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Reactions of *N,N'*-Dichlorobarbital and Related Compounds with Organic Compounds*1,*2,*3

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N,N'-Dichlorobarbital (NDCB) reacted as a highly-reactive oxidizing or chlorinating reagent with ether, aldehyde, ketone, olefin and toluene. NDCB also showed a stereospecific chlorination of *d*-camphor, giving exclusively *exo*-3-chloro-*d*-camphor, and one of chloestanone, giving 2β-chlorocholestanone in part. The reactivities of a variety of *N*-halo compounds were compared and discussed in terms of the polarographic reduction potentials of the N–halogen bond in the compounds.

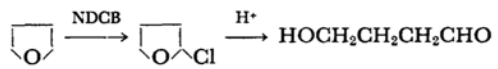
N-Halogenoimides have been known as effective halogenating or oxidizing reagents for olefins, alcohols and carbonyl compounds.[1] In the past, attention has been paid mostly to *N*-bromosuccinimide (NBS) because of its accessibility.[1] However, the usefulness of other *N*-halo compounds as reagents for organic syntheses seems to be open for further investigation.

During the course of our studies of the chemistry of barbital derivatives, we have found that *N,N'*-dichlorobarbital (NDCB) is a reactive reagent for organic compounds. NDCB has been synthesized by Ziegler *et al.* and found to be effective for the halogenation of olefins.[2] However, the other chemical properties of NDCB have not been much elucidated.

This paper will deal with the reactions of NDCB with a variety of organic compounds. A comparison of the reactivity of NDCB with those of other *N*-halo compounds will also be made in the light of the polarographic reduction potentials.

Results and Discussion

Reactions of NDCB with Organic Compounds. When NDCB was added to tetrahydrofuran at room temperature, a vigorous reaction took place. The product isolated after an acid-catalyzed hydrolysis was 3-hydroxybutyraldehyde.



A similar vigorous reaction was also observed in carbon tetrachloride at room temperature, but no reaction took place with NBS in carbon tetrachloride even at the reflux temperature.

NDCB reacted smoothly with toluene under reflux to give benzyl chloride in a high yield both in the absence of a solvent and in carbon tetrachloride. NBS did not react with toluene at all under these conditions. These results clearly demonstrate that NDCB is a reagent more reactive than NBS. The results are summarized in Table 1.

Benzaldehyde readily reacted with both NDCB and NBS to form benzoyl chloride and bromide reaspectively. The reaction of NDCB with excess butanol without a solvent afforded a mixture of *n*-butyraldehyde (47%) and *n*-butyric acid (16%), plus a trace of butyl butyrate, while the reaction in carbon tetrachloride yielded butyl butyrate as the main product, along with traces of butyraldehyde and butyric acid. With NBS, butyl butyrate was obtained as the main product irrespective of the presence or absence of carbon tetrachloride. Butyl butyrate would be obtained by the oxidation of the hemiacetal (**1**), which had been produced by the reaction of butyraldehyde and butanol, with *N*-halo compounds.

$$C_3H_7CHO + C_4H_9OH \rightarrow C_3H_7CH(OH)OC_4H_9$$

1

$$\mathbf{1} + \text{NDCB or NBS} \rightarrow C_3H_7CO_2C_4H_9$$

Butyraldehyde, when oxidized with NDCB and NBS, usually gave butyric acid in a relatively high yield. However, when NDCB was allowed to react with butyraldehyde in the absence of a solvent at room temperature, a vigorous reaction took place to give a mixture of butyric acid and a condensation product, 2-ethyl-2-hexenylaldehyde, in a molar

*1 Part XII of a series on "Reactivities of the Heterocyclic Compounds."

*2 Part XI: Y. Ueno, S. Asakawa and E. Imoto, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **89**, 101 (1968).

*3 Presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

1) For example, L. Horner and E. H. Winkelmann, "Newer Methods of Preparative Organic Chemistry," Vol. 3, ed. by W. Foerst, Academic Press, New York (1964), p. 151.

2) K. Ziegler, A. Späth, Eschaaf, W. Schumann and E. Winkelmann, *Ann.*, **551**, 80 (1942).

TABLE 1. PRODUCTS OBTAINED BY THE REACTIONS OF NDCB AND NBS WITH ORGANIC COMPOUNDS

Compound	NDCB[a]			
	No Solvent	Yield (%)	In CCl_4	Yield (%)
Tetrahydrofuran	3-Hydroxybutyraldehyde	51	3-Hydroxybutyraldehyde	21
Toluene	Benzyl chloride	72	Benzyl chloride	—
Benzaldehyde	Benzoyl chloride	96	Benzoyl chloride	76
Butanol	Butyraldehyde	47	Butyraldehyde	trace
	Butyric acid	16	Butyric acid	trace
	Butyl butyrate	trace	Butyl butyrate	29
Butyraldehyde	Butyric acid	58	Butyric acid	74
	2-Ethyl-2-hexenylaldehyde	37		

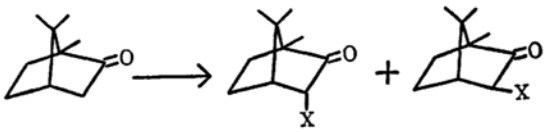
Compound	NBS[b]			
	No Solvent	Yield (%)	In CCl_4	Yield (%)
Tetrahydrofuran	———		None[c]	
Toluene	None[c]		None[c]	
Benzaldehyde	Benzoyl bromide	—	Benzoyl bromide	—
Butanol	Butyraldehyde	7	Butyraldehyde	trace
	Butyric acid	trace		
	Butyl butyrate	44	Butyl butyrate	12
Butyraldehyde	Butyric acid	65	———	

a) The yield was calculated on the basis that two chlorine atoms in NDCB were paticipated in the reaction as active halogen atoms.
b) The yield was calculated on the basis that one bromine atom in NBS was participated in the reaction.
c) The starting material was recovered.

ratio of 3 : 2. A similar condensation was also observed in cyclohexanone; it will be described later.

These results suggest that NDCB reacts in two distinct ways, depending on the reaction medium. In heterogeneous media (in non-polar solvents such as carbon tetrachloride) the reaction chiefly proceeds in homolytic fashion, causing free radical halogenation. On the other hand, in homogeneous media (in polar solvents) the reaction proceeds in heterolytic fashion, the N–Cl bond reacting in the polarized form and behaving like a Lewis acid. A tendency of this kind, though to a lesser extent, has also been observed for NBS.[1]

Stereochemistry. The stereochemistry of halogenation with NDCB was studied, taking *d*-camphor and cholestanone as substrates. *d*-Camphor has been found to be halogenated with molecular chlorine to give *endo*-3-chloro-camphor (**2**)[3] exclusively. However, when an equimolar mixture of *d*-camphor and NDCB was heated at 140°C for 40 min, *exo*-3-chlorocamphor (**3**) was obtained in a 95% yield. The similar treatment of *d*-camphor with NBS gave *endo*-3-bromocamphor in an 80% yield.



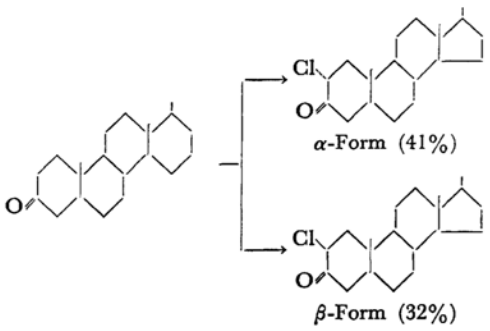
	2	**3**
NDCB	0	95%
NBS	80%	0

An abnormal stereochemistry in the halogenation with NDCB was also found for cholestanone. The literature has shown that the chlorination of cholestanone can be carried out by passing chlorine gas into the solution of the compound in carbon tetrachloride or acetic acid, affording the 2α-chloro-derivative exclusively.[4] However, when a mixture of NDCB and cholestanone was heated at 140°C for 30 min, a mixture consisting of 3 parts of 2α-chloro- and 4 parts of 2β-chloro-derivatives was obtained in a total yield of 73%.

These products were nicely separated by column chromatography on alumina, using chloroform as an eluent, and were identified by the measurement of their melting points, infrared spectra, and optical rotations, which were all in satisfactory agreement

3) S. H. Harper, "Chemistry of Carbon Compounds," Vol. II, ed. by E. H. Rodd, Elsvier Publishing Company, New York, N. Y. (1953), p. 602.

4) a) J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 3500 (1953); b) B. Ellis and V. Petrow, *J. Chem. Soc.*, **1953**, 3869.



with the literature values. Unfortunately, we can not reasonably explain the abnormal stereochemistry observed in the reaction of NDCB.

Polarographic Reduction Potentials of *N*-Halo Compounds. There have been found many *N*-halo compounds which can potentially serve as halogenating or oxidizing reagents for organic compounds. The reactivities of these *N*-halo compounds can primarily be characterized by the polarity of the *N*-halogen bonds, which in turn determines the reductivity of those bonds. The polarographic half-wave potential seems to be a good index for the reductivity.

Very few polarographic data of *N*-halo compounds have been published. Recently, however, *N*-bromosuccinimide has been polarographically investigated in detail in water by Nagai and Matsuda.[5] The polarograms obtained have shown the appearance of complicated waves due to the hydrolysis of *N*-halo compounds. For this reason, we measured the half-wave potentials for *N*-halo compounds in dimethylformamide (DMF). Figure 1 shows the

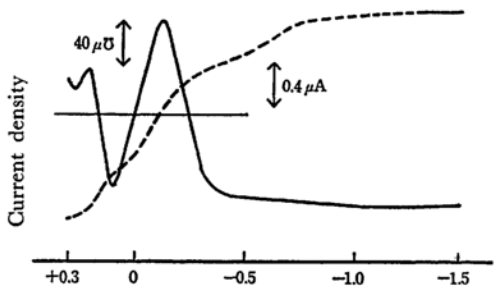
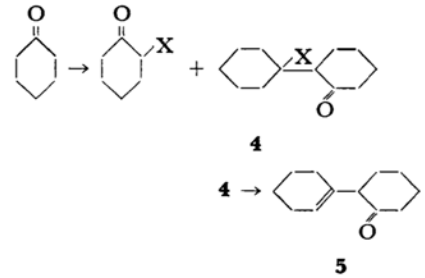


Fig. 1. Polarogram of *N,N'*-dichlorobarbital in DMF at 20°C.
—— AC Polarogram
---- DC Polarogram

polarogram for NDCB. The peaks in the AC polarogram were in accordance with the $E_{1/2}$ values obtained by DC polarography, and the shape of the polarogram was reproducible in three experiments. These results indicate that the waves are attributable to the true electrochemical reduction. Barbital itself did not show the reduction waves above −1.5 V. The wave at −0.12 V would seem, therefore, to be the result of the reduction of the N–Cl bond. Other *N*-halo compounds behaved similarly. The $E_{1/2}$ values (V) measured at 20°C were as follows: *N,N',N''*-trichloroisocynanuric acid (−0.07), NDCB (−0.12), *N*-chlorophthalimide (−0.15), *N*-chlorosuccinimide (−0.21), and NBS (−0.26). These values indicate that the polarity of *N*-halo compounds decreases in the above order.

Correlation between the Reactivities of *N*-Halo Compounds and Their $E_{1/2}$ Values. *Rractions of Cyclohexanone with N-Halo Compounds.* It is reasonable to assume that, if the more polar N–halogen bond is contained in the *N*-halo compound, a much higher yield would be expected in the condensation product, since the condensation should be a polar reaction which could sometimes be catalyzed by Lewis acid.[6] On the basis of this assumption, the reactions of cyclohexanone with several *N*-halo compounds were studied. The treatment of cyclohexanone with the *N*-halo compounds in the absence of a solvent afforded 2-halogeno-cyclohexanone and 2-(1-halogenocyclohexyl)cyclohexanone (**4**) in yields depending on the *N*-halo compounds used, as is represented in Table 2.



4

5

The structure of **4** was established as follows: **4** was converted to 2-(1-cyclohexenyl)cyclohexanone (**5**) by treatment with pyridine. The properties of **5** thus obtained were identical with those of

Table 2. Products obtained by the reactions of *N*-halo compounds with cyclohexanone

N-Halo compound	Yield of the product (%) 2-Halogeno-cyclohexanone	2-(1-Halogeno-cyclohexyl)-cyclohexanone
N,N',N''-Trichloro-isocyanuric acid	39	61
N,N'-Dichlorobarbital	50	45
N-Bromosuccinimide	75	0

* The yield was calculated on the basis that three chlorine atoms in *N,N',N''*-trichloroisocyanuric acid, two chlorine atoms in NDCB, and one bromine atom in NBS were participated in the reactions.

5) T. Nagai and T. Matsuda, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **88**, 66 (1967).

6) J. Reese, *Ber.*, **75**, 384 (1942).

5 prepared by the method described in the literature.[7]

Table 2 shows that *N,N',N''*-trichloroisocyanuric acid, which contains the most polar N–Cl bond, produced the condensation product in the highest yield. The second highest yield of the condensation product was obtained with NDCB, which has less polarity in the N–Cl bond. The weakest polar compound, NBS, did not afford the condensation product in a detectable yield.

Halogenation of Cyclohexene. The halogenation of cyclohexene with *N*-halo compounds can be a good measure of the polarity of the N–halogen bond in the compounds. The compounds which contain more polar N–halogen bond would facilitate the addition of halogen to the double bond over an allylic halogenation which proceeds through a free radical mechanism. If the *N*-halo compound contains a less polar N–halogen bond, the allylic halogenation would be favored over the addition reaction. This expectation was verified by those of our experiments shown in Table 3. The reaction of NDCB with cyclohexene afforded a mixture of 3-chlorocyclohexene, the product due to the radical substitution and 1,2-dichlorocyclohexane, the product due to the polar addition, in the molar ratio of 53 : 14. However, with the less polar *N*-halo compound, NBS, the sole product isolated was 3-bromocyclohexene, which was the product due to the free radical substitution. Thus, we may suppose that the polarity of the N–halogen bond which could be estimated by the polarographic measurement, would provide a good method for the systematization of the reactivities of *N*-halo compounds.

TABLE 3. PRODUCTS OBTAINED BY THE REACTIONS OF *N*-HALO COMPOUNDS WITH CYCLOHEXENE

Product	Yield of product (%)*		
	NDCB	NCS	NBS
3-Chlorocyclohexene	53	42	—
3,6-Dichlorocyclohexene	trace	21	—
1,2-Dichlorocyclohexane	14	4	—
3-Bromocyclohexene	—	—	68
3,6-Dibromocyclohexene	—	—	17
1,2-Dibromocyclohexane	—	—	—

* The yield was calculated on the basis that two chlorine atoms in NDCB, one chlorine atom in NCS and one bromine atom in NBS were participated in the reactions.

Experimental

All melting points are uncorrected. The infrared spectra were recorded with a Hitachi EPI-S_2 infrared spectrometer. The glc data were obtained using a Yanagimoto GCG-5 DH gas chromatograph. Microanalyses were performed with a Yanagimoto MT-1 CHN Corder. The optical rotations were measured with a Perkin-Elmer 141 Polarimeter.

Materials. *N*-Bromosuccinimide (NBS), mp 174—175°C,[1] *N*-chlorosuccinimide (NCS),[8] mp 148—149°C, *N*-chlorophthalimide, mp 183°C,[1] and *N,N',N''*-trichloroisocyanuric acid, mp 245°C (dec.),[9] were prepared by the methods described in the literature and were used after purification by recrystallization from benzene.

N,N'-Dichlorobarbital (NDCB) was prepared by passing chlorine gas into an aqueous solution of barbital at room temperature. After the chlorine had been saturated, the reaction mixture was cooled and filtered. The solid thus obtained was washed with water and recrystallized from benzene, mp 125—127°C. The yield was almost quantitative.

Found: C, 38.19; H, 3.64; N, 11.29%. Calcd for $C_8H_{10}O_3N_2Cl_2$: C, 37.97; H, 3.98; N, 11.07%

The other reagents were of a commercial grade and were used after purification by recrystallization or distillation.

Proof of Structure and Determination of Yields of Products. The reaction products were usually identified by a comparision of their infrared spectra with those of the respective authentic samples. For liquid products, the retention times in glc were compared with those of the authentic samples. For solid products, mixture-melting point examinations and microanalyses were also performed.

The yields of products were determined by glc analyses or by measurement of the weights of the products.

The glc analysis was used for toluene, tetrahydrofuran, butanol, cyclohexene, butyraldehyde and cyclohexanone.

In the cases of carbonyl compounds, they were also converted to their 2,4-dinitrophenylhydrazones and weighed.

Preparation of the Authentic Samples. Authentic samples of butyl butyrate,[10] 2-chlorocyclohexanone,[11] 2-bromocyclohexanone,[12] 3-chlorocyclohexene,[2] 3-bromocyclohexene,[2] 1,2-dichlorocyclohexane,[13] and 2-(1-cyclohexenyl)cyclohexanone[5] were prepared according to the procedures described in the literature. 2-Ethyl-2-hexenylaldehyde was kindly provided by the Kyowa Hakko Kogyo Co., Ltd.

General Procedure for Reactions with NDCB. *In the Absence of a Solvent.* To an excess organic compound (20—30 g) NDCB (5—10 g) was added at room temperature with shaking. The reaction usually proceeded smoothly and exothermally. The mixture was then warmed for 30 min, if necessary. After standing for 30 min, the mixture was cooled and then filtered to remove the precipitated barbital. The filtrate was distilled, and the distillate was subjected to analysis.

In Carbon Tetrachloride. A saturated solution of 10 g of NDCB in carbon tetrachloride was added to a solution of 10 g of an organic compound in 50 m*l* of the same

7) W. S. Rapson, *J. Chem. Soc.*, **1941**, 16.

8) E. L. Hirst and A. K. MacBeth, *ibid.*, **121**, 2174 (1922).

9) H. J. Schmidt and K. Geiersberger, German Pat. 1141641 (1962).

10) G. R. Robertson, "Organic Syntheses," Coll. Vol. 1, p. 138 (1941).

11) M. S. Newman, M. D. Farbman and H. Hipsher, "Organic Syntheses," Coll. Vol. 3, p. 188 (1955).

12) P. Z. Bedoukian, *J. Am. Chem. Soc.*, **67**, 1430 (1945).

13) S. Kharasch and H. C. Brown, *ibid.*, **61**, 3432 (1939).

solvent at room temperature. The mixture was then usually heated at reflux for 1 hr and cooled. The precipitated barbital was separated by filtration, the filtrate was concentrated to remove the solvent, and then the residue was distilled. The distillate was subjected to analysis.

General Procedure for Reactions with NBS. *In the Absence of a Solvent.* To an excess organic compound (10—15 g) NBS (2 g) was added at room temperature with shaking, and then the mixture was refluxed for several hours under nitrogen. (In the reactions with NBS, much more severe reaction conditions were required for the completion of reactions than those used for the reactions with NDCB.) After the mixture had then been cooled, succinimide was separated as a solid and removed by filtration. The filtrate was distilled, and the distillate was subjected to analysis.

In Carbon Tetrachloride. A solution of 2 g of an organic compound in 10 m*l* of carbon tetrachloride was added to a solution of 2 g of NBS in 20 m*l* of carbon tetrachloride at room temperature. After the mixture had then been refluxed for several hours and cooled, the solvent was evaporated. The residue was distilled, and the distillate was subjected to analysis. Succinimide was usually recovered from the residue as a solid.

Reactions of Camphor. *With NDCB.* A mixture of 5 g of NDCB and 5 g of *d*-camphor was heated at 140°C for 40 min and then sublimed at 80°C/5 mmHg. Sublimation gave 5.8 g (95%) of *exo*-3-chlorocamphor, mp 117—118°C; $[\alpha]_D^{20}$ +47.7° (*c* 0.52, C_2H_5OH) (lit., mp 117°C,[3] $[\alpha]_D^{20}$ +35°[3] (*c* 10, C_2H_5OH)).

Found: C, 60.39; H, 8.05%. Calcd for $C_{10}H_{15}OCl$: C, 60.77; H, 7.81%.

With NBS. A mixture of 4 g of NBS and 4 g of *d*-camphor was treated in the manner described above. The sublimation of the mixture at 60—70°C/4 mmHg afforded 4.1 g (80%) of *endo*-3-chlorocamphor, mp 75—77°C, $[\alpha]_D^{18}$ +117.0° (*c* 0.52, benzene) (lit., mp 77°C,[3] $[\alpha]_D^{18}$ +117.1°[3] (*c* 10, benzene)).

Found: C, 51.98; H, 6.54%. Calcd for $C_{10}H_{15}OBr$: C, 52.01; H, 6.46%.

Reaction of Cholestanone with NDCB. A mixture of 1 g of NDCB and 2 g of cholestanone was heated at 150°C for 30 min. The reaction mixture was then chromatographed on a column of alumina, using chloroform as an eluent. One fraction contained 700 mg (32%) of 2β-chlorocholestanone, which, after recrystallization from ethanol-water, showed a mp of 119—121°C, $[\alpha]_D^{22}$ +120.6° (*c* 0.34, $CHCl_3$) (lit., mp 120°C,[14] $[\alpha]_D^{22}$ +124°[14] (EtOH)), $\nu_{C=O}$; 1715 cm^{-1}.

Found: C, 77.32; H, 11.19%. Calcd for $C_{27}H_{45}OCl$: C, 77.00; H, 10.79%.

The other fraction contained 900 mg (41%) of 2α-chlorocholestanone, which, after recrystallization from ethanol-water, showed a mp of 174—179°C, $[\alpha]_D^{20}$ +42° (*c* 0.67, EtOH) (lit., mp 182°C, $[\alpha]_D^{20}$ +41° (EtOH)), $\nu_{C=O}$; 1730 cm^{-1}.

Found: C, 77.27; H, 10.66%. Calcd for $C_{27}H_{45}OCl$: C, 77.00; H, 10.79%.

Polarographic Measurements. The polarographic data were obtained with a Yanagimoto Model PA-102 recording polarograph, using a H-cell equipped with a Hg reference electrode. The capillary characteristics were: $m=0.544$ mg/sec, $t=3.5$ sec/drop at 60 cm. Sample solutions were prepared by dissolving *N*-halo compounds in dry DMF at a concentration of 0.1 mol/*l*. Potassium perchlorate, 0.1 mol/*l* and a few drops of a solution of polyvinyl chloride in DMF were added to the sample solutions as a supporting electrolyte and as a maximum suppressor, respectively. Measurements were made at room temperature after bubbling nitrogen into the solutions for 30 min.

Reaction of Cyclohexanone with *N,N',N''*-Trichloroisocyanuric Acid. A mixture of 3 g of *N,N',N''*-trichloroisocyanuric acid and 10 g of cyclohexanone was refluxed for 1 hr and then cooled. Cyanuric acid, which was separated as a solid, was removed by filtration. The distillation of the filtrate under reduced pressure afforded 1.42 g (39%) of 2-chlorocyclohexanone, 94—96°C/14 mmHg and 2.23 g (61%) of 2-(1-chlorocyclohexyl)cyclohexanone, 108—110°C/4 mmHg.

Conversion of 2-(1-Chlorocyclohexyl)cyclohexanone to 2-(1-Cyclohexenyl)cyclohexanone. A solution of 1 g of 2-(1-chlorocyclohexyl)cyclohexanone in 10 m*l* of pyridine was refluxed for 1 hr. After cooling, the mixture was acidified with dilute hydrochloric acid and extracted with ether. The ether was then evaporated, and the residue was distilled under reduced pressure; bp 105—108°C/3 mmHg. The product was identical with the authentic sample of 2-(1-cyclohexenyl)-cyclohexanone in every respect.

Reaction of Cyclohexene with NCS. A mixture of 1.5 g of NCS and 10 m*l* of cyclohexene was refluxed for 1 hr, and then cooled. The precipitated succinimide was removed by filtration, and the filtrate was distilled under reduced pressure. The glc analysis of the distillate showed that the distillate consisted of 3-chlorocyclohexene (42%), 3,6-dichlorocyclohexene (21%) and 1,2-dichlorocyclohexane in the yields indicated in parentheses.

The authors wish to thank Dr. J. Nakaya for his suggestions concerning the polarographic measurements.

14) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, **1954**, 4284.