[Contribution from the Department of Organic Chemistry, Radium Institute,
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HALOGENATION OF SATURATED COMPOUNDS WITH N-CHLORO- AND N-BROMO-SUCCINIMIDE

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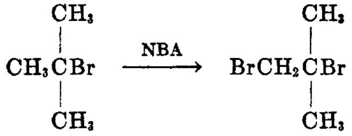
The N-halogenated amides now generally rank among the most useful tools in organic chemistry for the halogenation of ethylene compounds in the allylic position (1) and of aromatic and heterocyclic compounds in either the nuclei or the side chains (2). We have recently pointed out that this method of indirect substitution can successfully be extended to saturated compounds (3), and this opens up a new field in the use of N-halogenated amides.

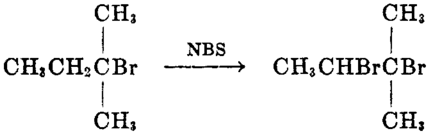
As early as 1919 Wohl (4) found that N-bromoacetamide reacted upon *tert*-butyl bromide in ether to give 1,2-dibromoisobutane (I):



$$\mathrm{CH_3}\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{Br} \xrightarrow{\mathrm{NBA}} \mathrm{BrCH_2}\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{Br}$$

I

This unusual type of halogenation, which we found also to occur with N-bromosuccinimide in carbon tetrachloride and in the presence of benzoyl peroxide, gave but little 1,2-dibromoisobutane, but when methylene groups were present in the molecule, the halogenation was effected more easily. Thus *tert*-amyl bromide gave 2,3-dibromo-2-methylbutane (II) in acceptable yield:



$$\mathrm{CH_3CH_2}\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{Br} \xrightarrow{\mathrm{NBS}} \mathrm{CH_3CHBr}\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{Br}$$

II

In the alicyclic series, halogenation with N-chloro- or N-bromo-succinimide proceeded noticeably more smoothly, and a 42% yield of cyclohexyl chloride could be prepared from cyclohexane and N-chlorosuccinimide after 12 hours' refluxing; cyclohexyl bromide was likewise obtained from N-bromosuccinimide, although this latter reagent proved less convenient because of slight decomposition on prolonged heating. Technical decalin was similarly converted to chloro- and bromo-decalin, which were probably mixtures of several isomeric products.

The proposed method of halogenation, aside from its interest in theoretical organic chemistry, has also some practical value, as for instance in the preparation of cycloheptyl chloride or bromide, which now becomes a more direct process than methods hitherto employed (5).

Another useful application is the halogenation of esters of saturated aliphatic acids. Although ethyl acetate gave only traces of substitution products, it was possible to effect halogenation when methylene groups were present; thus, ethyl propionate gave sizable amounts of ethyl α-chloro- and α-bromo-propionate, and methyl laurate yielded a mixture of methyl α-chlorolaurate and an ethyl dichlorolaurate of undetermined constitution. Esters of aliphatic diacids also underwent substitution; ethyl malonate readily yielded with N-chlorosuccinimide a mixture of ethyl chloromalonate and ethyl dichloromalonate; methyl adipate was smoothly converted to methyl α-chloroadipate and a methyl dichloroadipate of undetermined constitution. Under the same conditions, N-bromosuccinimide gave the corresponding bromo compounds. It should be mentioned that a similar reaction was described in a Ciba patent (6) concerning the bromination of steroids in the position α to an ester group. Simple aliphatic ketones were found to be highly susceptible to this method of indirect halogenation; 2-heptanone, for instance, gave with N-chlorosuccinimide a 60% yield of a monochloro derivative, along with large quantities of a dichlorinated product. Several instances of bromination of cyclic ketones with N-bromosuccinimide have already been reported in the literature (7), but aliphatic compounds have only occasionally been studied (8), and N-chlorosuccinimide has not been used in this field.

These successful chlorinations are of particular interest in view of the manifold synthetic uses of chloro compounds, and of the inconveniences attached to the handling of other chlorinating agents such as the free halogen or sulfuryl chloride. The present research is being extended to the halogenation of saturated terpenes and petroleum products.

EXPERIMENTAL

Halogenation of cyclohexane. (*a*) *With N-chlorosuccinimide.* A mixture of 18 g. (0.2 mole) of redistilled cyclohexane, 13.4 g. (0.1 mole) of N-chlorosuccinimide, and 30 ml. of carbon tetrachloride was refluxed for 12 hours with 0.5 g. of benzoyl peroxide. After cooling, the reaction product was filtered from the succinimide, washed with an aqueous solution of sodium carbonate, then with water, and dried over sodium sulfate. Fractional distillation yielded 5.5 g. (42%) of cyclohexyl chloride, b.p. 142°, n_D^{20} 1.4630.

Anal. Calc'd for $C_6H_{11}Cl$: Cl, 29.9. Found: Cl, 30.2.

(*b*) *With N-bromosuccinimide.* A similar reaction, performed with 17.8 g. (0.1 mole) of N-bromosuccinimide, gave 5 g. (about 30% yield) of cyclohexyl bromide, b.p. 52°/13 mm., n_D^{25} 1.4915.

Anal. Calc'd for $C_6H_{11}Br$: Br, 49.1. Found: Br, 49.4.

A slight decomposition was noted during the last stages of the reaction.

Chlorination of cycloheptane. Cycloheptane, b.p. 118–120°, was best prepared from suberone by the Kishner-Wolff reaction; halogenation, performed as above, gave 4 g. (30%) of cycloheptyl chloride, b.p. 172–173°; lit. (5) b.p. 174°.

Anal. Calc'd for $C_7H_{13}Cl$: Cl, 26.7. Found: Cl, 26.9.

Halogenation of decalin. (*a*) *With N-chlorosuccinimide.* Redistilled technical decalin (a mixture of isomers) (28 g.), 13.3 g. of N-chlorosuccinimide, 0.5 g. of benzoyl peroxide, and 30 ml. of carbon tetrachloride were refluxed for six hours, and the reaction product was worked up in the usual way. Vacuum-fractionation gave 8.2 g. (48%) of *monochlorodecalin*, probably a mixture of several isomers, b.p. 123–124°/20 mm.; lit. (9), b.p. 121–122°/18 mm.

Anal. Calc'd for $C_{10}H_{17}Cl$: Cl, 20.6. Found: Cl, 20.3 and some *dichlorodecalin* (0.5 g.), b.p. 144–146°/20 mm., which could not be purified further.

Anal. Calc'd for $C_{10}H_{16}Cl_2$: Cl, 34.3. Found: Cl, 33.9.

(*b*) *With N-bromosuccinimide.* The reaction was more rapid, but at the expense of some decomposition. After six hours' refluxing, 13.2 g. (42%) of *bromodecalin* was obtained, b.p. 90–92°/16 mm. (10); this product was evidently a mixture of several isomers.

Anal. Calc'd for $C_{10}H_{17}Br$: Br, 36.9. Found: Br, 37.3.

Bromination of tert-amyl bromide. Bromination of *tert*-butyl bromide with N-bromosuccinimide in the usual way proceeded far less satifactorily than with N-bromoacetamide in ether, and sizable amounts of 1,2-dibromoisobutane were obtained only when no solvent was present; in the case of *tert*-amyl bromide, carbon tetrachloride was used, and *2, 3-dibromo-2-methylbutane* was obtained in 20% yield, b.p. 170–172°, n_D^{20} 1.5102 (11). This compound was further identified by conversion into methyl isopropyl ketone (semicarbazone m.p. 113°) in agreement with the literature (12).

Chlorination of methyl laurate. A mixture of 46 g. (0.2 mole) of methyl laurate (n_D^{22} 1.4380), 13.3 g. of N-chlorosuccinimide, 0.5 g. of benzoyl peroxide, and 30 ml. of carbon tetrachloride was refluxed for 12 hours; the reaction product, worked up in the usual way, gave on vacuum-fractionation 10 g. (40%) of *methyl α-chlorolaurate*, b.p. 178–180°/19 mm., n_D^{22} 1.4515; the α-position of the chlorine atom was shown by alkaline hydrolysis to α-hydroxylauric acid, m.p. 74–75° (13).

Anal. Calc'd for $C_{13}H_{25}ClO_2$: C, 62.8; H, 10.1.
Found: C, 63.0; H, 10.4.

The higher-boiling fraction consisted of 4 g. of a *methyl dichlorolaurate*, b.p. 199–201°/20 mm., n_D^{27} 1.4630.

Anal. Calc'd for $C_{13}H_{24}Cl_2O_2$: Cl, 25.1. Found: Cl, 25.5.

Halogenation of ethyl propionate. Halogenation of ethyl propionate, similarly performed with N-chloro- and N-bromo-succinimide, gave *ethyl α-chloropropionate*, b.p. 146–147°, n_D^{20} 1.4182 (40% yield; further characterized by the corresponding *amide*, m.p. 80–81°), and *ethyl α-bromopropionate*, b.p. 158–160°, n_D^{20} 1.4460 (42% yield).

Halogenation of methyl adipate. (*a*) *With N-chlorosuccinimide.* A mixture of 35 g. (0.2 mole) of redistilled methyl adipate ($n_D^{22.5}$ 1.4340), 13.3 g. of N-chlorosuccinimide, 0.5 g. of benzoyl peroxide, and 30 ml. of carbon tetrachloride, refluxed for 12 hours, yielded 8 g. (38%) of *methyl α-chloroadipate*, b.p. 130–131°/15 mm., n_D^{21} 1.4420. The constitution of this product was ascertained by hydrolysis with a 10% solution of sodium hydroxide in methanol at room temperature to *α-hydroxyadipic acid*, which crystallized as shiny colorless prisms, m.p. 150–151°, from benzene; hydrolysis under more drastic conditions (by refluxing with a solution of potassium hydroxide in ethanol) resulted in much Δ^{α}-dihydromuconic acid, crystallizing as shiny needles, m.p. 169°, from ether (14).

The higher-boiling fraction yielded 3 g. of *methyl α-dichloroadipate*, b.p. 144–145°/15 mm., n_D^{21} 1.4558, of undetermined constitution.

Anal. Calc'd for $C_8H_{12}Cl_2O_4$: Cl, 29.2. Found: Cl, 28.9.

(*b*) *With N-bromosuccinimide. Methyl α-bromoadipate*, b.p. 146–148°/20 mm., (7.5 g., 30%), resulted; its constitution was established by conversion into the same α-hydroxyadipic acid, m.p. 150–151°, and Δ^{α}-dihydromuconic acid, m.p. 169°.

Chlorination of ethyl malonate. A mixture of 32 g. of ethyl malonate (n_D^{19} 1.4226), 13 g. of N-chlorosuccinimide, and 50 ml. of carbon tetrachloride was refluxed with 0.5 g. of benzoyl peroxide as above. Yield: 15 g. of *ethyl chloromalonate*, b.p. 115–116°/14 mm., n_D^{24} 1.4375, further characterized by the corresponding *amide* m.p. 172–173°, and 3 g. of *ethyl dichloromalonate*, b.p. 130–132°/15 mm., n_D^{24} 1.4554 (15).

Chlorination of 2-heptanone. A mixture of 23 g. of redistilled heptanone (n_D^{27} 1.4132), 13.3 g. of N-chlorosuccinimide, 0.5 g. of benzoyl peroxide, and 30 ml. of carbon tetrachloride was refluxed for six hours. The usual treatment gave a 60% yield of *x-chloro-2-heptanone*, b.p. 169–170°, n_D^{27} 1.4268; this compound was probably a mixture of isomers.

Anal. Calc'd for $C_7H_{13}ClO$: C, 56.6; H, 8.8.
Found: C, 56.7; H, 9.0.

The higher-boiling fraction gave 3 g. of *x,x'-dichloro-2-heptanone*, b.p. 192–194°, n_D^{27} 1.4449.

Anal. Calc'd for $C_7H_{12}Cl_2O$: C, 45.9; H, 6.6.
Found: C, 46.2; H, 6.4.

SUMMARY

1. N-Chloro- and N-bromo-succinimide are shown to be suitable agents for the halogenation of saturated compounds.

2. As in the case of halogenation of allylic or aromatic compounds, methylene groups are more readily attacked than methyl groups.

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