol was obtained from IXa or IXb in 95% or 80% yield respectively.

Reduction of 1,2-Dihydro-4-oxo-3,1-benzoxazines (XIIa—e,k) and 4-oxo-3,1-benzoxazines (XVd—j)——All reductions were carried out in a similar manner using 2—3 mol equivalents of $NaBH_4$ in THF or EtOH. The results were summarized in Table IV.

TABLE IV. Reduction of 1,2-Dihydro-4-oxo-3,1-benzoxazines and 4-Oxo-3,1-benzoxazines

Starting comp. No.	Product comp. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIIa	XIVa	47	122—122.5	$C_{15}H_{14}ClNO_3$	66.79	4.90	4.87	66.71	4.96	4.71
XIIb	XIVb	80	169—170	$C_{16}H_{16}ClNO_2$	67.21	5.97	4.61	66.92	5.92	4.69
XIIc	XIVc	33	190—191	$C_{13}H_{11}ClN_2O_2$	59.44	4.22	10.66	59.26	4.11	10.53
XIIe	XIVe	93	115—116	$C_{16}H_{14}ClNO_2$	61.76	4.84	4.80	61.60	4.92	4.89
XIIk	XIc	37.5	148—149	*a*)						
XVd	XId	60	140—142	*a*)						
XVe	XIe	86	186—187	$C_{16}H_{14}ClNO_2$	66.79	4.90	4.87	66.42	4.77	4.76
XVf	XIVf	50[b)]	89— 90	$C_9H_{10}NO_2Cl$	54.51	5.12	7.05	54.47	4.98	7.06
XVg	XIVg	50	133—134	$C_{15}H_{14}ClNO_2$	65.34	5.12	5.08	65.78	4.78	5.05
XVh	XIh	62[c)]	Oil	$C_{12}H_{17}NO_2$			*d*)			
	XIVh	29[c)]	106—107	$C_{12}H_{17}NO_2$	69.54	8.27	6.76	69.79	8.32	6.51
XVi	XId	86	92— 93	$C_{14}H_{13}NO_2$	73.99	5.77	6.16	73.61	5.68	6.03
XVj	XIj	100	142—143	$C_{12}H_{10}ClNO_2S$	53.83	3.16	5.23	54.08	3.64	5.14

a) XIc and XId were obtained by the reduction of Xc and Xd with $NaBH_4$ respectively.
b) Showed the result in EtOH. When the reduction was carried out in THF, XIc and XIVf were obtained in 32 and 49% yield respectively.
c) Showed the result in EtOH. When the reduction was carried out in THF, the yield of XIh and XIVh were 55 and 35% respectively.
d) The structure of XIh was confirmed by the following spectral data: IR $\nu_{max}^{liq.}$ cm^{-1}: 3350 (OH). NMR (in $CDCl_3$) δ ppm: 1.25 (9H, singlet), 4.60 (2H, singlet), 6.9—7.4 (4H, multiplet), 8.00 (1H, amide NH).

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