Tetrahedron, 1964, Vol. 20, pp. 2185 to 2194. Pergamon Press Ltd. Printed in Northern Ireland

THE ELECTROPHILIC SUBSTITUTION OF BENZOCYCLOBUTENE—I

NITRATION, ACETYLATION AND HYDROBROMINATION

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(*Received* 27 *April* 1964; *in revised form* 15 *May* 1964)

Abstract—Nitration, Friedel-Crafts acetylation and hydrobromination of benzocyclobutene result in extensive displacement of a methylene group by the reagent giving *o*-substituted *β*-phenethyl and polystyrene derivatives. Where ring opening does not occur substitution is mainly at the 4-position and only to a negligible extent at the 3-position. The product proportions obtained from the acetylation are highly dependent on temperature and on the solvent used. The results are discussed in terms of solvation and strain effects.

THE electrophilic substitution reactions of the now readily available benzocyclobutene (I)[1] are an interesting extension of those reactions of the less strained homologues indane and tetralin. Nitration and *β*-chloropropionylation of I have already been carried out by Horner *et al.*[2,3] and the kinetics of benzoylation have been examined by Jensen and Maciel.[4] Our own results in this field show that the conclusions of these authors must be revised.

Horner *et al.*[2] nitrated benzocyclobutene using a ten-fold excess of fuming nitric acid in acetic acid at room temperature. The products, which were not obtained pure, were 4-nitrobenzocyclobutene (II) and *o*-nitro-*β*-phenethyl nitrate (III) in 25% and 16 to 20% yields respectively; (the working-up, which involved steam distillation, resulted probably in some decomposition of the nitro-nitrate). The remainder of the product was described as "poly-nitro compounds".

Our repetition of this gives a similar result. Recrystallization of the crude product from light petroleum—diethyl ether mixtures at −75°, yields a pure sample of II. This on permanganate oxidation gives a mixture of 4-nitrophthalic and *p*-nitrobenzoic acids, the former compound predominating. Although the pure acids isolated correspond to only 25% of the original nitro compound, Horner *et al.* reported[2] for the same oxidation 70% yield of crude *p*-nitrobenzoic acid.

The nitro-nitrate fraction shows strong acetate frequencies in the IR which suggests that solvent molecules are incorporated during the ring opening and, indeed, nitration in acetic anhydride—acetic acid mixtures using a minimum of nitric acid produces 27% of crystalline II and 31% of *o*-nitro-*β*-phenethyl acetate (IV) contaminated with a small quantity of nitrate. The remainder of the product appears to be polymeric and on IR evidence is probably an *o*-nitropolystyrene (V) representing

[1] [a] M. P. Cava and A. A. Deana, *J. Amer. Chem. Soc.* **81**, 4266 (1959); [b] J. A. Oliver and P. A. Ongley, to be published.
[2] L. Horner, H.-G. Schmelzer and B. Thompson, *Chem. Ber.* **95**, 1774 (1960).
[3] L. Horner, K. Muth and H.-G. Schmelzer, *Chem. Ber.* **92**, 2953 (1959).
[4] F. R. Jensen and G. Maciel, *J. Org. Chem.* **25**, 640 (1960).

34% of the starting material (this is probably an overestimate, as the sample also shows strong frequencies characteristic of acetate and nitrate groupings which are probably present as end groups). The mother-liquors from the recrystallization of II, on freeing from esterified material, yield a small fraction of mainly II together with a compound possessing three adjacent aryl hydrogen atoms (IR), as would 3-nitrobenzocyclobutene (VI). The quantity of this compound, if present, probably corresponds to no more than 5% of the original hydrocarbon.

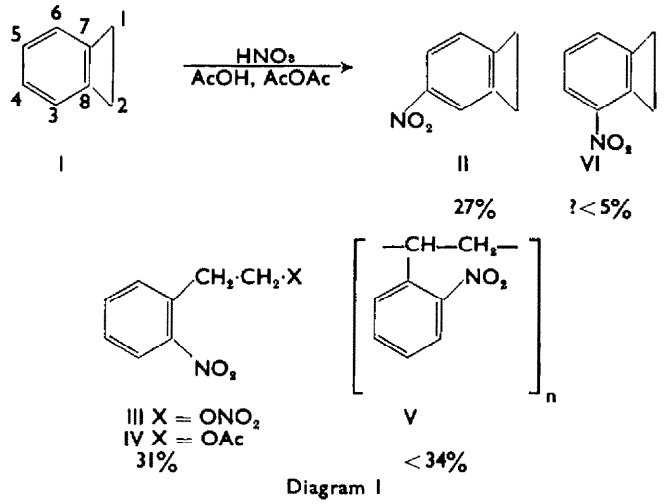

Diagram I

Horner *et al.*[2] suggest that their ring opening product III is produced through VI, which compound is a primary nitration product that is unstable under the reaction conditions. However, it does not seem reasonable to suppose on the basis of either electronic or steric effects that VI should differ markedly in stability from II, which is, obviously, stable under the reaction conditions. Two other routes for the ring opening are available:

(i) addition of HNO_3 or AcOH across the 1,7 bond of I, to give a β-phenethyl compound followed by *o*-nitration; and certainly β-phenethyl acetate nitrates extensively in the *o*-position[5].

(ii) displacement of a methylene group on the benzene ring by a nitronium ion, followed by uptake of an anion derived from the solvent.

Although the products obtained in the nitration do not allow the matter to be decided, the results of Friedel-Crafts acetylation are unambiguous in this respect.

The Friedel-Crafts β-chloropropionylation of I in solvent nitromethane is reported by Horner *et al.*[3] to give 4-β-chloropropionylbenzocyclobutene in 29% yield, as sole product. In carbonbisulphide aluminium chloride acetylation gives, in up to 50% yield, a halogenated methylketone $C_{10}H_{11}OCl$ (VII). Both the IR spectrum and oxidation to phthalic acid indicate the presence of a 1,2-disubstituted benzene nucleus. Since the NMR spectrum shows the presence of three methyl, four methylene and four aryl protons the compound is *o*-aceto-β-phenethyl chloride (VII). The remainder of the product is a sulphur containing *o*-acetopolystyrene (VIII).

[5] S. Sabetay, J. Bleger and Y. De la Strange, *Bull. Soc. Chim.* **49**, 3 (1931).

A similar result is obtained from aluminium chloride acetylation at 0° in methylene chloride scrubbed with nitrogen.

When nitromethane is used as solvent for the aluminium chloride acetylation the mixture obtained exhibits IR frequencies characteristic of VII together with out of plane aryl hydrogen deformations suggestive of a 1,2,4-trisubstituted benzene nucleus. Chromatography on alumina separates the mixture into a halide containing fraction, eluted by light petroleum containing 10% benzene, and a halide free methylketone $C_{10}H_{11}O$ (IX), running off in neat benzene. The IR spectrum of IX possesses the medium intensity band near 1210 cm^{-1}, which has been generally present in the benzocyclobutenes substituted in the C_6 ring examined, as well as in the parent hydrocarbon, and characteristically split aryl hydrogen out of plane deformations typical of a 1,2,4-trisubstituted nucleus. The UV spectrum is comparable with that of 3,4-dimethylacetophenone. Hypobromite oxidation gives the corresponding carboxylic acid $C_9H_8O_2$ (X) whose amide (XI) undergoes a Hoffman reaction yielding 60% of the 4-aminobenzocyclobutene (XII) prepared by Horner *et al.*,[2] from the corresponding nitro compound II. Hence IX is a 4-acetobenzocyclobutene and X the 4-carboxylic acid.

The polymeric fraction from the nitromethane acetylation appears, as before, to be an *o*-acetopolystyrene.

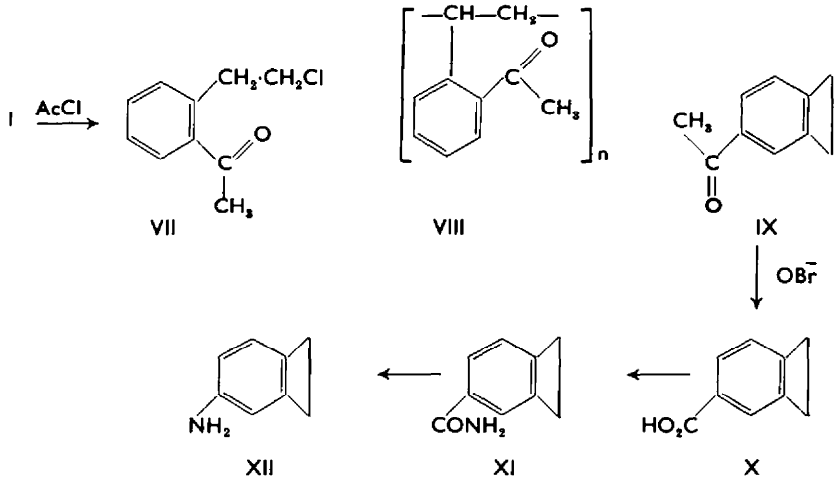

Diagram 2

At room temperature and using Perrier's[6] addition sequence (other sequences give lower yields) the yields of IX and VII are about 17% each. This estimate is based on the halide content of the combined nonpolymeric products and confirmed in a number of cases by near quantitative isolation of IX. Since the yields are unaffected by increasing the reaction time from 25 mins. to 2½ hr the products are stable in the reaction mixture.

Now modified orientations resulting from the use of nitrohydrocarbon solvents in Friedel-Crafts reactions have been ascribed to steric effects arising in the formation of bulky solvates,[7] which in the present case could be diverting substitution into the

[6] G. Perrier, *Ber. Dtsch. Chem. Ges.* **33**, 815 (1900).
[7] G. Baddeley, *J. Chem. Soc.* S 55 (1949).

less sterically hindered 4-, from either the 7- or 3-, positions. It was anticipated that the concentration of such solvates should be increased by reducing the reaction temperature. Indeed, at temperatures down to −40° there is produced 29% of IX and 11% of VII; and with stannic chloride as catalyst, at low temperatures, the product composition becomes 36% IX and 24%VII, the usual polymer VIII accounts for the remainder.

Whereas the results of nitration leading to β-phenethyl compounds are ambiguous in indicating when and where ring opening occurs, the acylation results allow the point to be determined. If ring opening occurs before acylation, then β-phenethyl chloride should be formed. But the acetylation of this compound is reported[8] to yield *p*-aceto-β-phenethyl chloride, and the polymer it forms in the presence of aluminium chloride contains 1,4-disubstituted benzene nuclei.[9] The intervention of styrene can be excluded by a similar argument. Hence only one possibility remains, that an acyl-dealkylation is taking place.

An unequivocal demonstration of an electrophilic dealkylation, rather than formation of an unstable 3-substituted compound, is available where the electrophile is a proton. In dilute acid benzocyclobutene is quite stable.[10] However, on treatment with hydrogen bromide in acetic acid at 100° there is slowly formed β-phenethyl bromide together with a small amount of the corresponding acetate, a reaction which can only be interpreted as a protodealkylation. We suggest that this is probably the process operating when 4-acetamidobenzocyclobutene hydrolyses in aqueous hydrochloric acid to *m*-amino-β-phenethyl chloride.[2]

Although proven acyl-dealkylations are rather few in number, they have been shown to occur on *p*-di-t-butylbenzene[11] and hexamethyl and hexaethyl benzenes.[12] Such processes must be subject to considerable steric effects which could, in part, be relieved by a lengthening of aryl-alkyl bond in the transition state. In acyl-deprotonation, at least as exemplified in the benzoylation of the benzene, there is some evidence to indicate that this may be so, Jensen[13] having found a primary hydrogen isotope effect in this reaction. And certainly a driving force for aryl-alkyl bond lengthening is provided by the strain present in the ground state of benzocyclobutene.

On the basis of kinetic data for the aluminium chloride catalyzed benzoylation of *o*-xylene, indane, tetralin and benzocyclobutene, all in ethylene chloride, Jensen and Maciel[4] have argued that since the observed rate-acceleration of benzocyclobutene in this series is small any decreased stability of the ground state in this molecule must be counteracted by an equal degree of transition state destabilization. Suppose, however, that in the case of benzocyclobutene it was a dealkylation reaction that Jensen and Maciel measured. Then any rate-acceleration due to a decreased activation enthalpy, resulting from relief of strain on forming the dealkylation transition state, might well be obscured by a reduction in activation entropy arising in the greater restriction placed upon the interactants by steric effects, relative to acyl-deprotonation. The reported data[4] (rate constants at one temperature, products not characterized) do not

[8] G. Baddeley, E. Wrench and R. Williamson, *J. Chem. Soc.* 2110 (1953).

[9] K. Sisido and S. Kato, *J. Soc. Chem. Ind., Japan* **43**, suppl. binding 450 (1940), *Chem. Abstr.* **35**, 3246 (1941).

[10] M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.* **80**, 2255 (1958).

[11] C. F. Hennion and S. F. de C. McLeese, *J. Amer. Chem. Soc.* **64**, 2421 (1942).

[12] H. Hopff and A. K. Wick, *Helv. Chim. Acta* **43**, 1475 (1960).

[13] F. R. Jensen, Thesis, Purdue (1955).

allow the matter to be settled; we therefore hope to commence an investigation upon it.

Though the modified Friedel-Crafts orientation often observed in nitrohydrocarbon solvents may well involve steric effects, and there are exceptions of course,[14] the possibility that acylation may be facilitated by a weakening of the leaving group-aryl bond suggests an alternative explanation, particularly where two different leaving groups are involved. If solvent nucleophilicity with respect to one leaving group e.g. an incipient proton, is increased relative to the other e.g. an alkyl group, then the acyl-deprotonation will be facilitated relative to dealkylation. Pertinent here is Olah's observation[15] that the use of nitromethane in Friedel-Crafts alkyl-deprotonations stabilizes the proton formed to an extent sufficient to inhibit its further involvement in alkyl rearrangement reactions. The production of primary rather than secondary halides in the benzocyclobutene dealkylation suggests that either the alkyl group is not released as a carbonium ion, or at least that transfer of halide to such a species occurs more rapidly than its rearrangement. There is therefore, probably little demand for solvation here. Even if the polymer obtained represents the fate of such an intermediate, the observed orientation in this product would nevertheless suggest that its formation is initiated by an acyl-dealkylation.

Finally the results of nitration; we have to choose between (i) a proto-dealkylation giving β-phenethyl acetate or nitrate, followed by *o*-nitration, and (ii) a nitro-dealkylation. In acetic acid–acetic anhydride, using a minimum of nitric acid and taking into consideration the relatively vigorous conditions required for the hydrogen bromide proto-dealkylation, process (i) would seem to be precluded. This would indicate that (ii) is the observed reaction. But this introduces an anomaly: *o*-xylene[16] and tetralin[17] nitrate predominantly (about 60 %) and indane[18] extensively (about 40 %) adjacent to their alkyl substituents, whereas, ignoring Horner's route to II, the extent of nitration on benzocyclobutene in this position is probably negligible. Longuet-Higgins and Coulson[19] have discussed the orientation of electrophilic substitution on 5-hydroxyindane in terms of the stress system set up in the benzene ring by the cycloalkene substituent. A similar but exaggerated state of affairs will exist in benzocyclobutene. Expressing tensions as T (>t) and compressions C (>c) then in the ground state:

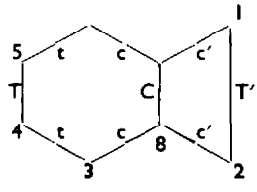

Diagram 3

Consider the benzeneonium ions intermediate in 3- and 4- substitution; their production involves a localization of these positions from the pi-system and a consequent

[14] P. H. Gore, *Bull. Chem. Soc., Japan* **35**, 1627 (1962) and references cited therein.
[15] G. A. Olah, *Friedel-Crafts and Related Reactions*, p. 925. Interscience (1963).
[16] K. A. Kobe and P. W. Pritchett, *Ind. Eng. Chem.* **44**, 1598 (1952).
[17] W. Davis, J. L. Everett and W. C. J. Ross, *J. Chem. Soc.* 1331 (1950).
[18] J. Lindner and J. Bruhin, *Ber. Dtsch. Chem. Ges.* **60**, 435 (1927).
[19] H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **42**, 756 (1946).

lengthening of adjacent bonds. Insofar as the transition states possess benzeneonium character, then in 3-substitution any facilitative effect that the relief of tension in the 3–4 bond might have will be counteracted by work done against the 3–8 compression, whereas in 4-substitution the stress system is entirely favourable to localization over the 3–4 and 4–5 bonds. The dealkylation process is of course particularly propensiated by the relief of strain over the whole system which accompanies rupture of the C_4 ring.

EXPERIMENTAL

M.ps are uncorrected, IR spectra were determined using a Perkin-Elmer IR spectrophotometer, uv spectra were plotted manually using a Hilger and Watts Uvispek H. 700. Benzocyclobutene was obtained by Oliver and Ongley's[15] modification of the preparation of Cava and Deana[16] by pyrolysis of 1,3-dihydroisothianapthene-2,2-dioxide.

Nitration of benzocyclobutene with excess fuming nitric acid.[8] Benzocyclobutene (15 g; 0·144M) was nitrated using a solution of fuming HNO_3 (60 ml; ca. 1·4M) in 50 ml glacial acetic acid and worked-up using steam and vacuum distillation following the procedure of Horner *et al.*[8] Obtained were: impure 4-nitrobenzocyclobutene b.p. 108–120°/2 mm, $n_D^{15°}$ 1·5818, 4·9 g (0·033M 23%) and impure *o*-nitro-β-phenethyl nitrate b.p. 120–140°/2 mm, $n_D^{15°}$ 1·5799–1·5779, 3·7 g (0·0183M, 13%), IR neat liquid: maxima (cm^{-1}) at 1745 s (ester C=O), 1645 vs (ONO_2) 1530 vs 1350 vs ($ArNO_2$), 1285 vs (ONO_2) 1240 m (acetate), 890 m 840 s (1,2,4-trisubstituted benzene), 760 m 730 m 705 m (4-nitrobenzocyclobutene), 745 s (1,2-disubstituted benzene). The unaccounted material remained as involatiles after the two distillations.

The impure 4-nitrobenzocyclobutene was recrystallized from light petroleum–diethyl ether mixtures at −75° to yield 1·27 g pure 4-nitrobenzocyclobutene m.p. 18·8–19·0° IR neat liquid: maxima (cm^{-1}) at 1617 m 1610 m (externally conjugated benzene), 1530 vs 1345 vs ($ArNO_2$), 1210 m (benzocyclobutene methylenes?), 898, s 840–830 s (1,2,4-trisubstituted benzene), 765 s 730 s 705 s (useful 'fingerprints'); in CCl_4 the 840–830 absorption split giving 840 m 832 s. UV in n-heptane, maxima (mμ) at 267 (ε = 8,230). (Found: C, 64·50; H, 4·78; N, 9·56. Calc. for $C_8H_7O_2N$: C, 64·42; H, 4·73; N, 9·38%).

Nitration in acetic anhydride—acetic acid. To a stirred solution of 5 g (0·048M) benzocyclobutene in 20 ml acetic anhydride at 0° was added, over a period of 1¾ hrs, a solution of 3·2 ml (ca. 0·05M) fuming HNO_3 in 5 ml glacial acetic acid. The resulting pale yellow solution was left in the ice bath overnight, poured into 350 ml water and the product collected in 20 ml $CHCl_3$ (2 × 10 ml washings). The $CHCl_3$ solution was washed with 2N NaOH aq, with 50 ml water, dried (Na_2SO_4) and the solvent distilled off. Vacuum distillation gave: (a) 87–94°/0·3 mm, 1·26 g (b) 94–102°/0·3 mm, 0·93 g (c) 102–110°/0·3 mm, 0·63 g (d) 110–114°/0·3 mm, 3·10 g (e) involatiles 2·41 g. Fractions (a) to (c) exhibited the characteristic 4-nitrobenzocyclobutene frequencies at 765, 730 and 705 cm^{-1} which decreases in intensity from (a) to (c) and frequencies at 1745 and 1240 cm^{-1} (acetate) which increased in intensity from (a) to (c). Each of these fractions solidified on cooling and yielded a total of 1·91 g (0·0128M, 27%) 4-nitrobenzocyclobutene, m.p. 18–19°, undepressed, on recrystallization. The residue obtained from the mother liquors was refluxed ½ hr in 50 ml NaOH aq and steam distilled; the distillates were extracted into diethyl ether, washed with alkaline $KMnO_4$ aq to remove unsaturated material (formation of which was shown to accompany saponification of the acetate contaminant) and the solvent removed to leave a residue which distilled between 66 and 74° at 0·3 mm as 0·64 g (0·0043M, 9% as $C_8H_7O_2N$) pale yellow oil: IR, neat liquid, maxima (cm^{-1}) at 1615 m (externally conjugated benzene), 1525–1520 vs ($ArNO_2$), 1205 m (benzocyclobutene methylenes?), 895 m 830 s (1,2,4-trisubstituted benzene), 790 s (1,2,3-tri- or 1,3-disubstituted benzene), 760 s 730 s 700 m (4-nitrobenzocyclobutene). Fraction (d) was *o*-nitro-β-phenethyl acetate containing some *o*-nitro-β-phenethyl nitrate (ca. 0·015M, 31% as acetate); IR neat liquid, maxima (cm^{-1}) at 1740 vs (ester C=O), 1635 (ONO_2), 1615 m (externally conjugated benzene), 1535–1545 vs 1350 s ($ArNO_2$), 1280 m (ONO_2), 1235 s (acetate), 745 s (1,2-disubstituted benzene, however, bands at 790 s and 860 s render this assignment equivocal). 3·0 g (0·014M) fraction (d) was refluxed in 25 ml 1·5N NaOH aq for 1½ hrs; steam volatile materials (0·4 g unsaturated nitro compounds, 19% as nitrostyrenes) were removed and the residue distilled to give 1·15 g (0·0069M, 49%) *o*-nitro-β-phenethyl alcohol b.p.

128°/0·7 mm $n_D^{21°}$ 1·5642 (lit.[5] 144–147°/1·3 mm, $n_D^{28°}$ 1·5620); IR identical with known *o*-nitro-β-phenethyl alcohol; benzoate m.p. 54–55°, undepressed (lit.[5] 55°). Oxidation of 200 mg (1·20 mM) the hydrolysate in alkaline permanganate gave 130 mg (0·78 mM, 65%) *o*-nitrobenzoic acid m.p. 145–146°, undepressed (lit. 144–148°); IR identical with known *o*-nitrobenzoic acid; amide m.p. 173–174°, undepressed (lit. 174°). Fraction (e) was a dark brown oil (0·016M, 33% as nitropolystyrenes); this was steamed to remove trace volatiles, treated with charcoal in $CHCl_3$ and the solvent removed to leave a yellow-brown viscous liquid; IR closely comparable with fraction (d) together with a partly obscured band at 2950 cm^{-1}.

Permanaganate oxidation of 4-nitrobenzocyclobutene. To 1·0 g (6·7 mM) recrystallized 4-nitrobenzocyclobutene in 150 ml refluxing 0·7% Na_2CO_3 aq was added portionwise, over a period of 16 hrs, 10·0 g (63·5 mM) $KMnO_4$. At the end of this time all odour of nitro compound had disappeared and a small quantity of $KMnO_4$ remained. MnO_2 was filtered off, SO_2 passed through the solution until it was acid and the solution extracted with diethyl ether (×6, 100 ml). The combined extracts were dried (Na_2SO_4) and the solvent removed leaving a brown oil which on recrystallization from water gave 55 mg (0·33 mM, 4·9%) *p*-nitrobenzoic acid m.p. 238–240° with some sublimation, undepressed (lit. 240° sub.); IR identical with known *p*-nitrobenzoic acid; benzylisothiuronium salt m.p. 186–187°, undepressed (lit. 186°). The aqueous mother liquors were evaporated to dryness and the residue recrystallized from acetone:benzene (ca. 1:10) to yield 258 mg (1·22 mM, 18·2%) of 4-nitrophthalic acid, m.p. 164–165°, undepressed (lit. 165°); IR identical with known 4-nitrophthalic acid; anhydride m.p. 119–120°, undepressed (lit. 119). Uncharacterized material was recovered as 70 mg brown solid indicated by IR to be mainly 4-nitrophthalic and *p*-nitrobenzoic acids.

Friedel–Crafts acetylation in CS_2. A solution of 10 g (0·096M) benzocyclobutene and 8·35 g (0·106M) acetyl chloride in 35 ml CS_2 was added over 45 mins to a stirred suspension of 16·0 g (0·120M) powered $AlCl_3$ in 40 ml CS_2; the solvent refluxed gently during the addition. After standing 48 hrs at room temp the CS_2 layer, which was shown to contain no significant quantity of dissolved material, was decanted from a red-brown oil. To the oil was added, with cooling, 100 ml water and the product taken into CH_2Cl_2 (100 ml). This solution was shaken with 5% $HgCl_2$ aq to give a HgS containing emulsion which was broken by filtration at the pump. The organic phase was washed with Na_2CO_3 aq, dried (Na_2SO_4) and the solvent removed. Vacuum distillation of the residue gave 8·40 g *o-aceto-β-phenethyl chloride* (0·046M, 48%) b.p. 115–116°/2·2 mm, $n_D^{17·6}$ 1·5498, which crystallized from 30–40° light petroleum as 7·11 g colourless needles m.p. 13·8–14·5°; IR neat liquid, maxima (cm^{-1}) at 1688 s (aryl, alkyl C=O), 1608 m 1580 m (externally conjugated benzene), 765 s (1,2-disubstituted benzene); NMR in CCl_4—two multiplets around 2·3 and 2·7 τ (one and three aryl protons respectively), A_2B_2 system centered round 6·6τ (four methylene protons), singlet at 7·5τ (three methyl protons). (Found: C, 65·80, 65·78; H, 6·26, 6·10; Cl, 20·80, 21·04. $C_{10}H_{11}OCl$ requires C, 65·55; H, 6·07; Cl, 19·42%). *2,4-dinitrophenyl hydrazone*: yellow-orange fibres from methanol aq m.p. 148·5–149° (Found: C, 52·96, 52·73; H, 4·28, 4·09; N, 15·41, 15·35; Cl, 10·50, 10·09. $C_{16}H_{15}O_4N_4Cl$ requires: C, 52·93; H, 4·17; N, 15·44; Cl, 9·77%). The involatile material from the vacuum distillation weighed 7·7 g. It was steamed out, treated with charcoal in $CHCl_3$ and the solvent removed to leave a friable S-containing solid; IR KBr disc, maxima (cm^{-1}) at 1685–1690 s (aryl, alkyl C=O), 760 s 1,2-disubstituted benzene).

A second acetylation of 2·5 g benzocyclobutene under the same conditions except that after mixing the reactants 16 hrs elapsed before work-up yielded 49% of *o*-aceto-β-phenethyl chloride (not recrystallized, IR identical with pure compound).

Oxidation of o-aceto-β-phenethyl chloride. 450 mg (2·47 mM) *o*-aceto-β-phenethyl chloride was dissolved in 50 ml dioxan. To this was added 5 g (31.2 mM) of Br_2 and 3·6 g (90·0 mM) NaOH dissolved in 40 ml water. The homogeneous mixture was heated at 70° for 1½ hrs, cooled freed from $CHBr_3$ and much of the dioxan by extraction with diethyl ether (50 ml × 4), and SO_2 passed through it until the solution was strongly acid. The solution was extracted with diethyl ether (20 ml × 4), the extract dried (Na_2SO_4) and the solvent removed. The product was rinsed with light petroleum to remove a small quantity of Br-containing contaminant to yield 250 mg (1·51 mM, 61%) of phthalic acid as white needles m.p. 198°, undepressed, unmodified by crystallization from water (lit. 195°, variable), base equivalent 83·5, $C_8H_6O_4$ requires 83·0; IR identical with phthalic acid; benzylisothiuronium salt m.p. 155–156°, undepressed (lit. 156°); anhydride m.p. 131°, undepressed (lit. 132°).

Acetylation in methylene chloride. 5 g (0·048M) benzocyclobutene was dissolved in 35 ml CH_2Cl_2. The solution was cooled in ice and a stream of N_2 passed through it. To this was added dropwise, over 15 mins, a solution of 4·0 g (0·051M) acetyl chloride and 6·8 g (0·051 M) $AlCl_3$ in CH_2Cl_2. The stream of N_2 was maintained during the addition and for a further 15 mins. The mixture was poured on to 200 g crushed ice, the CH_2Cl_2 solution removed, the aqueous layer washed with a further 100 ml solvent and the extracts combined. After washing with 100 ml water, 100 ml Na_2CO_3 aq and drying (Na_2SO_4) the solvent was removed leaving a yellow-brown oil. Vacuum distillation yielded 2·91 g (0·016M, 33%) pale yellow liquid b.p. 106–109°, 1·1 mm, $n_D^{19°}$ 1·5490, IR identical with that of *o*-aceto-*β*-phenethyl chloride and which from light petroleum–diethyl ether at −75° yielded white needles m.p. 15°, undepressed; 2,4-dinitrophenylhydrazone m.p. 148–149°, undepressed. A residue of 3·4 g polymeric chlorine-containing material remained from the vacuum distillation.

Acetylation in nitromethane. The −40°, $AlCl_3$-catalyzed reaction is given as an example; the results of other experiments using modifications of this procedure are summarized in the Table below.

A stirred solution of 4·5 g (0·057M) acetyl chloride and 7·5 g (0·056M) $AlCl_3$ in 25 ml nitromethane was cooled to −40°. A solution of 5 g (0·048M) benzocyclobutene in 5 ml nitromethane was added to the acylating mixture at such a rate that the reaction temp did not exceed −40°; this required 15 mins. A further 5 ml solvent was used to wash in remaining benzocyclobutene. By this stage some needle-shaped crystals had separated; after a further 20 mins at −40° a thick slurry had formed and the presence of appreciable quantities of HCl was noted. The temp of the mixture was allowed to rise to −8° overnight, and the resulting dark brown homogeneous solution then poured into 500 ml water. The product was extracted into CH_2Cl_2 (25 ml, × 4), the extract shaken under the cold tap with 100 ml 10% NaOH aq to remove nitromethane, washed with 100 ml water, dried ($MgSO_4$) and the solvent removed. Vacuum distillation gave 2·95 g chlorine-containing liquid b.p. 86–89°/0·4 mm, shown by the IR spectrum to be mixture of *o*-aceto-*β*-phenthyl chloride and 4-*acetobenzocyclobutene*. Analysis gave 6·06% Cl which showed that the mixture contained 0·93 g (5·11 mM, 10·6% yield) *o*-aceto-*β*-phenthyl chloride and 2·02 g (13·8 mM, 28·8% yield) 4-acetobenzocyclobutene. The distillate was recrystallized from light petroleum–diethyl ether mixtures at −75° to yield 1·63 g of 4-acetobenzocyclobutene m.p. 34–35° (colourless needles). IR in hexachlorobutadiene and nujol mulls; maxima (cm^{-1}) at 1690 s (aryl alkyl C=O), 1600 m 1595 m (externally conjugated benzene nucleus), 1207 m (benzocyclobutene methylenes?), 880 m 835 s 820 s (1,2,4-trisubstituted benzene, the two lower frequencies are probably a doublet). UV in *n*-heptane: maxima, mμ (ε) at 248 (13,100), 282·5 (2,000), 291·5 (1,660), inflexion at 320 (65). (Found: C, 81·94, 82·00; H, 7·01, 6·89. $C_{10}H_{10}O$ requires: C, 82·10; H, 6·89%). *Oxime;* colourless leaflets from methanol aq, m.p. 134–135°. (Found: C, 74·26, 74·45; H, 6·88, 6·90; N, 8·61, 8·78. $C_{10}H_{11}ON$ requires: C, 74·45; H, 6·88; N, 8·69%).

The residue obtained on evaporation of the mother-liquors from the 4-acetobenzocyclobutene recrystallization were loaded on to a column containing 130 g neutral alumina (Brockmann activity 1) in 60–80° light petroleum. 9:1 v/v petroleum:benzene eluted 307 mg material (between 1190 and 2665 ml) containing quantities of Cl decreasing to nil as elution proceeded and neat benzene (615 ml) eluted 230 mg halide-free material. From both fractions there was obtained on recrystallization 4-acetobenzocyclobutene, 250 mg m.p. 33–35°, 122 mg m.p. 28–34°. Hence the overall yield of 4-acetobenzocyclobutene was 1·88 g (0·13M, 27%) m.p. 33–35° and 0·12 g (0·8 mM, 1·7%) m.p. 28–34°. The experiments at room temp or using $SnCl_4$ as catalyst yielded (after vacuum distillation) products which could not be worked up directly by recrystallization because of the quantities of *o*-aceto-*β*-phenethyl chloride present. 4-Acetobenzocyclobutene was separated from them either by chromatography on alumina or by refluxing the mixture in NaOH or Na_2CO_3 aq followed by steam distillation of the 4-acetobenzocyclobutene out of the steam involatile hydrolysis products. The best yields were obtained from the Na_2CO_3 hydrolysis. The results may be tabulated, as shown opposite.

Samples of the distillation residues from $AlCl_3$ and $SnCl_4$ acetylations were freed from steam volatile material, extracted into $CHCl_3$, dried, and the solvent removed to yield a brown, highly viscous gum from the $AlCl_3$ reactions and a vitreous solid where $SnCl_4$ had been used. IR in CS_2 ($AlCl_3$) or KBr disc ($SnCl_4$): maxima (cm^{-1}) at 1690 s (aryl, alkyl C=O), 755 s (1,2-disubstituted benzene).

Hypobromite oxidation of 4-acetobenzocyclobutene. 0·80 g (5·47 mM) of 4-acetobenzocyclobutene

NITROMETHANE ACETYLATIONS

Catalyst	Reaction conditions	%VII*	%IX†	% IX isolated
$AlCl_3$	−40°, 35 mins, to −8° over 16 hrs	11	29	27, m.p. 33–35°, +1·7, m.p. 28–34°
$AlCl_3$	20–25°, 25 mins	16·5	17	11, m.p. 29–35°
$AlCl_3$	20–25°, 2½ hrs	19	18	12, m.p. 33–34°
$SnCl_4$	−40°, 1 hr, to −5° over 16 hrs	24	36	39, m.p. 29–33° 26, m.p. 35–36°

* *o*-aceto-*β*-phenethyl chloride, (estimated from Cl content of mixture).

† 4-acetobenzocyclobutene (estimated by difference).

was dissolved in 40 ml dioxan. To this was added a solution of 3·2 g (20·1 mM) Br_2 and 2·1 g (52·5 mM) NaOH in 32 ml water to give a homogeneous mixture which was allowed to stand at room temp overnight. $CHBr_3$ and dioxan were extracted from the mixture with diethyl ether (100 ml, × 5) and the resulting aqueous solution saturated with SO_2; 0·690 g of slightly discoloured material melting over the range 120–130° precipitated. This was separated, dissolved in 10 ml diethyl ether and the solution passed through a column containing 1 g charcoal:kieselguhr 1:1, a further 50 ml solvent was used to elude the column. The solvent was removed and the colourless product recrystallized once from petroleum (b.p. 100–120°) and once from water to give 0·594 g (4·02 mM, 73·5%) of *benzocyclobutene-4-carboxylic acid* as white needles, m.p. 139–140°. IR KBr disc: maxima (cm^{-1}) at 1680 s (aryl carboxylic acid C=O), 1210 m (benzocyclobutene methylenes?), 855 m 780 s (1,2,4-trisubstituted benzene, frequency lowered below normal range by carboxyl substituent). UV in ethanolic 0·05N HCl maxima mμ, (ε): 237·5 (12,250), 278·5 (2,080), 289·5 (1,880). Base equivalent found: 150; $C_9H_8O_2$ requires: 148 (Found: C, 72·69, 72·61; H, 5·44, 5·50. $C_9H_8O_2$ requires: C, 72·93; H, 5·44%). *Benzylisothiuronium salt*; colourless leaflets from water m.p. 173–174° (Found: S, 9·75. $C_{17}H_{18}N_2OS$ requires: S, 10·19%).

Benzocyclobutene-4-carboxamide. 1·58 g (0·107M) of benzocyclobutene-4-carboxylic acid was refluxed 30 mins in 5 ml $SOCl_2$. Excess $SOCl_2$ was removed under vacuum leaving *benzocyclobutene-4-carbonyl chloride* as a pale yellow oil. This was dissolved in 50 ml anhydrous diethyl ether, dry NH_3 was passed through the solution for 10 mins and again after an interval of 2 hrs. After standing overnight the mixture was poured into water and the ether layer separated. The aqueous phase, in which was suspended undissolved amide, was extracted four times with 100 ml aliquots of diethyl ether, the extracts dried (Na_2SO_4) and the solvent removed. The product was treated with charcoal in, and recrystallized from water to give 1·44 g (0·098M, 91%) of benzocyclobutene-4-carboxamide as colourless needles m.p. 142–143°. IR KBr disc, maxima (cm^{-1}) at 3350–3150 s (internally bonded amide N-H), 1670 s (amide C=O), 1620 s (amide NH_2), 905 m 845 m (1,2,4-trisubstituted benzene). (Found: C, 73·09, 73·40; H, 5·89, 5·90; N, 9·77, 9·85. C_9H_9ON requires: C, 73·50; H, 6·16; N, 9·52%). The compound was shown to be neutral, contained no chlorine and liberated NH_3 on heating with NaOH aq.

Hoffmann reaction of benzocyclobutene-4-carboxamide. A solution of 505 mg (9·0 mM) KOH and 535 g Br_2 (3·35 mM) in 5 ml water at 0° was added to 535 mg (3·63 mM) of benzocyclobutene-4-carboxamide. The mixture was maintained at 0° and shaken for 3 mins. 720 mg (12·8 mM) KOH in 3 ml water was added and the mixture immediately steam distilled, 25 ml distillate was collected. Diethyl ether (10 ml × 3) extracted from the distillate 285 mg (2·39 mM, 66%) 4-aminobenzocyclobutene as a yellow brown oil. This was dissolved in 1:1 v/v methanol:diethyl ether and treated with 119 mg (ca. 1·19 mM) H_2SO_4 dissolved in 0·5 ml water. The solid, which immediately separated, was removed and washed by repeated suspension in, and filtration from, diethyl ether. On drying was obtained 363 mg (1·08 mM, 59·5%) of di-(benzocyclobutene-4-ammonium) sulphate m.p. 207–208°, undepressed (lit. 207–208°), IR identical with that of the known compound prepared according to Horner, Schmelzer and Thompson.[3] 200 mg (1·19 mM) of the Hoffmann reaction product (sulphate) was dissolved in 40 ml acetone containing 0·4 ml (ca. 4·3 mM) of acetic anhydride and 0·4 ml pyridine. After 15 min at room temp the solvent was removed under vacuum and the residual solid, after treatment with charcoal, recrystallized from methanol aq. The product was 147 mg

(0·91 mM 77%) 4-acetamidobenzocyclobutene, m.p. 142–143°, undepressed (lit.[8] 141–142°): IR identical with the known compound.

Hydrobromination of benzocyclobutene. 5·0 g (48 mM) benzocyclobutene was dissolved in 25 ml glacial acetic acid. To this was added 25 ml of a 45% w/v solution of HBr in the same solvent. The mixture was heated at 100° and a further 25 ml HBr solution added dropwise over a period of 6 hrs. The solution was cooled, poured into 250 ml water, the product worked up through CH_2Cl_2 and distilled to give 4·30 g (23 mM) β-phenethylbromide b.p. 90–91°/10 mm, $n_D^{25°}$ 1.5527 (lit. 92°/11 mm, $n_D^{25°}$ 1·5543) whose IR spectrum was identical to that of the known compound and in addition exhibited weak intensity bands characteristic of the stronger bands of β-phenethyl acetate. (Found: Br, 43·0, 42·5. Calc for C_8H_9Br; Br, 43·2%). From 0·5 g (2·7 mM) of the product was prepared β-phenethylisothiuronium picrate 0·92 g (2·25 mM, 83%) m.p. 138–139°, undepressed (lit. 139°). The forerun from the distillation comprised 1·41 g (14 mM) benzocyclobutene (IR) b.p. 111–115°, 150 mm, containing a trace of bromide and 1·05 g mixture b.p. 60–90°, 10 mm, of benzocyclobutene, β-phenethyl acetate and β-phenethyl bromide (IR) (Found: Br, 39·20; 39·45%). Hence the overall yield of bromide on unrecovered benzocyclobutene was 83%. A negligible quantity of bromine-containing material remained in the distillation flask.

Acknowledgements—We are indebted to Mrs A. A. Johnson for the IR spectra, to Dr. J. MacMillan, Bristol, for the NMR spectrum and to Drs G. Weiler and F. B. Strauss, Oxford, for the microanalyses. We are grateful to Professor P. B. D. de la Mare of London, Dr. S. H. Graham of Aberystywyth and Dr. J. F. W. McOmie of Bristol for their extremely helpful advice. One of us (J.B.F.L.) is indebted to the College of Advanced Technology, Birmingham, for a Research Fellowship.