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Reductive Cleavage Reaction of N,N′-, N,O- and N,S-Linked Alkylidene Compounds by Sodium Borohydride

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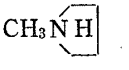
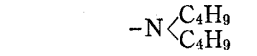
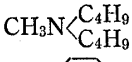
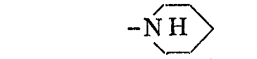
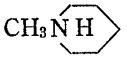
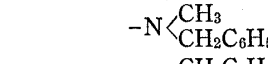
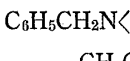
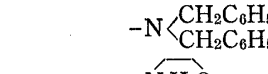
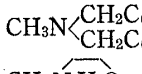
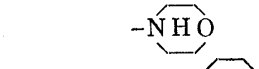
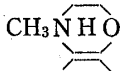
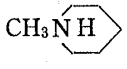
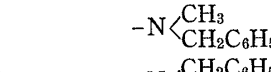
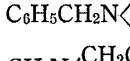
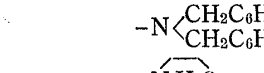
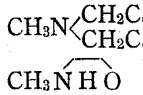
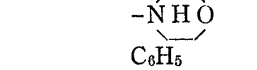
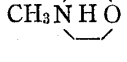
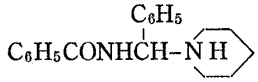
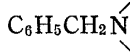
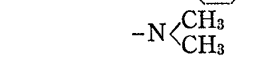
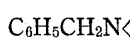
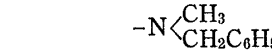
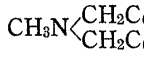
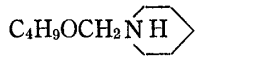
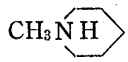
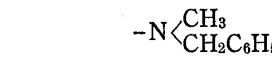
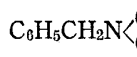
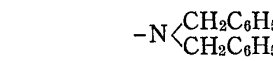
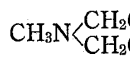
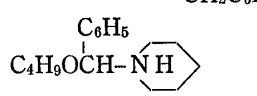
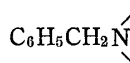
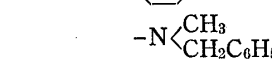
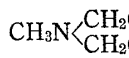
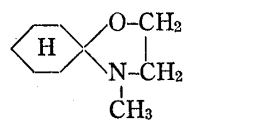
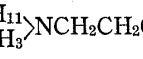
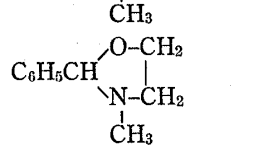
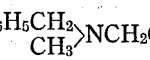
Sodium borohydride reduction was undertaken with a variety of N,N′-, N,O- and N,S-linked alkylidene compounds in aqueous ethanolic medium at room temperature. It has been realized that reductive cleavage of one of these two alkylidene carbon-heteroatom bonds is generally effected in this reduction, disclosing which alkylidene bond is initially cleaved when the two bonds are different.

In chemical literature there have been described numerous N,N′-, N,O- and N,S-linked alkylidene compounds as the types of methylene and benzylidene and as the particular ones of other alkylidenes linked in the ring systems. With some N,N′- and N,O-linked compounds the catalytic hydrogenation[2–6] and the formic acid reduction[7,8] have been reported to effect the reductive cleavage of one of the two alkylidene carbon-heteroatom bonds. Very recently the sodium borohydride reduction of N-(arylaminomethyl)succinimides in dimethyl sulfoxide to monomethylanilines has also been reported.[9] In this laboratory an investigation was undertaken to see behavior of the above N,N′-, N,O- and N,S-linked alkylidene compounds in the system, sodium borohydride in aqueous ethanolic medium. With a wide range of these compounds the reductive cleavage of one of the two alkylidene carbon-heteroatom bonds was realized in the sodium borohydride reduction. It would be of chemical significance to see which of the two bonds initially suffers the reductive cleavage when the two are different. We now wish to disclose the detail of our work on the sodium borohydride reduction in this view.

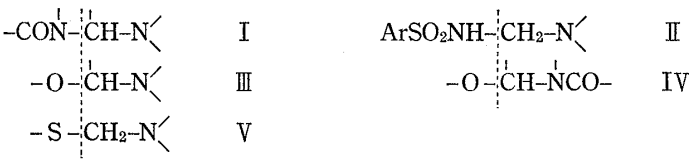
As substrate compounds for the sodium borohydride reduction were chosen those, in which the two alkylidene carbon-heteroatom bonds are different each other. As can be seen in Table I the twenty-three substrates available by the known method were employed for the reduction. In those substrates (X–$\overset{\displaystyle R}{\overset{|}{C}}$H–Y) X and Y are grouped in the following: amide (or imide) nitrogen, amine nitrogen; sulfonamide nitrogen, amine nitrogen; alkoxy oxygen, amine nitrogen; alkoxy oxygen, amide (or imide) nitrogen; alkylthio sulfur, amine nitrogen. These substrate compounds were subjected to the reduction under the following standardized condition. The substrate dissolved or suspended in ethanol was allowed to react at about 15° with aqueous alkaline solution of sodium borohydride (molar proportion to substrate: 0.75). Results are summarized in Table I. In every run of these the reductive cleavage of one of the alkylidene carbon-heteroatom bonds was effected, as shown by the dotted lines in the following.

1) Location: *2–2–1 Oshika, Shizuoka.*
2) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **14**, 996 (1966).
3) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **14**, 1007 (1966).
4) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **15**, 1339 (1967).
5) N. Sakura, K. Ito, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1156 (1972).
6) K. Ito and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1762 (1972).
7) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **12**, 677 (1964).
8) K. Ito, H. Oba, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 2112 (1972).
9) S.B. Kadin, *J. Org. Chem.*, **38**, 1348 (1973).

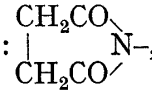
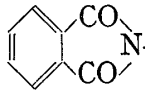
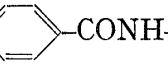
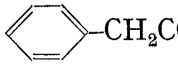
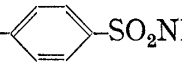
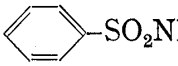
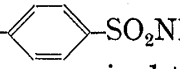
TABLE I. Sodium Borohydride Reduction[a] of N,N′-, N,O- and N,S-Linked Alkylidene Compounds

Run No.	Substrate	Reaction period (hr)	Product isolated	Yield[b] (%)
1		2		85[c]
2		2		75
3		2		74[c]
4		2		54
5		2		48
6		2		35[c]
7		2		84[c]
8		2		83
9		2		30
10		2		46[c]
11		2		9
12		2		7
13		2		3
14		2		86[c]
15		2		62
16		2		36
17		2		87
18		2		62
19		2		76
20		2		74
21		30	$C_6H_5CH_2NHCOCH_2CH_2OH$	74
22		72	$C_2H_5NHCOCH_2CH_2OH$	49
23		10		53[c]

a) molar ratio: $NaBH_4$/substrate=3/4; reaction medium: aqueous ethanolic solution; reaction temperature: 15±3°
b) based on the product isolated
c) obtained as picrate



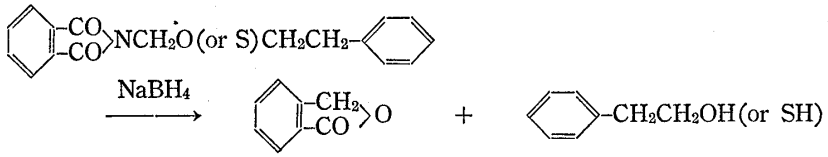
Among these structural patterns of the substrate, IV and V showed greater resistance to the reduction, requiring much longer reaction period when compared with the others.

In each pattern of the substrates variation of the residue linked to alkylidene carbon should also concern the reactivity. Using representative N-(piperidinomethyl)amide and -arylsulfonamide as the types of I and II, control experiments were undertaken under the standard condition (2 hr reaction period) in variation of their amide and sulfonamide residues. Results showed the following yields of the cleaved N-methylpiperidine; with N-(piperidinomethyl) amide:  , 74%;  , 48%;  , 12%;  , 0%; with N-(piperidinomethyl)arylsulfonamide:  , 86%;  , 84%;  , 81%. From the former result the succinimido- as the amide residue was recognized to be most sufficient. In Table I effect of the amine residues on the reactivities can be seen in the runs with the substrates, N-(dialkylaminomethyl)succinimides, N-(dialkylaminomethyl)benzenesulfonamides, N-(α-dialkylaminobenzyl)benzamides and N-(butoxymethyl)dialkylamines varying their amine residues. The previous papers dealing with the catalytic hydrogenation[2-4] and the formic acid reduction[7] where the same fashion of the reductive cleavage has been reported to occur suggest that decrease of basicity of the amine residue in I and decrease of acidity of the amide residue in I and II restrain the reductive cleavages. The above results as to the reactivity with respect to the amide residue of the N-(piperidinomethyl)amide and with respect to the amine residue seen in Table I appear consistent with this reported assumption. In additional experiments the reduction of N-(anilinomethyl)succinimide and N-(N-methylanilinomethyl)succinimide was extremely restrained under the condition, probably owing to the low basicity of these amine residues.

The reductive cleavages exhibited in the sodium borohydride reduction of the above various alkylidene compounds afford the synthetically useful N-methylated amines, N-benzylated amines and, in the case of the ring substrates, open-chain compounds.

In the present borohydride reduction the resulting substitution with hydride at one of the alkylidene carbon-heteroatom bonds is mechanistically conceivable to proceed by direct hydride substitution. For the sodium borohydride reduction of N-(arylaminomethyl)succinimides another path involving elimination to CH_2=NAr followed by hydride addition has been proposed[9] on the basis of no formation of N,N-dimethyl-*p*-toluidine from N-(N-methyl-*p*-toluidinomethyl)succinimide (no hydrogen at toluidino nitrogen). This assumption is, however, undoubtedly eliminated for the present borohydride reduction of N-(dialkylaminomethyl)succinimides and the others such as those lacking hydrogen at the nitrogen linked to the alkylidene carbon.

Abnormal results were obtained in the use of the substrates, N-(phenethyloxymethyl)-phthalimide and N-(phenethylthiomethyl)phthalimide, where phthalide was obtained in addition to 2-phenylethanol and 2-phenylethanethiol, respectively. In the former this reaction proceeded in about 43% for 60 hr reaction period and in the latter in about 9% for 10 hr reaction period.



N-Alkylphthalimide has been known[10] to react with sodium borohydride to give phthalide. Consequently, phthalide is referred to as a reaction product from N-methylphthalimide formed by the initial cleavage.

Experimental[11]

Materials——Of the N,N'-, N,O-, and N,S-linked alkylidene compounds used for the sodium borohydride reduction, the following compounds shown with their melting or boiling points were prepared by the known method: N-(pyrrolidinomethyl)succinimide,[12] mp 53—54°; N-(piperidinomethyl)succinimide,[13] mp 104—105°: N-(N-methylbenzylaminomethyl)succinimide,[12] mp 72°; N-(dibenzylaminomethyl)succinimide,[12] mp 123°; N-(morpholinomethyl)succinimide,[14] mp 108°; N-(piperidinomethyl)benzenesulfonamide,[15] mp 78—79°; N-(α-piperidinobenzyl)benzamide,[16] mp 142—144°; N-(α-dimethylaminobenzyl)benzamide,[16] mp 107—108°; N-[α-(N-methylbenzylamino)benzyl]benzamide,[16] mp 112—113°; N-(butoxymethyl)piperidine,[17] bp 98—99° (19 mmHg), n_D^{12} 1.4495; N-(butoxymethyl)-N-methylbenzylamine,[8] bp 134—138° (18 mmHg), n_D^{12} 1.4910; N-(butoxymethyl)dibenzylamine,[8] bp 152—156° (0.2 mmHg), n_D^{19} 1.5409; N-(α-butoxybenzyl)-piperidine,[18] bp 113—115° (0.1 mmHg), n_D^{26} 1.5051; N-(α-butoxybenzyl)-N-methylbenzylamine,[5] bp 125—126° (0.01 mmHg), n_D^{28} 1.5312; 4-methyl-1-oxa-4-azaspiro[4,5]decane,[19] bp 89—92° (16 mmHg), n_D^{19} 1.4632; 3-methyl-2-phenyloxazolidine,[19] bp 128—130° (26 mmHg), n_D^{19} 1.5274; tetrahydro-2-phenyl-4*H*-1,3-oxazin-4-one,[6] mp 117—119°; tetrahydro-2-methyl-4*H*-1,3-oxazin-4-one,[6] mp 124—125°; N-(piperidinomethyl)-phthalimide,[20] mp 117—118°; N-(piperidinomethyl)benzamide,[21] mp 131°; N-(piperidinomethyl)phenylacetamide,[22] mp 110°; N-(piperidinomethyl)-*p*-toluenesulfonamide,[2] mp 85—88°; N-(phenethyloxymethyl)-phthalimide,[23] mp 72—73°; N-(phenethylthiomethyl)phthalimide,[24] mp 100—103°.

The following five compounds which have not been known were newly prepared for the present work.

N-(Dibutylaminomethyl)succinimide——In 100 ml of MeOH 5.0 g of succinimide, 4.1 g of 37% CH_2O and 6.5 g of dibutylamine were dissolved, and the solution was refluxed for 1 hr. Concentration of the reaction solution and distillation of the residue under high reduced pressure gave a viscous oil, bp 114—120° (0.001 mmHg), which gradually solidified on standing. Recrystallization from EtOH gave plates, mp 32—33°. Yield 9.5 g (75%). *Anal.* Calcd. for $C_{13}H_{24}O_2N_2$: C, 64.96; H, 10.07; N, 11.66. Found: C, 64.66; H, 9.81; N, 11.64.

N-(Piperidinomethyl)-*p*-chlorobenzenesulfonamide——A solution of 16.0 g of *p*-chlorobenzenesulfonamide, 6.5 g of 37% CH_2O and 6.8 g of piperidine dissolved in 100 ml of MeOH was refluxed for 2 hr. Concentration of the reaction solution under reduced pressure left the crude product. Needles from MeOH, mp 110—111°. Yield 22.6 g (98%). *Anal.* Calcd. for $C_{12}H_{17}O_2N_2SCl$: C, 49.90; H, 5.93; N, 9.70. Found: C, 49.98; H, 6.01; N, 9.73.

N-(Dibenzylaminomethyl)benzenesulfonamide——A solution of 12.5 g of benzenesulfonamide, 7.6 g of 37% CH_2O and 18.8 g of dibenzylamine dissolved in 50 ml of EtOH was refluxed for 30 min and treated as above. Needles from MeOH, mp 135—136°. Yield 26.5 g (91%). *Anal.* Calcd. for $C_{21}H_{22}O_2N_2S$: C, 68.80; H, 6.06; N, 7.65. Found: C, 68.65; H, 6.09; N, 7.50.

N-(N-Methylbenzylaminomethyl)benzenesulfonamide——A solution of 4.7 g of benzenesulfonamide, 2.9 g of 37% CH_2O and 4.4 g of N-methylbenzylamine in 20 ml of EtOH was refluxed for 2 hr. The residue obtained on removal of the solvent was washed with petr. ether followed by extraction with hot isopropyl ether. The crude product crystallized out of the isopropyl ether solution on cool, which was collected and recrystallized from isopropyl ether–EtOH (3: 1) to give needles, mp 120°. Yield 4.6 g (53%). *Anal.* Calcd. for $C_{15}H_{18}O_2N_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 62.41; H, 5.93; N, 9.52.

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N-(Butylthiomethyl)piperidine——To a stirred solution of 10.9 g (0.06 mole) of dipiperidinomethane dissolved in 50 ml of dry ether were successively added at room temperature 8.4 g (0.06 mole) of benzoyl chloride in 10 ml of dry ether, 7.1 g (0.07 mole) of triethylamine and 6.3 g (0.07 mole) of butanethiol in 15 ml of dry ether. After stirring for further 3 hr at room temperature, the reaction mixture was filtered to remove deposited triethylamine hydrochloride. Concentration of the filtrate and distillation of the residue under reduced pressure gave the product, bp 135—137° (20 mmHg), n_D^{17} 1.4940. Yield 8.4 g (77%). *Anal.* Calcd. for $C_{10}H_{21}NS$: C, 64.11; H, 11.30; N, 7.48; S, 17.11. Found: C, 64.26; H, 10.91; N, 7.31; S, 17.52.

Sodium Borohydride Reduction General Procedure——A solution of 1.71 g (0.045 mole) of sodium borohydride in 9 ml of H_2O, to which three drops of 10% NaOH was added, was dropwise added to a solution or a suspension of 0.06 mole of the substrate in 150 ml of EtOH while stirred at room temperature (15±3°). Stirring was continued for additional hours as indicated in Table I. Hydrochloric acid was added to decompose excess hydride until the reaction mixture became pH 5—6. EtOH was distilled off from the reaction mixture and filtration was followed when crystals were deposited. Isolation of the products were worked up as follows.

In the runs of the reaction producing the amine, addition of excess KOH liberated amine as an oil. Extraction with ether or benzene followed by removal of the solvent gave the amine product which was distilled. As shown in Table I, N-methylpyrrolidine (Run 1), N-methylpiperidine (Runs 3, 7, 14, and 23) and N-methylmorpholine (Runs 6 and 10) were isolated as their picrates from the ether extract.

In Run 21 the N-benzylhydracrylamide was isolated by extraction of the concentration residue with iso-PrOH followed by concentration. In Run 22, after removal of the unreacted substrate by extraction with benzene, the concentration residue was distilled under reduced pressure to give the product.

In the runs with N-(phenethyloxymethyl)phthalimide and N-(phenethylthiomethyl)phthalimide, the concentration residue was extracted with benzene and dried. Phthalide and the other products, 2-phenylethanol and 2-phenylethanethiol, were obtained by fractional distillation of the benzene extract under reduced pressure.

Identities of the products, which are listed in the following, were made by noting no depression of their melting points on admixture with authentic samples and well consistence of their infrared spectra with those of authentic samples. N-Methylpyrrolidine, picrate mp 218° (lit.[25] mp 223—225°), *Anal.* Calcd. for $C_{11}H_{14}O_7N_4$: C, 42.04; H, 4.49; N, 17.83. Found: C, 42.09; H, 4.66; N, 17.82; N-methyldibutylamine, bp 86—89° (81 mmHg), n_D^{12} 1.4205 (lit.[26] bp 155—163°), *Anal.* Calcd. for $C_9H_{21}N$: C, 75.44; H, 14.77; N, 9.78. Found: C, 75.07; H, 14.67; N, 9.96; N-methylpiperidine, picrate mp 148—150°; N,N-dimethylbenzylamine, bp 71—73° (23 mmHg), n_D^{18} 1.5057; N-methyldibenzylamine, bp 113—115° (0.1 mmHg), n_D^{16} 1.5624, hydrochloride mp 195—197°; N-methylmorpholine, picrate mp 218—220°; N-benzylpiperidine, bp 146—150° (24 mmHg), n_D^{12} 1.5277; 2-(N-methylcyclohexylamino)ethanol, bp 118—119° (17mmHg), n_D^{14} 1.4894 (lit.[27] 127—129° (26 mmHg)), *Anal.* Calcd. for $C_9H_{19}ON$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.71; H, 11.94; N, 8.60; 2-(N-methylbenzylamino)ethanol, bp 138—140° (19 mmHg), n_D^{19} 1.5621 (lit.[28] bp 136—138° (16 mmHg)), *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.98; H, 8.86; N, 8.20; N-benzylhydracrylamide, mp 62—64° (lit.[29] mp 63—64°), *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.01; H, 7.31; N, 7.81. Found: C, 66.85; H, 7.52; N, 7.89; N-ethylhydracrylamide, bp 90—95° (0.1 mmHg) (lit.[29] bp 100—106° (0.1 mmHg)), *Anal.* Calcd. for $C_5H_{11}O_2N$: C, 51.26; H, 9.47; N, 11.96. Found: C, 51.50; H, 9.42; N, 12.08; phthalide, bp 109—110° (0.4 mmHg), mp 72—73°; 2-phenylethanol, bp 108—111° (18 mmHg), n_D^{19} 1.5330; 2-phenylethanethiol, bp 109—113° (23 mmHg), n_D^{17} 1.6530.

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