541. *The Relative Stabilising Influences of Substituents on Free Alkyl Radicals. Part V.*[1] *Selective Bromination by* N-*Bromosuccinimide.*

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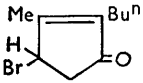
It has been established that in bromination by *N*-bromosuccinimide, a phenyl group has a greater stabilising effect than a benzoyl or a carboxyl group on the intermediate free radical.

Wohl–Ziegler bromination of unsaturated substances is highly specific, occurring invariably on the carbon atoms adjacent to the unsaturated centres. This follows from the mechanism of the reaction,[2] in which the radical intermediate involved is stabilised by resonance by the unsaturated group. In a substance $X\cdot CH_2\cdot CH_2\cdot Y$, therefore, in which both X and Y are unsaturated substituents, both methylene groups would be open to attack and, provided steric complications are absent, bromination would proceed by the route involving the radical intermediate of greater stability. Selective bromination therefore provides a means by which such stabilising effects can be compared. To this end we have studied the bromination, under catalysis by light or benzoyl peroxide, of nine substances of the general structure $X\cdot CH_2\cdot[CH_2]_n\cdot CH_2\cdot Y$ (n = 0 or 2), in which X and Y are phenyl, acetyl, ethoxycarbonyl, carboxyl, or benzoyl.

Few of the many published results[3] are useful for our purpose. Buu-Hoï[4] reports that bromination of 6-methylhept-5-en-2-one gives the α-bromo-ketone but quotes no yields. For a decisive evaluation of the relative stabilising effects of the substituents a yield of 50% or higher of the bromo-compound is necessary; but on the assumption that the main product isolated indicates the main course of the reaction, it can be inferred that the carbonyl group stabilises the intermediate alkyl radical more than the olefinic double bond does. Gensler *et al.*,[5] in a synthesis of elaidic acid, brominated methyl undec-10-enoate and obtained a mixture of the 9- and the 11-bromo-ester, for which the intermediate would be the mesomeric radical, $CH_2\dot{:}CH\cdot\dot{C}H\cdot[CH_2]_7\cdot CO_2Me$. However, since the total yield did not exceed 42%, no conclusion could be drawn regarding the stabilising influences of the olefinic double bond and the ester group. Dihydrocinerone, on bromination, gave the product (I);[6] here, although a direct comparison cannot be made of the carbonyl group and the olefinic double bond because they are in conjugation, the position of bromination is not surprising considering the presence in the radical intermediate involved of the extended conjugated system O=C–C=C–C· which is not found in the alternative radical (C=C–CO–C·). This situation finds some analogy in the benzoyl and the phenyl group (Ph > Ph·CO) (see below).



(I)

The present work involved selective bromination of (*a*) β-phenylpropionic acid, (*b*) its ethyl ester, (*c*) 4-phenylbutan-2-one, (*d*) 6-phenylhexan-2-one, (*e*) lævulic acid, (*f*) 6-oxoheptanoic acid, (*g*) 6-oxo-6-phenylhexanoic acid, (*h*) ethyl 6-oxo-6-phenylhexanoate, and (*i*) 4-benzoyl-1-phenylbutane. Of these, only (*a*) and (*i*) afforded unambiguous indications of the relative stabilising influences of the substituents compared, namely, Ph > CO_2H or Ph·CO. In the other cases the bromo-compound could not be isolated, or was obtained in less than 50% yields, while in (*e*) and (*f*) no product was isolated.

Bromination of β-phenylpropionic acid proceeded smoothly to give the β-bromo-acid

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[1] Part IV, Huang and Singh, *J.*, 1958, 891.

[2] Bloomfield, *J.*, 1944, 114; Ford, *J.*, 1955, 2529.

[3] See Djerassi, *Chem. Rev.*, 1948, **43**, 271; Waugh, "*N*-Bromosuccinimide, Its Reactions and Uses," Arapahoe Chemicals, Inc., Boulder, Col., U.S.A., 1951.

[4] Buu-Hoï, *Experientia*, 1946, **2**, 310.

[5] Gensler, Behrman, and Thomas, *J. Amer. Chem. Soc.*, 1951, **73**, 1071.

[6] Soloway and LaForge, *ibid.*, 1947, **69**, 979.

in 58% yield (both the α- and the β-bromo-acids have previously been reported). The intermediate radical $Ph\cdot\dot{C}H\cdot CH_2\cdot CO_2H$ was clearly involved, so the phenyl group has more stabilising effect than a carboxyl group.

Bromination of ethyl β-phenylpropionate also took place readily, but the resulting bromo-ester could not be isolated. An attempt to convert it into the bromo-acid by treatment with an excess of acetic acid in the presence of hydrogen bromide gave cinnamic acid.

6-Oxo-6-phenylhexanoic acid gave a bromo-acid (48% yield) which is considered to be the 5-bromo-acid, on the following evidence. With boiling pyridine or dimethylaniline, or with potassium acetate in hot acetic acid it gave, not an unsaturated acid, but a hydroxy-acid (42—57%) which was oxidised by potassium permanganate to succinic and benzoic acid, both in yields of over 50%. Although the α-hydroxy-acid would afford these products, so would the δ-hydroxy-acid (by analogy with the permanganate oxidation of 3-hydroxytridecan-2-one to decanoic, and not undecanoic, acid [7]). Conversion of the bromo-acid by pyridine and dimethylaniline into a hydroxy-acid could be explained by the intermediate formation of a δ-lactone (formed by nucleophilic attack of the carboxylate ion) although this would not be possible with the α-hydroxy-acid. This, together with the observation that the hydroxy-acid reacted with periodic acid, favours the δ-bromo-acid structure for the bromination product.

The bromination product of ethyl 6-oxo-6-phenylhexanoate could not be isolated, and hydrolysis by a variety of reagents gave only small quantities of the hydroxy-acid obtained as above.

4-Benzoyl-1-phenylbutane reacted with *N*-bromosuccinimide readily on irradiation, giving high yields (66%) of the δ-bromo-ketone $Ph\cdot CO\cdot[CH_3]_3\cdot CHBrPh$, whose constitution was ascertained by hydrolysis with aqueous potassium hydroxide to the hydroxy-ketone $Ph\cdot CO\cdot[CH_2]_3\cdot CHPh\cdot OH$, which on Oppenauer oxidation afforded the known 1 : 5-diketone. That the bromo-derivative was not the alternative α-bromo-ketone was further substantiated by its failure to form an aminothiazole derivative with thiourea,[7] and by the inertness of the derived hydroxy-ketone towards periodic acid. The course of bromination is therefore without doubt, and indicates that the phenyl group has greater stabilising capacity than the benzoyl group.

Among the unsuccessful studies, lævulic acid decomposed *N*-bromosuccinimide in chloroform or benzene (the acid being insoluble in carbon tetrachloride) under a variety of conditions. 6-Oxoheptanoic acid behaved similarly, though to a smaller extent. 4-Phenylbutan-2-one gave a highly unstable product, while 6-phenylhexan-2-one afforded a liquid which on degradation by the established methods gave a mixture from which no information concerning the structure of the bromo-compound could be obtained.

EXPERIMENTAL

Unless otherwise stated, bromination was carried out in " AnalaR " carbon tetrachloride in an atmosphere of nitrogen, with illumination by a 100 w incandescent lamp. *N*-Bromosuccinimide was crystallised quickly from hot water, and thoroughly dried before use. Microanalyses were by Dr. W. Zimmermann of Melbourne.

β-Phenylpropionic Acid.[8]—This acid (3·1 g., 0·021 mole) and *N*-bromosuccinimide (2·86 g., 0·016 mole) gave the β-bromo-acid, m. p. 141—142° (2·1 g.). Fittig and Binder [9a] report m. p. 137° for the β-bromo-acid and Senter and Martin [9b] record m. p. 52° for the α-bromo-acid.

Ethyl β-Phenylpropionate.—The ester (n_D^{24} 1·4927; 6·23 g., 0·035 mole) and *N*-bromosuccinimide (4·9 g., 0·028 mole) were irradiated in carbon tetrachloride (25 c.c.) for 35 min. A pale yellow solution resulted. Succinimide (m. p. 126—127°; 2·7 g., 0·028 mole) was filtered off, and the filtrate concentrated under reduced pressure at <50°. The residue was kept in a mixture of glacial acetic acid (35 c.c.) and hydrobromic acid (*d* 1·7; 13 c.c.) at 28° for 5 days.

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[7] Cf. Huang, *J.*, 1957, 2528.

[8] Huang, *J.*, 1957, 1342.

[9] (*a*) Fittig and Binder, *Annalen*, 1879, **195**, 132; (*b*) Senter and Martin, *J.*, 1917, 447.

After the second day the ethyl acetate produced was removed at 50—60° under partial vacuum. On addition of water and chilling cinnamic acid separated (3·8 g., 93% yield), having m. p. and mixed m. p. 131—134° after recrystallisation from chloroform–carbon tetrachloride (mixed with β-bromo-β-phenylpropionic acid it melted at 110—121°).

6-Oxo-6-phenylhexanoic Acid.—This acid [10] (m. p. 77—79°; 5·4 g., 0·026 mole) and *N*-bromosuccinimide (4·0 g., 0·022 mole) in carbon tetrachloride (50 c.c.), were irradiated for 1·75 hr., some bromine and hydrogen bromide being evolved. On cooling, the succinimide was filtered off (1·8 g., 0·018 mole). The filtrate was taken up in much ether, washed twice with water (to remove traces of succinimide), once with aqueous sodium hydrogen sulphite, and dried, and the solution was concentrated. On addition of light petroleum (b. p. 40—60°), *5-bromo-6-oxo-6-phenylhexanoic acid* separated (5·6 g., 89%), having m. p. 107—109° (2·95 g., 48%) after recrystallisation from benzene–*cyclo*hexane (Found: C, 50·8, 50·3; H, 4·6, 4·6; Br, 28·4. $C_{12}H_{13}O_3Br$ requires C, 50·55; H, 4·6; Br, 28·0%). Other bromination experiments included: (*a*) use of a higher molar proportion of the bromo-imide, which gave a somewhat lower yield; (*b*) illumination for 1 hr., which resulted in incomplete reaction; (*c*) catalysis by benzoyl peroxide (without irradiation) which caused deterioration of the yield and purity of the product; and (*d*) use of chloroform as solvent, which appeared to bring about much more decomposition of the reagent (evolution of hydrogen bromide and bromine).

The bromo-acid (0·3 g.) was boiled with pyridine (5 c.c.) for 21 hr., then poured on ice and hydrochloric acid, and the product isolated by ether-extraction, giving *5-hydroxy-6-oxo-6-phenylhexanoic acid*, m. p. 107—110° (0·1 g., 50%); it had m. p. 125—127° after recrystallisation from ethanol–benzene, from which it separated in needles (Found: C, 64·7; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). Alternatively, the bromo-acid (1 g.) was boiled with dimethylaniline (15 c.c.) for 40 min. in nitrogen, to give the same hydroxy-acid (0·4 g., 59% yield); and when the bromo-acid (2·8 g.) and potassium acetate (3·4 g.) were heated in acetic acid (20 c.c.) at 100° for 4 hr., then boiled gently for 0·5 hr., working up gave the above hydroxy-acid, m. p. and mixed m. p. 124—126° (47%) (Found: C, 65·2; H, 6·25%).

The hydroxy-acid (0·13 g.) in acetone (5 c.c.) was treated during 1·5 hr. with potassium permanganate (0·5 g.) and magnesium sulphate (0·06 g.) in water–acetone in 4 portions. After 0·5 hour's refluxing, 10% aqueous sodium carbonate (10 c.c.) was added, and the manganese dioxide filtered off. The filtrate was heated to remove acetone, then washed once with ether, acidified with 5N-sulphuric acid and extracted 4 times with light petroleum. The aqueous layer was then continuously extracted (24 hr.) with ether. Both extracts were dried and concentrated. Benzoic acid separated from the petroleum extract (m. p. and mixed m. p. 120—123°; 30 mg., 50%), and succinic acid (m. p. and mixed m. p. 183—185°; 33 mg., 53%) was obtained from the ethereal extract.

4-Benzoyl-1-phenylbutane.—Cinnamylideneacetophenone (m. p. 102—104°, prepared in 88% yield from acetophenone and cinnamaldehyde by the method described for benzylideneacetophenone [11]) was hydrogenated in ethyl acetate over Raney nickel to give 4-benzoyl-1-phenylbutane, m. p. 45—47° (87% yield) after recrystallisation from methanol (lit.,[12] m. p. 47°). This ketone (3·5 g., 0·015 mole) and *N*-bromosuccinimide (2·1 g., 0·012 mole) in carbon tetrachloride (15 c.c.) after illumination for 0·75 hr. and removal of succinimide (1·1 g., 0·011 mole), gave *4-benzoyl-1-bromo-1-phenylbutane*, needles (from *cyclo*hexane), m. p. 109—111° (2·2 g., 59%) raised to m. p. 112—114° (needles) on further recrystallisation from the same solvent (Found: C, 64·7; H, 5·3; Br, 25·4. $C_{17}H_{17}OBr$ requires C, 64·3; H, 5·4; Br, 25·2%). Irradiation for 2 hr. gave 66% of a product of m. p. 111—113°.

This bromo-ketone (0·95 g.) in dioxan (10 c.c.) was boiled with 5% aqueous potassium hydroxide (25 c.c.) for 1·5 hr. The organic product was taken up in ether, washed with much water, dried, and concentrated, to give *4-benzoyl-1-phenylbutan-1-ol*, m. p. 77—78° (0·4 g., 53%) raised to m. p. 79—80° after recrystallisation from *cyclo*hexane from which the alcohol separated as needles (Found: C, 79·8; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). Treatment of the bromo-ketone with boiling pyridine or dimethylaniline in the usual way gave intractable oils.

The above hydroxy-ketone (1·25 g.) in *cyclo*hexanone (30 c.c.; freshly distilled) was refluxed with aluminium *iso*propoxide (3 g.) in toluene (150 c.c.) for 1·25 hr. The *cyclo*hexanone was

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[10] Fieser and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1948, **70**, 3352.

[11] *Org. Synth.*, Coll. Vol. I, 1st edn., p. 71; cf. Scholtz, *Ber.*, 1895, **28**, 1730.

[12] Borsche and Wolleman, *Ber.*, 1912 **45**, 3721.

steam-distilled, and the aqueous residue extracted with ether (*ca.* 200 c.c.), washed twice with 2N-sulphuric acid and once with water, dried, and concentrated, giving 1 : 3-dibenzoylpropane, m. p. 58—62° (1·1 g., 92%). Recrystallisation from methanol gave laminae, m. p. 67—68° (0·8 g., 67%) (Found: C, 80·45; H, 6·5. Calc. for $C_{17}H_{16}O_2$: C, 80·95; H, 6·35%). Japp and Michie [13] report m. p. 67·5°. The dioxime, recrystallised from methanol, melted at 162—163°. A faster rate of heating gave m. p. 156—158° (Found: C, 72·5; H, 6·4; N, 9·5. Calc. for $C_{17}H_{18}O_2N_2$: C, 72·35; H, 6·4; N, 9·9%). Milone and Venturillo [14] report m. p. 165—166°.

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[13] Japp and Michie, *J.*, 1901, **79**, 1023.
[14] Milone and Venturillo, *Gazzetta*, 1936, **66**, 808.