SOME OBSERVATIONS ON THE REGIOSELECTIVE RING OPENING OF TETRAHYDRO-1,3-OXAZINIUM METHIODIDES BY SODIUM BOROHYDRIDE IN ALCOHOLIC AND ETHEREAL SOLVENTS

Angel Alberola, Celia Andrés, Manuel Delgado, Alfonso González, and Rafael Pedrosa*

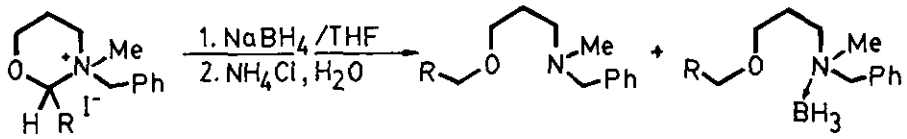
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid
Dr. Mergelina s/n.47011-Valladolid, Spain

Abstract- 2-Substituted N-benzyl-N-methyltetrahydro-1,3-oxazinium iodides react with sodium borohydride in anhydrous THF leading to a mixture of 3-alkoxypropylamines and their borane complexes. On the contrary, when anhydrous methanol or ethanol is used as solvent, the corresponding transacetalization product is obtained as single compound.

The reductive cleavage of carbon-oxygen bond in N,O-acetals[1] or hydroxymethylamines[2] with complex metal hydrides has been widely used in the synthesis of aminoalcohols and amines. By contrast, the reactivity of the corresponding quaternary salts has been less studied and there is only one reference to the reductive ring opening of 6-phenyl-7-oxa-5-azoniadispiro[4.2.5.1]-tetradecane perchlorate to N-(1-benzyloxycyclohexylmethyl)pyrrolidine by lithium aluminium hydride.[3]

In a previous work[4] we have studied the behaviour of tetrahydro-1,3-oxazines and their methiodides towards lithium aluminium hydride; the reductive ring opening is always regioselective, affording 3-tert-aminopropanol derivatives by cleavage of the C-O bond in the parent compounds or 3-tert-aminopropylethers by cleavage of the C-N bond in their salts. This behaviour could be referred to that showed by ammonium salts towards complex metal hydrides.[5] In this respect, tertiary amines have been synthesized from quaternary ammonium salts by nucleophilic displacement of an alkyl group by a hydride ion from lithium aluminium hydride[6,7] or lithium triethylborohydride,[8] while pyridine-borane or trimethylamine-borane complexes are obtained by reaction of anhydrous pyridine hydrochloride with sodium borohydride[9] or trimethylammonium hydrocloride with lithium borohydride[10] respectively. Otherwise, steroidal iminium salts are also reduced by sodium borohydride in pyridine or lithium borohydride in THF affording a mixture of tertiary amines and their amine-borane adducts.[11] As a part of our interest in the ring opening of tetrahydro-1,3-oxazines and their salts by nucleophiles we report now our results on the reaction with sodium borohydride.

The 2-substituted tetrahydro-1,3-oxazinum methiodides (**1a-f**), obtained by reaction of N-benzyltetrahydro-1,3-oxazines with excess of methyl iodide,[4,12,13] react with sodium borohydride in anhydrous THF leading to a mixture of 3-tert-aminopropyl ethers (**2a-f**) and the corresponding amino-borane complexes (**3a-f**).

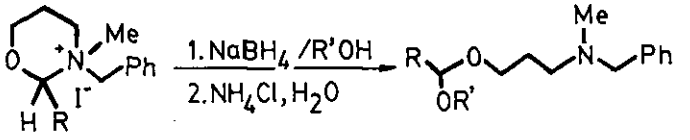


1a-f 2a-f 3a-f

Table 1. Reaction of 2-substituted N-benzyl-N-methyltetrahydro-1,3-oxazinium iodides with $NaBH_4$ in THF

Entry	Substrate	R	Reaction conditions time(h)	T(°C)	Products Yield(%)	
1	1a	Et	72	20	2a(6)	3a(8)
2	1a	Et	20	60	2a(30)	3a(40)
3	1b	Pr	72	20	2b(7)	3b(11)
4	1b	Pr	16	60	2b(28)	3b(58)
5	1c	i-Pr	14	60	2c(36)	3c(48)
6	1d	i-Bu	16	60	2d(32)	3d(48)
7	1e	Ph	224	20	2e(35)	3e(36)
8	1e	Ph	2	60	2e(6)	3e(10)
9	1f	p-$MeOC_6H_4$	66	20	2f(40)	3f(54)

The results summarized on Table 1 show that the transformation of 2-alkyl substituted salts (1a-d) into the amino ethers (2a-d) and their borane complexes (3a-d) is very low at room temperature, and the best results are obtained at reflux of the solvent (compare entries 1 and 3 versus 2,4-6). On the contrary, 2-aryl substituted substrates (1e,f) lead to a complex mixture of compounds after 2 hours at reflux of THF, and amino ether (2e) and its borane complex (3e) are obtained as minor products (entry 8), whereas the highest yield is obtained at room temperature (entries 7,9). Finally, in a reaction of 2a with $NaBH_4$ at reflux of THF and molar ratio 2a:hydride 1:2 the ratio of amino ether and its borane complex remains practically unchanged(2a, 29 % , and 3a, 38 %), but when anhydrous ether is used as solvent, the salts are recovered unchanged after 72 hours at reflux, probably as a consequence of their low solubility. The reactivity changes dramatically when an alcohol is used as solvent; thus, compounds (1a,c-f) lead to amino acetals (4a,c-f) in anhydrous methanol and 1 mol equivalent of sodium borohydride, whereas 1e yields the acetal (5e) in anhydrous ethanol and sodium borohydride.



1a,c-f 4a,c-f (R' = Me)
5e (R' = Et)

Table 2. Reaction of 2-substituted N-benzyl-N-methyltetrahydro-1,3-oxazinium iodides with $NaBH_4$ in anhydrous methanol or ethanol

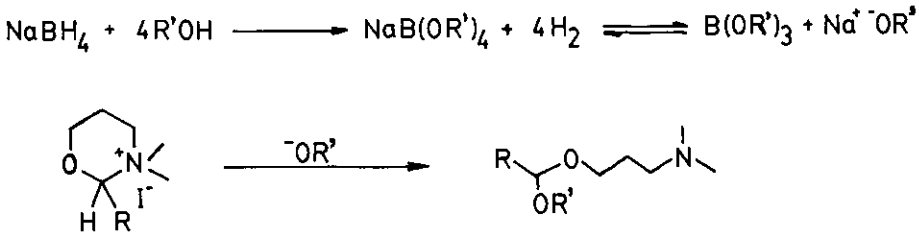
Entry	Substrate	Reaction conditions time(h)	T(°C)	solvent	Products Yield(%)
1	**1a**	72	20	MeOH	**4a**(7)
2	**1a**	15	65	MeOH	**4a**(74)
3	**1c**	72	20	MeOH	**4c**(6)
4	**1c**	15	65	MeOH	**4c**(88)
5	**1d**	72	20	MeOH	**4d**(14)
6	**1d**	15	65	MeOH	**4d**(32)
7	**1e**	53	20	MeOH	**4e**(63)
8	**1e**	10	76	EtOH	**5e**(85)
9	**1f**	72	20	MeOH	**4f**(78)
10	**1f**	8	65	MeOH	**4f**(95)

In this case, substrates (**1e,f**) (R= aryl) are also more reactive than 2-alkyl substituted ones; thus, acetals (**4e,f**) are obtained in good yields at room temperature, whereas compounds (**1a,c,d**) are transformed into the corresponding **4a,c,d** in very poor yields in the same experimental conditions (compare entries 7and 9 versus 1,3 and 5 in Table 2). Otherwise, the oxazinium salts are recovered unchanged after heating at reflux of anhydrous methanol or ethanol for 15 hours.

The behaviour of tetrahydro-1,3-oxazinium methiodides towards $NaBH_4$ in anhydrous THF can be easily explained as a nucleophilic displacement of the charged nitrogen in the heterocycle by a hydride ion, and subsequent formation of an equivalent of borane, that partially appears as a very stable adduct of the tertiary amine present in the reduction product. On the other hand, amino ethers (**2a-f**) are not decomposition products of their borane adducts (**3a-f**) because both compounds are present in the reaction mixture before the hydrolysis as can be showed by tlc.

The formation of acetals when methanol or ethanol is used as solvents is unclear, but it could be rationalized on the basis of the following experimental facts: i) The starting compounds are recovered unchanged after 15 hours at reflux of these alcohols; ii) The reaction of the methiodides (**1a,c-f**) with $NaBH_4$ is slower than the formation of sodium tetramethoxy- or tetraethoxyborohydride from $NaBH_4$ and methanol or ethanol.[14] iii) Sodium tetraalkoxyborohydrides decompose to trialkylborates and sodium alkoxides.[15] Taking into account all these facts, the formation of compounds (**4a,c-f**) and (**5e**) would be attributed to a nucleophilic cleavage of the heterocycle by the methoxide or ethoxide ion present in the reaction mixture. An alternative way involves the transacetalization of the heterocycle by the nucleophilic solvent catalysed by a trialkylborate acting as Lewis acid. Attempting to prove these hypothesis we have assayed the reactions of **1c** with triethyl borate in ethenol and **1c** and **1e** with sodium methoxide in methanol. The starting compound (**1c**) was recovered unchanged after refluxing in ethanol for 20 hours in the presence of one equivalent of triethyl borate, whereas **1c** and **1e** were transformed into **4c** and **4e** in 82 and 80 %, respectively, when a solution of the corresponding methiodides in methanol was stirred at room temperature for 10 hours with one equivalent of sodium methoxide. These facts allow to propose that the transformation of **1a-f** into **4a-f** must be depicted as a nucleophilic ring opening of the heterocycle by an alkoxide ion formed from sodium tetralkoxyborate as

summarized in the following Scheme.



EXPERIMENTAL

Nmr spectra were registered on a Bruker AC80 at 80 MHz, and chemical shifts are given in ppm downfield from TMS used as internal standard. Ir were recorded on a Philips PU9706 IR spectrophotometer as liquid film, and mass spectra on a Hewlett-Packard 5988A mass spectrometer, by electronic impact at 70 eV. N-Benzyl-N-methyltetrahydro-1,3-oxazinium iodides were prepared by reaction of the corresponding 2-substituted tetrahydro-1,3-oxazines with excess of methyl iodide as previously described.[4] Anhydrous THF was used after distillation from CaH_2, and anhydrous MeOH and EtOH were prepared by a literature method.[16]

Reaction of 2-Substituted N-Benzyl-N-methyltetrahydro-1,3-oxazinium Iodides with $NaBH_4$ in THF. General Procedure. A mixture of 480 mg(10 mmol) of $NaBH_4$ and 10 mmol of the corresponding methiodides (**1a-f**) in 125 ml of anhydrous THF was stirred at room temperature or reflux under nitrogen until total desappearance of the salt (tlc). The solution was cooled to room temperature and quenched with 10 ml of a saturated solution of NH_4Cl in H_2O. After filtration of the solid, the volume of the mixture was reduced to ca. 50 ml by elimination of THF (Rotavapor) and the residue was extracted with $CHCl_3$ (3x50 ml). The organic layer was sequentially washed with 2M solution of $Na_2S_2O_3$, water and brine, and dried over anhydrous $MgSO_4$. The solvents were eliminated, and the residue was chromatographed on silica gel using CH_2Cl_2 as eluent.

The physical and spectroscopic characteristics of compounds (**2a-f**) have been previously described,[4] and for their borane-complexes (**3a-f**) are as follows:

N-Benzyl-N-methyl-3-propoxypropylamine-Borane Complex (3a). Colorless oil. Ir: 2340; 2260 cm^{-1}. Nmr($CDCl_3$): 0.90(t, J=6 Hz, 3H); 1.60(m, 2H); 2.18(m, 2H); 2.44(s, 3H); 2.73(m, 2H); 3.39(m, 4H); 3.85(d, J=13 Hz, 1H); 4.03(d, J=13 Hz, 1H); 7.35(s, 5H). Ms, m/z(%): 234(M^+-1, 5); 134(15), 91(100). $C_{14}H_{26}NOB$ requires: C, 71.50; H, 11.14; N, 5.95. Found: C, 71.68; H, 11.01; N, 5.80.

N-Benzyl-N-methyl-3-butoxypropylamine-Borane Complex (3b). Colorless oil. Ir: 2340; 2260 cm^{-1}. Nmr($CDCl_3$): 0.90(t, J=6 Hz, 3H); 1.42(m, 4H); 2.14(m, 2H); 2.44(s, 3H); 2.70(m, 2H); 3.34 (t, J=5 Hz, 2H); 3.37(t, J=5 Hz, 2H); 3.89(d, J=14 Hz, 1H); 4.01 (d, J=14 Hz, 1H); 7.35(s, 5H). Ms, m/z(%): 248(M^+-1, 2); 134(7); 91(100). $C_{15}H_{28}NOB$ requires: C, 72.29; H, 11.32; N, 5.62. Found: C, 72.44; H, 11.19; N, 5.48.

N-Benzyl-N-methyl-3-isobutoxypropylamine-Borane Complex (3c). Colorless oil. Ir: 2340; 2260 cm^{-1}. Nmr($CDCl_3$):0.88(d, J=7 Hz, 1H); 1.72(m, 1H); 2.12(m, 2H); 2.42(s, 3H); 2.68(m, 2H); 3.12 (d, J=6 Hz, 2H); 3.40(t, J=5 Hz, 2H); 3.88(d, J=13 Hz, 1H); 4.00(d, J=13 Hz, 1H); 7.35(s, 5H). Ms, m/z(%): 248(M^+-1, 1); 134(6); 91(100). $C_{15}H_{28}NOB$ requires: C, 72.29; H, 11.32; N, 5.62. Found: C, 72.14; H, 11.18; N, 5.76.

N-Benzyl-N-methyl-3-isovaleryloxypropylamine-Borane Complex (3d). Colorless oil. Ir: 2340; 2250 cm^{-1}. Nmr($CDCl_3$): 0.89(d, J=5 Hz, 6H); 1.49(m, 3H); 2.14(m, 2H); 2.42(s, 3H); 2.65(m, 2H); 3.42 (m, 4H); 3.89 (d, J=13 Hz, 1H); 4.02(d, J=13 Hz, 1H); 7.35(s, 5H). Ms, m/z(%): 263(M^+, 1);

262(M^+-1, 6); 134(14); 91(100). $C_{16}H_{30}NOB$ requires: C, 73.00; H, 11.48; N, 5.32. Found: C, 73.17; H, 11.34; N, 5.20.

N-Benzyl-N-methyl-3-benzyloxypropylamine-Borane Complex (3e). Colorless oil. Ir: 2345; 2260 cm^{-1}. Nmr($CDCl_3$): 2.10(m, 2H); 2.38(s, 3H); 2.64(m, 2H); 3.44(t, J=5 Hz, 2H); 3.82(d, J=13 Hz, 1H); 3.96(d, J=13 Hz, 1H); 4.41(s, 2H);7.26(s, 5H); 7.33(s, 5H). Ms, m/z(%): 282(M^+-1, 1); 134(10); 91(100). $C_{18}H_{26}NOB$ requires: C, 76.33; H, 9.25; N, 4.94. Found: C, 76.19; H, 9.39; N, 4.81.

N-Benzyl-N-methyl-3-(p-methoxy)benzyloxypropylamine-Borane Complex (3f). Colorless oil. Ir: 2340; 2260 cm^{-1}. Nmr($CDCl_3$): 2.12(m, 2H); 2.40(s, 3H); 2.68(m, 2H); 3.43(t, J=5 Hz, 2H); 3.73(s, 3H); 3.88(d, J=13 Hz, 1H); 3.96(d, J=13 Hz, 1H); 4.40(s, 2H); 6.84(d, J=9 Hz, 2H); 7.20(d, J=9 Hz, 2H); 7.40(s, 5H). Ms, m/z(%): 312(M^+-1, 1); 134(6); 91(100). $C_{19}H_{28}NO_2B$ requires: C, 72.85; H, 9.01; N, 4.47. Found: C, 72.71; H, 9.15; N, 4.61.

Reaction of 2-Substituted N-Benzyl-N-methyltetrahydro-1,3-oxazinium Iodides with $NaBH_4$ in alcohols. General procedure. To 480 mg (10 mmol) of $NaBH_4$ in 10 ml of anhydrous methanol or ethanol, was added under nitrogen, a solution of 10 mmol of the corresponding salt (**1a,c-f**) in 40 ml of the same solvent and the mixture was stirred at room temperature or reflux for the time indicated in Table 2. After this time, the reaction mixture was quenched with 10 ml of a saturated solution of NH_4Cl in H_2O and extracted with ether (4x50 ml). The ethereal layer was sequentially washed with a 2M solution of $Na_2S_2O_3$, water and brine, and dried over anhydrous $MgSO_4$. The solvent was eliminated and the residue was purified by vacuum distillation. In this way, the following compounds were obtained:

N-Benzyl-N-methyl-3-(1-methoxy)propoxypropylamine (4a). Colorless oil, bp 84-86°C/0.1 torr. Ir: 1450; 1365; 1130; 745; 710 cm^{-1}. Nmr($CDCl_3$): 0.90(t, J=7 Hz, 3H); 1.72(m, 4H); 2.20(s, 3H); 2.47(m, 2H); 3.35 (s, 3H); 3.50(s, 2H); 3.55(m, 2H); 4.30(t, J=6 Hz, 1H); 7.30 (s, 5H). Ms, m/z(%): 251(M^+, 1); 134(30); 91(100). $C_{15}H_{25}NO_2$ requires: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.76; H, 10.13; N, 5.68.

N-Benzyl-N-methyl-3-(1-methoxy)isobutoxypropylamine (4c). Colorless oil, bp 92-95°C/0.1 torr. Ir: 1455; 1390; 1120; 750; 715 cm^{-1}. Nmr($CDCl_3$): 0.95(d, J=7 Hz, 6H); 1.75(m, 3H); 2.10(s, 3H); 2.36(m, 2H); 3.25 (s, 3H); 3.50(s, 2H); 3.55(m, 2H); 4.15(d, J=6 Hz, 1H); 7.30 (m, 5H). Ms, m/z(%): 265(M^+, 1); 178(10); 134(30); 91(100). $C_{16}H_{27}NO_2$ requires: C, 72.41; H, 10.25; N, 5.27. Found: C, 72.29; H, 10.36; N, 5.18.

N-Benzyl-N-methyl-3-(1-methoxy)isovaleryloxypropylamine (4d). Colorless oil, bp 99-101°C/0.1 torr. Ir: 1455; 1370; 1125; 745; 710 cm^{-1}. Nmr($CDCl_3$): 0.95(d, J=6 Hz, 6H); 1.60(m, 3H); 1.80(m, 2H); 2.17(s, 3H); 2.45(m, 2H); 3.26(s, 3H); 3.50(s, 2H); 3.55(m, 2H); 4.30(t, J=6Hz, 1H); 7.30(m, 5H). Ms, m/z(%): 279(M^+, 1); 178(16); 134(32); 91(100). $C_{17}H_{29}NO_2$ requires: C, 73.07; H, 10.46; N, 5.01. Found: C, 72.96; H, 10.57; N, 5.14.

N-Benzyl-N-methyl-3-(1-methoxy)benzyloxypropylamine (4e). Colorless oil, bp 156-157°C/0.5 torr. Ir: 1490; 1360; 1250; 1100; 1050; 740; 700 cm^{-1}. Nmr($CDCl_3$): 1.80(m, 2H); 2.15(s, 3H); 2.45(m, 2H); 3.20 (s, 3H); 3.45(s, 2H); 3.55(m, 2H); 5.40(s, 1H); 7.20(m, 10 H). Ms, m/z(%): 299 (M^+, 1); 178(11); 134(40); 91(100). $C_{19}H_{25}NO_2$ requires: C, 76.22; H, 8.41; N, 4.67. Found: C, 76.29; H, 8.51; N, 4.76.

N-Benzyl-N-methyl-3-(1-methoxy)p-methoxybenzyloxypropylamine (4f). Colorless oil, bp 123-125°C/0.1 torr. Ir: 1510; 1455; 1360; 1180; 830; 800; 750; 710 cm^{-1}. Nmr($CDCl_3$): 1.75(m, 2H); 2.10(s, 3H); 2.45(m, 2H); 3.15 (s, 3H); 3.40(s, 2H); 3.45(m, 2H); 3.70(s, 3H); 5.40(s, 1H); 6.75 (d, J=8 Hz, 2H); 7.15(s, 5H); 7.20(d, J=8 Hz, 2H). Ms, m/z(%): 314(M^+-15, 2); 178(10); 134(29); 91(100). $C_{20}H_{27}NO_3$ requires: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.85; H, 8.38; N, 4.16.

N-Benzyl-N-methyl-3-(1-ethoxy)benzyloxypropylamine (5e). Colorless oil, bp 112-114°C/0.1 torr. Ir: 1500; 1450; 1360; 1250; 1105; 735; 705 cm^{-1}. Nmr($CDCl_3$): 1.15(t, J=7 Hz, 3H); 1.80(m, 2H);

2.10(s, 3H); 2.45(m, 2H); 3.45(s, 2H); 3.55(m, 4H); 5.45(s, 1H); 7.20(m, 10 H). Ms, m/z(%): 313(M^+, 1); 178(10); 134(36); 91(100). $C_{20}H_{27}NO_2$ requires: C, 76.64; H, 8.68; N, 4.46. Found: C, 76.52; H, 8.81; N, 4.35.

ACKNOWLEDGEMENTS

The financial support of this work, provided by the Spanish DGICYT (Project PB86-0145) is gratefully acknowledged.

REFERENCES

1. L. H. Briggs and R.H. Locker, J. Chem. Soc., **1950**, 3020; H. Heusser, P.T. Herzig, A. Fürst, and P. A. Plattner, Helv. Chim. Acta, **1950**, 33, 1093; E. D. Bergmann, D. Lavie, and S. Pinchas, J. Am. Chem. Soc., **1951**, 73, 5662; G. Fragantos, G. Kohan, and F. L. Chubb, Can. J. Chem., **1960**, 38, 1434; G. Drefahl and H. H. Hörhold, Chem. Ber., **1961**, 94, 1657; E. L. Eliel and R. A. Daignault, J. Org. Chem., **1965**, 30, 2450; R. C. Northrop and P. L. Russ, J. Org. Chem., **1975**, 40, 558; L. Gera, G. Bernáth, and P. Sohár, Acta Chim. Acad. Sci. Hung., **1980**, 105, 293; L. Guerier, J. Royer, D. S. Grieson, and H. P. Husson, J. Am.Chem. Soc., **1983**, 105, 7754; J. Barluenga, A. M. Bayón, G. Asensio, J. Chem. Soc., Chem. Commun., **1984**, 1334; J. M. McIntosh and L. C. Matassa, J. Org. Chem., **1988**, 53, 4452; J. Barluenga, A. M. Bayón, P.Campos, G. Asensio, E. González, and Y. Molina, J. Chem. Soc., Perkin Trans.1, **1988**, 1631.
2. S. Bose, J. Indian Chem. Soc., **1955**, 32, 450; I. Sallay and R. H. Ayers, Tetrahedron, **1963**, 19, 1397; K. Schreiber and H. Rönsch, Tetrahedron, **1965**, 21, 645; M. F. Bartlett, B. F. Lambert, H. M. Werblood, and W. I .Taylor, J. Am. Chem. Soc., **1963**, 85, 475.
3. N. J. Leonard, E. F. Kiefer, and L. E. Brady, J. Org. Chem., **1963**, 28, 2850.
4. A. Alberola, M. A. Alvarez, C. Andrés, A. González, and R. Pedrosa, Synthesis, **1990**, 153.
5. E. Schenker, "Newer Methods of Preparative Organic Chemistry", ed. by W. Foerst, Academic Press, New York, **1968**, Vol. IV, p. 239.
6. G .W. Kenner and M. A. Murray, J. Chem. Soc., **1950**, 406.
7. A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, J. Am. Chem. Soc., **1960**, 82, 4651.
8. M. P. Cooke, Jr. and R. M. Parlman, J. Org. Chem., **1975**, 40, 531.
9. M. D. Taylor, L. R. Grant, and C. A. Sands, J. Am. Chem. Soc., **1955**, 77, 1506.
10. G. W. Schaefer and E. R. Anderson, J. Am. Chem. Soc., **1949**, 71, 2143.
11. D. Burn, G. Cooley, M. T. Davies, A. K. Hiscock, D. N. Kirk, V. Petrow, and D. M. Williamson, Tetrahedron, **1965**, 21, 569.
12. H. Booth and R. V. Lemieux, Can. J. Chem., **1971**, 49, 777.
13. D. Gürne, T. Urbański, M. Witanowski, B. Karniewsk, and L. Stefaniak, Tetrahedron, **1964**, 20, 1173.
14. H. C. Brown, E. J. Mead, and B. C. Subba Rao, J. Am. Chem. Soc., **1955**, 77, 6209.
15. H. I. Schlesinger, H. C. Brown, H. R. Hoekstra, and L. R. Rapp, J. Am. Chem. Soc., **1953**, 75, 199.
16. VOGEL's Textbook of Practical Organic Chemistry, 4 th Edition, Longman, London, **1978**.

Received, 20th September, 1990