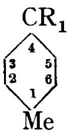
230. *Volume Effects of Alkyl Groups in Aromatic Compounds. Part II. Influence of a Group* CR_1R_2Alk *on Vicinal Substitution.*

By R. J. W. Le Fèvre.

In current theories of benzene substitution, the chief factor conducive to reaction at any position is considered to be electron availability at that point. Such an hypothesis is satisfactory for cases where the orienting radicals are small or where *powerful* polar effects enter, but where the latter are weak, *e.g.*, as in alkyl groups, it appears to be insufficient.

This is indicated *a priori* as follows: It is reasonable to assume (1) that the effective reagent in a substitution does not occupy a *smaller* volume than the group which is eventually installed in place of hydrogen, and (2) that, ultimately, the proportions of *o*-, *m*-, and *p*-products formed by substitution of a benzene derivative C_6H_5X depend upon the numbers of successful collisions between the reagent molecules and the *o*-, *m*-, and *p*-carbon atoms. Scale drawings of compounds (I) and (II) (Part I, preceding paper) and similar substances at once give point to the neglected views of Kehrmann (*Ber.*, 1890, **23**,

130) on the connexion between the bulk of a substituent and its orienting power. Thus, during the substitution of (A), attack by reagent molecules at the 3 : 5-positions might be impeded by the freely rotating CR_1R_2Me radical. The absolute number of reagent molecules colliding with these positions may be less than those colliding at 2- or 6- and/or some of the reagent molecules may succeed in penetrating to the 3 : 5-carbon atoms only after a preliminary collision. In the last case, their kinetic energies being reduced, the threshold energy of activation necessary for substitution is likely to be attained less frequently than among the more direct collisions occurring at positions 2 and 6.



(A.)

The net consequence will be a depression of substitution *o*- to the radical CR_1R_2Me in favour of other positions where substitution may be able to occur by default; *i.e.*, the order of diminishing *o*-directive powers will therefore be Me>Et>Pr>Bu, etc., in disagreement with the sequence required by electronic theories, *viz.*, Me<Et<Pr, etc.* (compare Allan, Oxford, Robinson, and Smith, J., 1926, 401). *Such anomalies must be expected with all alkyl substituents larger than methyl.*

The available relevant experimental evidence is mainly qualitative : 1-methyl-4-ethylbenzene gave the 2-bromo-derivative on bromination (Remsen and Morse, *Ber.*, 1878, **11**, 225); *p*-cymene (1-methyl-4-*iso*propylbenzene) gave the 2-derivative only on sulphonation (Jacobsen, *Ber.*, 1879, **12**, 431), chlorination and bromination (Vongerichten, *Ber.*, 1877, **10**, 1249; Landolph, *Ber.*, 1872, **5**, 267; Fittica, *Annalen*, 1874, **172**, 311; Remsen and Day, *Amer. Chem. J.*, 1883, **5**, 150), and nitration (Söderbaum and Widman, *Ber.*, 1888, **21**, 2126; Widman and Bladin, *Ber.*, 1886, **19**, 583; Andrews, *J. Ind. Eng. Chem.*, 1918, **10**, 453; Aschan, *Chem. Zentr.*, 1919, i, 226). *m*-Cymene (1-methyl-3-*iso*propylbenzene) gave the 6-derivative on sulphonation, bromination, and nitration (Kelbe, *Ber.*, 1882, **15**, 40; Kelbe and Warth, *Annalen*, 1883, **221**, 161; Müller, *Ber.*, 1909, **42**, 431). *iso*Propylbenzene apparently yields a greater amount of *p*-nitro-derivative on nitration (Constam and Goldschmidt, *Ber.*, 1888, **21**, 1157) than does *n*-propylbenzene (Schultz, *Ber.*, 1909, **42**, 3614). *tert.*-Butylbenzene is stated to form the 4-nitro-compound alone (Malherbe, *Ber.*, 1919, **52**, 319). In none of the above cases is the yield quoted.

Vavon and Callier (*Bull. Soc. chim.*, 1927, **41**, 357), however, describe the nitration of *iso*propylbenzene as proceeding 14% ortho and 86% para, in contrast to that of ethylbenzene (54% *o*- and 45% *p*-; Cline and Reid, *J. Amer. Chem. Soc.*, 1927, **49**, 3150) and toluene (58% *o*- and 37% *p*-; Ingold, Lapworth, Rothstein, and Ward, J., 1931, 1959).

In *p*-cymene Me and Pr^β will compete during a substitution. On electronic theories, the latter group—in which the normal $+I$ effect of methyl is reinforced by disubstitution of methyl—might be expected to surpass methyl alone as a promoter of *o*-substitution. Existing physical evidence suggests that it should at least *equal* the methyl group in this respect. The electric dipole moment of a molecule is a measure of the permanent inductive (I) electronic drift. It is therefore of interest here to know the value of μ for *p*-cymene, since this will indicate (μ_{CH_3} being opposed to μ_{Pr^β}) which of the alkyl groups has the larger $+I$ effect and hence which will activate its ortho-positions the more.

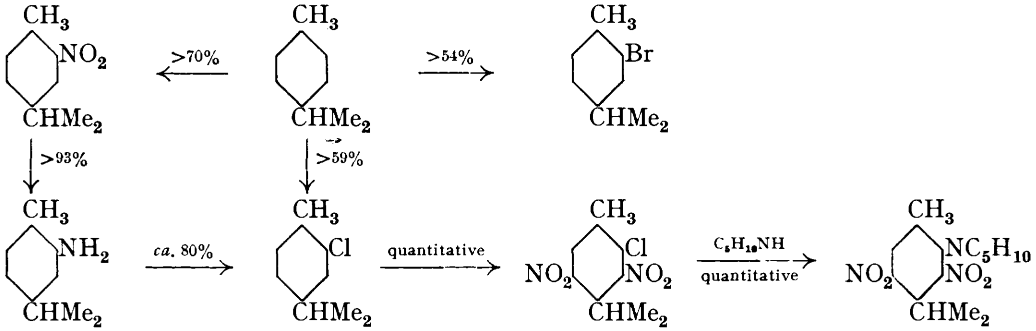
From various data (Landolt and Jahn, *Z. physikal. Chem.*, 1892, **10**, 289; Nernst, *ibid.*, 1894, **14**, 622; *Wied. Ann.*, **60**, 600) $\mu_{p\text{-cymene}}$ can be evaluated as $0{\cdot}1 \times 10^{-18}$ e.s.u., *i.e.*, effectively zero—indicating that $\mu_{Me} = \mu_{Pr^\beta}$. Therefore *p*-cymene should give on monosubstitution equal amounts of the 2- and the 3-isomeride, whereas (see above) it is stated to give exclusively the former.

Because of the closeness of b. p. and other properties between the 2- and the 3-halogeno-*p*-cymenes and the fact that nitration is said to give considerable oxidation,

---

* The fact that in catechol and quinol ethers the smaller groups cause the greater *o*-nitration is possibly due to the greater shielding action of larger groups on the ethereal oxygen atoms. *o*-Substitution in these compounds occurs mainly by operation of a $+T$ mechanism, and this cannot develop fully when the kationoid reagent molecules are in propinquity to the side of the oxygen atom remote from the nucleus. Hence OMe *appears* to be a weaker *o*-directive group than OEt. There are signs that the saturation effect, required by this explanation (effective screening not improved by further increase in the volume of the alkyl), occurs after OPr^β.

these experiments have been repeated, and yields of pure products measured. The homogeneity of the preparations was assured in the three processes as follows: (1) Nitration in each case gave a known (solid) dinitro-derivative in practically pure condition. (2) The carboxylic acid formed from the bromination product, *via* the corresponding Grignard compound and carbon dioxide, was different from the *acid* obtained by similar procedure from 3-bromocymene (Fileti and Crosa, *Gazzetta*, 1886, **16**, 292). (3) By the reduction of the mononitro-*p*-cymene an aminocymene was obtained, from which, by Sandmeyer's reaction, a monochlorocymene was prepared; this gave (i) on dinitration, the same chlorodinitro-*p*-cymene as that formed from the direct chlorination product, and (ii) on treatment with piperidine, 3 : 5-dinitro-2-piperidino-*p*-cymene (see Part I) in quantitative yield. The yields obtained are tabulated below.



2-*Substitution in* p-*cymene* (1-*methyl*-4-iso*propylbenzene*).

268 G. of cymene submitted to :—	Nitration.	Chlorination.	Bromination.
Total wt. of crude material isolated, g.	290	318	376
Unchanged cymene recovered, g.	—	1	19
Theor. wt. for monosubstitution, g.	358	338	396
Wt. of pure 2-substituted *p*-cymene, g.	252	200	214
Yield in total isolated, %	87	63	57
Yield on *p*-cymene used, %	70	59	54

The last line shows a *minimum* estimate of the amount of 2-derivative obtained in the experiment named; the actual 2-substitution is certainly greater in each case. Hence, methyl appears to possess a greater *o*-directive influence than *iso*propyl: on pure electronic theories the reverse should be the case.

No attempts have been made to estimate the concurrent 3-substitution: in nitration, this is evidently small. If the assumption is justifiable that the velocities of nitration of toluene, ethylbenzene, and *iso*propylbenzene are approximately the same—the values of their dipole moments show this to be probable—then, from figures cited earlier, the results of nitration of *p*-cymene can be calculated as 91% of 2- and 9% of 3-nitro-derivatives (for *p*-ethyltoluene the corresponding figures are 57% *o*- to methyl and 43% *o*- to ethyl). If oxidation could be avoided, it is believed that yields of this order would be achieved.

EXPERIMENTAL.

Purification of p-*Cymene*.—Commercial *p*-cymene, after standing over sodium wire for 1 week, was fractionated through a Dufton column. The b. p. rose steadily from 177° to 179°. Such a sample was partially frozen by addition of fresh liquid air after a preliminary cooling with solid carbon dioxide and ether. Drainage was easily performed by inversion of the Dewar flask. About one-third of the material was discarded. The cymene was redried over sodium before use.

Chlorination of p-*Cymene*.—The total chlorine obtainable from potassium permanganate (260 g.) and excess hydrochloric acid was slowly passed through water-cooled *p*-cymene (268 g.) containing a little iodine (Vongerichten, *Ber.*, 1877, **10**, 1249). The product was washed successively with water, aqueous sodium carbonate, sodium thiosulphate, and water, and dried (calcium chloride), and then fractionated through a long Dufton column: up to 175°, 1 g.;

187—195°, 11 g.; 195—210°, 13 g.; 213—215°, 217 g.; 220—240°, 45 g.; residue, 10 g. The main fraction on redistillation gave 200 g., b. p. 213—214°/764 mm.

Bromination of p-*Cymene*.—Bromine (344 g.) was added gradually to cymene (268 g.) containing iodine (2 g.) (water cooling). When the evolution of hydrogen bromide slackened, the flask was warmed on the steam-bath to complete the reaction. Water was then added, and the reaction product worked up as described for the chloro-analogue. Fractionation afforded: b. p. 170—180°, 19 g. (*p*-cymene); 180—228°, 10 g.; 229—230°/765 mm., 214 g.; 230—231°, 57 g.; residue, about 15 g.

3-*Bromocymene*.—Phosphorus tribromide (45 g.) was treated with bromine (26 g.) (cooling). Thymol (100 g.) was then added, and the mixture boiled under reflux for 3 hours. The product slowly obtained by steam distillation was washed, dried (calcium chloride), and collected at 234—235°/761 mm. (Fileti and Crosa, *loc. cit.*, quote b. p. 232—233°/741 mm.).

p-*Cymene*-2-*carboxylic Acid*.—2-Bromocymene (4·2 g.) was added to magnesium (0·5 g.) (previously activated with methyl iodide) in anhydrous ether (80 c.c.). The metal dissolved slowly. Anisole (40 c.c.) was then added and the solution boiled so that the bulk of the ether was lost. Through the gently boiling solution a slow stream of carbon dioxide was passed (3 hours). Then, after cooling, the dark solution was treated with dilute sulphuric acid and ice, etc. The anisole layer was shaken cautiously with sodium carbonate solution, acidification of which produced the acid, m. p. *ca.* 65°. After crystallisation from dilute alcohol, it had m. p. 70° (Found: C, 73·8; H, 7·9. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·8%) (Claus, *J. pr. Chem.*, 1891, **43**, 138, records m. p. 69°).

p-*Cymene*-3-*carboxylic Acid*.—This was obtained essentially as described for the 2-analogue. After crystallisation from much water, the *acid* formed needles, m. p. 82—83° (Found: C, 74·0; H, 7·7. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·8%).

A mixture of approximately equal parts of the 2- and the 3-acid had m. p. *ca.* 40°.

Mononitration of p-*Cymene*.—A mixture of nitric acid (55 g., *d* 1·42) and sulphuric acid (150 g.) was added during 3 hours to *p*-cymene (67 g.) in sulphuric acid (170 g.) and acetic acid (40 g.), the temperature being kept below — 3°. Mechanical stirring was continued for ½ hour, after which the mixture was poured on ice, separated with light petroleum (b. p. 40—60°), the extract washed with *N*-sodium hydroxide, and then with water. After removal of the solvent, steam was blown through, and the first condensate collected separately. Shaking with an excess of 2 : 4-dinitrophenylhydrazine in 2*N*-hydrochloric acid afforded an orange-red precipitate, m. p. 252—253° (raised by admixture with similarly prepared authentic *p*-methylacetophenone-2 : 4-dinitrophenylhydrazone, m. p. 259—260°).

The remaining yellow oil, which slowly distilled during 6 hours, was extracted with carbon tetrachloride, dried over calcium chloride, and fractionated in a vacuum. The main bulk (63 g.) had b. p. 149—150°/24 mm. (Found: N, 7·8. Calc. for $C_{10}H_{13}O_2N$: N, 7·82%).

Dissolution of a small specimen in nitric acid (*d* 1·5) at —15°, followed by immediate addition to ice, gave a dinitro-*p*-cymene, m. p. 53—54° (Found: N, 12·8. Calc. for $C_{10}H_{12}O_4N_2$: 12·5%).

Reduction. 2-Nitrocymene (51 g.) was added to previously activated iron powder and water (Fe, 200 g.; H_2O, 150 c.c.), and the well-shaken mixture heated on the steam-bath for 8 hours. After addition of water, steam distillation and extraction of the distillate with light petroleum (b. p. 40—60°, dried with sodium sulphate), etc., afforded the amine (38 g.), b. p. 233—234°/761 mm.

2-*Chloro*-p-*cymene*.—A suspension of the hydrochloride produced by cooling a warm solution of 2-aminocymene (45 g.) in concentrated hydrochloric acid (150 c.c.) was diazotised at 0° with sodium nitrite (21 g.) in the minimum quantity of water. The resulting solution was added to a concentrated hydrochloric acid solution of the cuprous chloride from sodium chloride (100 g.). Steam distillation of the mixture slowly produced 2-chloro-*p*-cymene, which, when worked up, weighed 40 g.

Nitration.—This, and the reaction with piperidine, were performed as described for the chlorination product (Part I, p. 980). Identities of products were established by mixed m. p.

[*Note, added July 5th*, 1933.]—In view of the possibility of contamination of the 2-nitro-*p*-cymene with the hitherto undescribed 3-compound (cf. *Chem. and Ind.*, 1933, **52**, 505) the following additional experiments are recorded in confirmation of those above.

(*a*) The 2-aminocymene, when added to concentrated hydrochloric acid, formed white plates of the hydrochloride, m. p. 209—212° (crude) and 210—212° after two crystallisations from dilute hydrochloric acid (Wallach, *Annalen*, 1894, **279**, 368, gives m. p. 207°).

(*b*) The crude acetamido-derivative had m. p. 65—70°, raised by two crystallisations from dilute alcohol to 70—71° (Wallach, *loc. cit.*, gives 71°). The 3-isomeride has m. p. 115° (Lloyd, *Ber.*, 1887, **20**, 1262).

(*c*) The *azo-β-naphthol* derivative had m. p. (crude) 122—125°. Crystallisation from dilute acetic acid afforded scarlet plates, m. p. 131—132° (Found : N, 9·3. $C_{20}H_{20}ON_2$ requires N, 9·2%).

(*d*) Diazotisation of 2-aminocymene sulphate in aqueous suspension, followed by steam distillation, gave, after extraction of the distillate with ether, etc., an oil which was nearly all soluble in aqueous sodium hydroxide. The alkaline solution was acidified with carbon dioxide, the precipitated oil re-extracted, and distilled. The fraction, b. p. 232—238°, represented a yield of 80% on the amine taken. The substance was identified as carvacrol by preparation of the *p*-nitrobenzoate, m. p. 50°, after recrystallisation from dilute alcohol (Found : N, 4·9. Calc. for $C_{17}H_{17}O_4N$: 4·7%).

UNIVERSITY COLLEGE, UNIVERSITY OF LONDON.

[*Received, May 5th*, 1933.]