View Online

914. *Free-radical Substitution in Aliphatic Compounds. Part VII.*[1] *The Halogenation of Derivatives of n-Valeric Acid.*

By Hari Singh and J. M. Tedder.

The chlorination and bromination of n-valeryl fluoride and chloride and methyl valerate have been studied in the gas phase using a static system. The acyl group deactivates halogenation at adjacent methylene groups, but less at the α-position than would be expected on purely polar grounds. The present results clear up a number of controversies created by previous qualitative work and are shown to be in excellent accord with existing theory.

Early work on the halogenation of carboxylic acids and their derivatives was complicated by simultaneous ionic and radical reactions. The Hell–Volhard–Zelinsky reaction represents the isolation of the ionic path and yields exclusively the α-halogeno derivative. Michael and Garner appear to have been the first to report that chlorination promoted by light yields all possible isomers with the α-isomer in the smallest amount.[2] Much later Kharash and Brown pointed out that there are homolytic and heterolytic reactions which yielded different products.[3] Since then the atomic chlorination of aliphatic acyl chlorides has been studied by Bruylants and his co-workers,[4] by Den Hertog and his co-workers,[5] and by Brown and Ash.[6] This work produced further controversy. The chlorinations were carried out in the gas phase, in the liquid phase, and in the liquid phase using sulphuryl chloride. The great difficulty encountered by all three groups of workers was the accurate separation and estimation of the products. Faulty separation led Bruylants to believe that the rate of chlorination at the β-position was abnormally high, and in order to account for this he proposed a cyclic transition state. However, neither Brown and Ash, nor Den Hertog, De Vries, and Van Bragt observed particularly rapid attack at the β-position of propionic or butyric acids and in subsequent work Bruylants to some extent retracts his original ideas.[7] By far the most satisfactory study is reported in a second Paper by Den Hertog.[8] He solved the problem of isolating a number of high boiling, thermo-labile products by converting the acid chlorides into esters and separating the esters by counter-current distribution. According to these results the chloro-acyl group deactivates not only the α-position but to a lesser extent the β-position and even the γ-position very slightly.

In view of the contradictory nature of this previous work, re-investigation using the more refined techniques of analysis and identification now available is clearly desirable. Even the one point on which the previous workers agree, *i.e.*, the very low reactivity of the α-position, is, as Walling points out,[9] not readily in accord with expectation and could

[1] Part VI, Clark and Tedder, *J. Phys. Chem.*, 1964, **68**, 2018.
[2] Michael and Garner, *Ber.*, 1901, **34**, 4047.
[3] Kharasch and Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 925.
[4] Bruylants, Tits, and Dauby, *Bull. Soc. chim. belges*, 1949, **58**, 310; Bruylants, Tits, Dieu, and Gauthier, *ibid.*, 1952, **61**, 366.
[5] Den Hertog, De Vries, and Van Bragt, *Rec. Trav. chim.*, 1955, **74**, 1561.
[6] Brown and Ash, *J. Amer. Chem. Soc.*, 1955, **77**, 4019.
[7] Magritte and Bruylants, *Bull. Soc. chim. belges*, 1957, **66**, 367.
[8] Den Hertog and Smit, *Rec. Trav. chim.*, 1958, **77**, 73; *Proc. Chem. Soc.*, 1959, 132.
[9] Walling, "Free Radicals in Solution," John Wiley & Sons, New York, 1957, p. 363.

View Online

do with fresh appraisal. The present work is intended to be very much more quantitative than the previous studies, and n-valeryl derivatives were chosen because they could be regarded as n-butane substituted in the 1-position and be compared with previous studies in this series. n-Valeryl fluoride and methyl valerate were chlorinated in addition to valeryl chloride so that some measure of the relative directing influence of the carbonyl group could be assessed. Finally bromination was also studied because previous work has shown how much more information can be obtained if both forms of halogenation are studied simultaneously. There are very little previous data on atomic bromination of derivatives of carboxylic acids.

Experimental

The chlorinations and bromination were carried out in a conventional vacuum line. The reaction vessel was made of Pyrex glass. The reactants were carefully degassed and the reaction vessel was filled with the halogen and the valeryl derivative at known pressures. The reaction vessel was surrounded with a heated bath (water or liquid paraffin) and then irradiated with light from two 150 watt lamps. At the end of the run the reaction products were condensed into a small trap from which samples could be taken for injection into the chromatography apparatus. Analysis was carried out on a Griffin and George D6 apparatus employing a density balance as detector. Identification of the products was achieved by the addition of compounds of known structure and by analogy. The first method required the unambiguous synthesis of the halogeno-compound; a very small trace of this compound added to the reaction products and by running a new chromatograph it was possible to see which peak had been enlarged. In all cases the 2-halogeno derivative was eluted first and the 5-halogeno derivative eluted last. It was also established that methyl 3-chlorovalerate was eluted before the 4-chloro-isomer. It was assumed that the 3- and 4-bromo derivatives were likewise eluted in this order.

Reactants.—n-Valeryl chloride was prepared from commercial valeric acid by treatment with thionyl chloride, and had b. p. 127°, n_D^{20} 1·420. n-Valeryl fluoride was prepared from the chloride by treatment with anhydrous potassium fluoride and had b. p. 92°.

Preparation of Authentic Halogeno-esters for Identification.—Chloromethyl n-valerate was prepared from paraformaldehyde and n-valeryl chloride with a trace of zinc chloride, according to the directions of Ulich and Adams (b. p. 165—166°).[10] Methyl 5-chlorovalerate was prepared by the sequence 1-bromo-4-chlorobutane ⟶ 5-chlorovaleronitrile ⟶ methyl ester (b. p. 77°/10 mm.).[11] Bromomethyl n-valerate was prepared from paraformaldehyde and n-valeryl bromide as above. Methyl 2-bromovalerate was prepared by treating n-valeryl chloride (30 g.) with bromine (40 g.) in the presence of phosphorus trichloride (0·5 c.c.) and converting the 2-bromovaleryl chloride so formed directly into the desired ester by addition of anhydrous methanol (b. p. 46—48°/1·5 mm.). Methyl 5-bromovalerate was synthesised by the sequence: adipic acid ⟶ methyl hydrogen adipate ⟶ silver salt of methyl hydrogen adipate ⟶ methyl 5-bromovalerate (b. p. 75—80°/4 mm.).[12]

Chlorination of n-Valeryl Chloride.—A mixture of n-valeryl chloride (10 parts) and chlorine (1 part) at a total pressure of approximately 22 mm. was illuminated for 2 hr. by two 150 watt tungsten lamps. The reaction vessel was surrounded by a bath of purified liquid paraffin heated to the required temperature. The results are expressed as relative selectivities:

Temp.	No. of runs	ClOC–CH_2	——CH_2——	——CH_2——	——CH_3
55—60°	10	0·16 ± 0·01	2·08 ± 0·10	3·96 ± 0·10	1
130	10	0·18 ± 0·01	1·99 ± 0·10	4·06 ± 0·10	1

At the end of the reaction the entire contents of the reaction vessel were condensed into a trap containing a slight excess of anhydrous methanol. The trap was allowed to warm up to room temperature and the resultant mixture of methyl valerate and methyl chlorovalerates was

[10] Ulich and Adams, *J. Amer. Chem. Soc.*, 1921, **43**, 660.
[11] Allen and Wilson, *Org. Synth.*, Coll. Vol. III, 578.
[12] Guest, *J. Amer. Chem. Soc.*, 1947, **69**, 300.

View Online

analysed on a column packed with 10% silicone on " Celite." Besides unchanged methanol and methyl valerate there were four chloro-ester peaks on the chromatogram. The reasonable supposition was that these would be eluted in order of their boiling points, *i.e.*, 2-chloro-, 3-chloro-, 4-chloro- and 5-chloro-, respectively. This supposition was confirmed by the individual addition of the 2-, 3-, and 5-chloro-esters.

Chlorination of n-Valeryl Fluoride.—A mixture of n-valeryl fluoride (10 parts) and chlorine (1 part) at a total pressure of approximately 22 mm. was illuminated for 2 hr. by two 150 watt tungsten lamps. The results are expressed as relative selectivities:

Temp.	No. of runs	FOC–CH_2	CH_2	CH_2	CH_3
65—70°	8	0·08 ± 0·01	1·57 ± 0·08	4·20 ± 0·12	1
100—102	8	0·10 ± 0·01	1·46 ± 0·04	3·85 ± 0·12	1
130	10	0·12 ± 0·01	1·70 ± 0·05	4·22 ± 0·08	1
160	8	0·08 ± 0·01	1·24 ± 0·03	3·53 ± 0·13	1

The products were isolated exactly as for n-valeryl chloride; thus the compounds being analysed were identical with those in the previous experiment and no additional identification was necessary.

Chlorination of Methyl n-Valerate.—A mixture of methyl n-valerate (10 parts) and chlorine (1 part) at a total pressure of approximately 28 mm. was illuminated for 2 hr. by two 150 watt tungsten lamps. The results are expressed as relative selectivities:

Temp.	No. of runs	CH_3–O–OC–CH_2	CH_2	CH_2	CH_2	CH_3
55—60°	7	0·07 ± 0·01	0·43 ± 0·07	2·42 ± 0·11	3·56 ± 0·14	1
100—104	8	0·09 ± 0·01	0·42 ± 0·02	2·36 ± 0·09	3·37 ± 0·08	1

The analysis was carried out as before except that no methanol was added. Thus the four methyl chlorovalerate peaks on the chromatograms were the same as before. When the same silicone column was used only four product peaks were obtained, but the peak which corresponded to the 3-chloro-ester was larger than expected (RS^3_5 = 3·07 instead of about 2·5 as expected). By changing the solvent on the column to tritolyl phosphate an additional peak was resolved between the 2- and 3-chloro-esters. This was shown to be chloromethyl valerate by the addition of authentic material to the reaction mixture.

Bromination of Methyl n-Valerate.—A mixture of methyl n-valerate (5 parts) and bromide (1 part) at a total pressure of approximately 20 mm. was illuminated by one 300 watt and one 150 watt lamps for 3 hr. The results are expressed as selectivities relative to carbon atom 4:

Temp.	No. of runs	CH_3OOC–CH_2	CH_2	CH_2	CH_3
50°	2	0·77 ± 0·03	0·43 ± 0·01	1	?
160	11	0·53 ± 0·03	0·45 ± 0·02	1	0·013 ± 0·004

The analysis was carried out using a column packed with 20% tritolyl phosphate on " Celite." The product mixture from the run at 50° contained too little of the 5-isomer for accurate estimation. The peaks were identified by the addition of authentic specimens of the 2- and 5-bromo-isomers. The remaining major peaks were assumed to be the 3- and 4-bromo-isomers eluted in that order. In addition a small peak was eluted between the starting material and the 2-bromo-ester which had the same retention time as had bromomethyl valerate.

Bromination of n-Valeryl Chloride.—A mixture of n-valeryl chloride (5 parts) and bromine (1 part) at a total pressure of 27 mm. was irradiated by one 300 watt and one 150 watt tungsten lamp for 3 hr. The results are expressed as relative selectivities:

Temp.	No. of runs	ClOC–CH_2	CH_2	CH_2	CH_3
160°	6	0·38 ± 0·01	0·42 ± 0·01	1·0	0·013 ± 0·001

The analyses were performed using a column packed with tritolyl phosphate (20%) on " Celite." The products of the reaction were condensed into a slight excess of anhydrous methanol (cf. chlorination experiment) and the analysis was made of the resulting bromo-esters. Their identification is discussed above.

View Online

Bromination of n-Valeryl Fluoride.—A mixture of n-valeryl fluoride (10 parts) and bromine (1 part) at a total pressure of 20 mm. was irradiated by two 150 watt lamps for 3 hr. The results are expressed as relative selectivities:

Temp.	No. of runs	FOC–CH_2–	–CH_2–	–CH_2–	–CH_3
150°	6	0·42 ± 0·04	0·33 ± 0·01	1·0	—

The products were condensed into anhydrous methanol as before. The analysis was carried out on a column packed with silicone (10%) on "Celite"; the order of elution was assumed to be the same as that established in the other experiments. In addition there was a small unidentified peak between the starting material and the methyl 2-bromovalerate.

Discussion

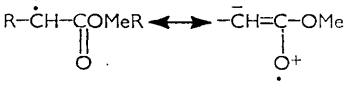
Comparison of the present chlorination results with the previous work gives a superficial appearance of similarity. The acyl group strongly deactivates the α-position and has some deactivating influence at the β-position. However, in contrast to the liquid phase results of Smit and Den Hertog, there is no evidence of deactivation at the γ-position. On the other hand the present results confirm the latter workers' conclusions that there is no activation at the β-position. In Table 1 the present chlorination results are compared with our previous data on the chlorination of the n-butyl halides [13] and of 1,1,1-trifluoropentane.[14] It is clear that in the gas phase none of the substituents has an appreciable effect at the γ-position. Deactivation at the β-position by the carbonyl group is of the

Table 1.

Relative selectivities RS_p^x for the chlorination of the n-butyl halides, 1,1,1-trifluoropentane, and derivatives of n-valeric acid at 75°.

X =	X–CH_2–	–CH_2–	–CH_2–	–CH_3
H	1	3·6	3·6	1
F	0·9	1·7	3·7	1
Cl	0·8	2·1	3·7	1
Br	0·4	—	3·6	1
CF_3	0·04	1·2	4·3	1
COF	0·08	1·6	4·2	1
COCl	0·2	2·1	3·9	1
$COOCH_3$	0·4	2·4	3·6	1

same order as that induced by a halogen atom. At the α-position the carbonyl group is more deactivating than a halogen atom, but less deactivating than the trifluoromethyl group. Since a methoxycarbonyl group exerts a more powerful electron withdrawal than the trifluoromethyl group, this means that the incipient radical must be stabilised to some extent by resonance (see Figure). Evidence for this effect has previously been obtained from other radical reactions,[9] but when chlorination was studied in isolation this phenomenon was masked by the powerful inductive effect.



Comparison of the relative selectivities for the chlorination of valeryl fluoride, valeryl chloride, and methyl valerate throws an interesting light on the way in which the remote group modifies the predominant influence of the carbonyl. The results show that there is little tendency for the halogen atoms adjacent to the carbonyl group to reduce its electron pull by means of their (+M) mesomeric effect; rather their inductive effect (—I) supplements the inductive pull of the carbonyl.

[13] Fredricks and Tedder, *J.*, 1960, 144.
[14] Galiba, Tedder, and Watson, *J.*, 1964, 1321.

View Online

Table 2 compares the present bromination results with our previous data on the bromination of the n-butyl halides and of 1,1,1-trifluoropentane. The value of doing both chlorination and bromination studies is again very clearly demonstrated. The importance of the resonance stabilisation depicted in the Figure is now clearly manifest. The decreasing importance of polarity and increasing importance of relative bond strength in determining the selectivity of bromination, in comparison with chlorination, has been discussed in detail previously.[13,15] Table 2 also shows that, as with the chlorination results, the sub-

TABLE 2.

Relative selectivities RS_p^X for the bromination of the n-butyl halides, 1,1,1-trifluoropentane and derivatives of n-valeric acid at 160°.

	X—CH_2—	—CH_2—	—CH_2—	—CH_3
X = H	1	80	80	1
F	9	7	90	1
Cl	34	32	80 *	1
CF_3	1	7	90	1
COF	34	26	80 *	1
COCl	29	32	77	1
$COOCH_3$	41	35	77	1

* Assumed values.

stituent has no effect beyond the β-carbon. This represents the limit of the inductive effect (Iσ) down the chain. In solution a direct field effect may well cause deactivation further down the chain and the results of Den Hertog and Smit provides evidence for this. A more detailed consideration of the effects of carrying out halogenation in the liquid phase with non-complexing solvents will be the subject of subsequent communications.

All the chlorinations were carried out at more than one temperature but the instability of the products prevented temperatures above 160° being employed. The differences in *relative* rates over the temperatures studied are small and the scatter of the experimental data is comparatively large. It is not very meaningful, therefore, to calculate Arrhenius parameters for each reaction. The results suggest that the changes in relative selectivities for different sites are principally due to changes in activation energy although the pre-exponential factors appear to be smaller for the α-position (*i.e.*, the low reactivity of the α-position is partly due to changes in the entropy term). The only bromination carried out at more than one temperature was that of methyl valerate. In this case, too, the low reactivity of the α-position is in part due to the entropy term; in fact the present results suggest that the activation energy for attack by a bromine atom at the α-position is slightly less than that at the γ-position (at the temperatures studied this is more than offset by the low entropy term). Although this is not an unreasonable result, it must be remembered that the α-bromo-ester is the least stable and it may have undergone slight decomposition at the higher temperature.

The present results for the halogenation of derivatives of n-valeric acid form a very concordant picture. They fit in very well with the previous results and are adequately accommodated by the existing qualitative theory.

The authors gratefully acknowledge that this work was supported in part by Aeronautical Systems Division, AFSC through the European Office, Aerospace Research, United States Air Force, and in part by the British Petroleum Company, Ltd.

THE UNIVERSITY, SHEFFIELD 10.

[Present Address: DEPARTMENT OF CHEMISTRY, QUEEN'S COLLEGE, DUNDEE.]

[*Received, February 17th,* 1964.]

[15] Tedder, *Quart. Rev.*, 1960, **14**, 336.