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THE MILLS NIXON EFFECT

BROMINATION AND NITRATION OF INDAN AND TETRALIN

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Abstract—Product distributions from the bromination and nitration of indan, tetralin and *o*-xylene have been determined by gas chromatography. Indan is shown to give a substantially greater proportion of *ar*-β product than *o*-xylene and tetralin. An explanation for this and for the original results of Mills and Nixon is offered.

THE behaviour of the two benzocycloalkanes, indan and tetralin, towards electrophilic reagents has been the subject of little systematic study, although the closely-related benzocyclobutene has recently received considerable attention.[1] Most of the work on tetralin and indan has been directed towards supporting or disproving the possibility, first postulated in 1935 by Mills and Nixon,[2] of bond fixation in the aromatic part of these compounds. An extensive review of this work is included in a paper by Berthier and Pullman,[3] and it is apparent from this that no quantitative examination of the product distribution resulting from electrophilic substitution in either indan or tetralin has been made. The most that can be said is that both compounds appear to give predominantly *ar*-β substitution. We have studied the bromination and nitration of indan, tetralin and *o*-xylene, and offer an explantion of the results obtained, and of the original results of Mills and Nixon.[2]

The results are shown in the Table. The bromination reactions give only the *ar*-α and *ar*-β products in each case; the Table shows the mole percent of *ar*-β product formed. Nitration in nitric acid–acetic anhydride produces the two *ar*-nitro isomers, together with large amounts of the *ar*-β acetoxylated hydrocarbon. This reaction has already been described in previous papers[4,5] and the kinetics of the acetoxylation and nitration reactions have been studied by Fischer *et al.*[6] It is clear from this latter work that the same species is responsible for both nitration and acetoxylation in this system, and for this reason the β figures used in the discussion are the total percentages for acetoxylation and nitration in this position. The absence of *ar*-α acetoxylation in all three hydrocarbons may be explained in terms of the critical dependence of acetoxylation on activation of the aromatic nucleus discussed in an earlier paper.[5]

Examination of molecular models of the three hydrocarbons shows that the methylene groups adjacent to the aromatic ring in indan offer less steric hindrance to electrophilic attack in the *ar*-α position than do the methyl or methylene groups in

[1] J. B. F. Lloyd and P. A. Ongley, *Tetrahedron* **20**, 2185 (1964).
[2] W. H. Mills and I. G. Nixon, *J. Chem. Soc.* 2510 (1930).
[3] G. Berthier and A. Pullman, *Bull. Soc. Chim. Fr.* 88 (1960).
[4] A. Fischer, J. Packer, J. Vaughan and G. J. Wright, *Proc. Chem. Soc.* 369 (1961).
[5] A. Fischer, J. Packer, J. Vaughan and G. J. Wright, *J. Chem. Soc.* 3687 (1964).
[6] A. Fischer, A. J. Read and J. Vaughan, *J. Chem. Soc.* 3691 (1964).

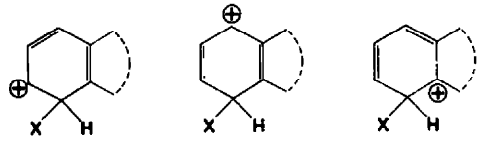
TABLE. PERCENTAGE OF *ar-β* PRODUCT

Hydrocarbon	Reaction conditions					
	Br_2/AcOH	Br_2/aq AcOH	BrOH/AcOH	HNO_3/Ac_2O *nitro-*	HNO_3/Ac_2O *acetoxy-*	HNO_3/Ac_2O *total*
o-Xylene	71 ± 2[a]	75 ± 1	58 ± 2	30 ± 1	55 ± 2	85 ± 3
Tetralin	56 ± 2	61 ± 2	48 ± 4	46 ± 1	28 ± 1	74 ± 2
Indan	78 ± 3	84 ± 2	73 ± 3	54 ± 2	26 ± 2	80 ± 4

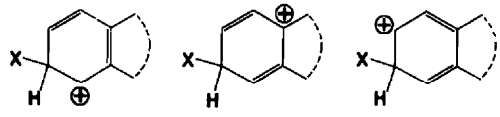
[a] The errors quoted are twice the standard deviation for at least six runs.

o-xylene or tetralin. Experimental evidence supports this conclusion.[7] The difference between tetralin and *o*-xylene is much less clear-cut, and the present discussion will be limited mainly to tetralin and indan. If this type of primary steric effect were governing the product distribution, indan would be expected to give less *ar-β* product than tetralin, but the results show that this is not the case. While this effect must undoubtedly operate, it is clearly outweighed by another factor leading to a much higher proportion of *ar-α* attack in tetralin than in indan.

It has sometimes been assumed that the fused alicycles of indan and tetralin have similar electronic effects, although there is no direct evidence to support this, and the α-hydrogens in indan are better situated for hyperconjugative release than are the corresponding hydrogens in tetralin. However, comparison of the transition states for *ar-α* and *ar-β* substitution shows that electronic effects of this kind can have no effect on the substitution ratios. The relevant resonance forms are likely to approximate to the following:



ar-α substitution



ar-β substitution

When the alternative positions for *ar-α* and *ar-β* substitution are also considered it is evident that, with similar contributions from all canonical forms, the change in charge for any given carbon atom is the same for both types of substitution. In other words, more effective hyperconjugative release in indan should simply result in an increase in the overall rate of substitution and not in a change in orientation.

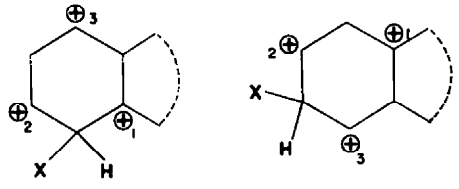
There is however one important difference between the two sets of resonance

[7] R. T. Arnold, V. J. Webers and R. M. Dodson, *J. Amer. Chem. Soc.* **74**, 368 (1952) and earlier papers.

forms. In *ar*-α substitution the bond common to the two rings has effectively ⅔ double bond character, while in *ar*-β substitution it has ⅓ double bond character. The effect of changes in the length and double bond character of this common bond has been discussed.[8,9] Such discussions have usually concerned the ground state, though there have been attempts to relate ground and transition states.[8,10] It has generally been assumed that increasing the double bond character of this common bond in indan will result in a less stable system because of the increased strain in the alicyclic ring, while in tetralin an increase in stability will result. Brown[11] reviews results that are in line with such an assumption. The simple comparison above indicates that these differences become important in forming the transition states, and that indan should favour *ar*-β substitution and tetralin *ar*-α substitution. The results support this conclusion. Further, in the case of the bromination reactions at least, *o*-xylene gives a product distribution which lies between indan and tetralin, as might be expected for the parent compound. This explanation can be satisfactorily extended to account for the results obtained by Mills and Nixon, and recently confirmed by Pascual,[12] i.e., that 5-hydroxyindan brominates and couples almost exclusively in the 6-position, whereas 6-hydroxytetralin undergoes these reactions in the 5-position. The resonance forms for the transition states now include a fourth form involving a positively-charged phenol group, giving ¾ double bond character for the common bond in *ar*-α attack and ¼ double bond character for *ar*-β attack. Whether or not the extra resonance forms make contributions to the transition state equal to or greater than the other forms, in each case the effect on the bond common to the two rings is in the direction required by this explanation. We assume that the added difference in stability between the two transition states arising from this extra resonance form is sufficient to lead to almost exclusive substitution in the favoured position.

The results of reactivity studies like those presented in this paper can give no information about the possible existence of significant bond fixation in the ground states of these molecules. Since the ground state of each hydrocarbon is the same for both positions of substitution, the factor determining the product distribution is the relative stability of the two transition states. Satisfactory investigations into the nature of the ground state have recently been carried out by modern physical techniques.[13]

The variations found in product distribution between the three bromination systems are of interest. It has been pointed out that the positions of the formal



ar-α ar-β

[8] H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **42**, 756 (1946).
[9] F. P. K. de Jong, *Het Mills-Nixon Effect* p. 118. Thesis Amsterdam (1951).
[10] A. Kossiakoff and H. D. Springall, *J. Amer. Chem. Soc.* **63**, 2223 (1941).
[11] H. C. Brown, J. H. Brewster and H. Shechter, *J. Amer. Chem. Soc.* **76**, 467 (1954).
[12] O. S. Pascual, *Chem. Abstr.* **60**, 10516f (1964).
[13] P. Madhaven Nair and G. Gopakumar, *Tetrahedron Letters* **20**, 709 (1964).

positive charges on the *ar*-α and *ar*-β transition states relative to the methylene groups are the same. Charges (1) are on tertiary carbons which will be less demanding of stabilization by the solvent, while charges (2) are equivalent and may be ignored when comparing the two transition states. Any significant differences must therefore arise from differences in the stabilization of charges (3) by the solvent. Charge (3) is much more readily accessible to solvent molecules in the *ar*-α transition state than it is in the *ar*-β state; thus the former state will be preferentially stabilized. This effect will tend to increase the amount of *ar*-α product formed in both indan and tetralin. The results obtained from bromination in glacial acetic acid and aqueous acetic acid allow this to be tested, since the brominating species, molecular bromine, is the same in both solvents.[14] In aqueous acetic acid, the smaller and more effectively solvating water molecules will suffer less steric hindrance at charge (3) in the *ar*-β transition state than will acetic acid molecules, and there will be less difference between solvent stabilization of the two states than in glacial acetic acid. There should therefore be more *ar*-β product formed in aqueous acetic acid than in glacial acetic acid, and the results support this conclusion. In acidified hypobromous acid the effective attacking species, $BrOH_2^+$,[15] is a much more vigorous electrophile than molecular bromine, and as expected, shows less selectivity than Br_2.

Two further points are of interest. Very recently Tanida and Muneyuki reported the nitration of indan and tetralin in nitromethane, as model compounds for their study of bridged hydronaphthalenes.[16] Although they find that both compounds give almost equal amount of *ar*-α and *ar*-β substitution, with very slightly more *ar*-α product in tetralin than in indan, these authors do not report the exact conditions used, or give any estimate of the accuracy of their analyses. We can report preliminary results which indicate that in nitromethane as solvent, with catalytic amounts of sulphuric acid, the differences between the product ratios in indan and tetralin are comparable with our main results. Finally, Granger *et al.*[17,18] report results for chloromethylation of indan and tetralin, and for positions of closure in the cyclisation of *o*-xylene-, indan- and tetralin-3-propionyl chlorides. The chloromethylation results are similar to our bromination figures. The cyclizations, carried out under Friedel-Crafts conditions, are less useful for comparison but show the same order of reactivity with much larger differences between indan and tetralin than found in the other results.

EXPERIMENTAL

M.ps are uncorrected. Hydrocarbons used were Laboratory Reagent grade, dried and distilled before use, and showing less than 0·5% detectable impurity on the gas chromatograph (4′ × ¼″ column packed with 10% tricresyl phosphate on 100–120 mesh Celite). Acetic acid and $AgNO_3$ were AnalaR grade chemicals used without further purification. HNO_3 used for nitrations in acetic anhydride was purified as previously described.[5] The Br_2 used had an assay of better than 99%. The purity of all compounds used for calibrating the gas chromatographs was shown by IR spectroscopy and gas chromatography to be better than 99·5%.

[14] P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution, Nitration and Halogenation.* Butterworths, London (1959).
[15] D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.* 564 (1950).
[16] H. Tanida and R. Muneyuki, *Tetrahedron Letters* No. 20, 2787 (1964).
[17] R. Granger and H. Orzalesi, *C.R. Acad. Sci., Paris* **252**, 1478 (1961).
[18] R. Granger, H. Orzalesi and A. Muratelle, *C.R. Acad. Sci., Paris* **252**, 1971 (1961).

Preparation of materials

3-*Bromo*-o-*xylene* was prepared from commercial 3-nitro-*o*-xylene by reduction to 3-amino-*o*-xylene, followed by a Sandmeyer reaction on the amine to give 3-bromo-*o*-xylene, b.p. 98°/18 mm.

4-*Bromo*-o-*xylene* was prepared from 4-nitro-*o*-xylene by the method described for the 3-isomer.

4-*Bromoindan.*[19] *o*-Bromotoluene (51 g) was refluxed for 6 hr with N-bromosuccinimide (60 g) in CCl_4 (600 ml) to give *o*-bromobenzyl bromide (59 g, 80%). Treatment of this with ethyl malonate (120 g) and Na (9 g) in dry EtOH (290 g) under reflux for 2 hr gave *o*-bromobenzyl malonic ester (40 g, 72%), and excess malonic ester. Hydrolysis of the *o*-bromobenzyl malonic ester for 24 hr at room temp with $Ba(OH)_2$ (60 g) in EtOH–water gave *o*-bromobenzyl malonic acid (30 g, 91%), and decarboxylation of the acid in boiling water gave *o*-bromobenzyl acetic acid (18·9 g, 76%). Treatment of the acid with thionyl chloride (50 g), followed by $AlCl_3$ (14 g) in CS_2 (400 ml) at reflux for 3 hr gave 4-bromoindan-1-one after removal of the solvent by steam distillation. The product (13·5 g, 78%) had m.p. 94° (lit.[19] 97°). Clemmenson reduction of the ketone using toluene as solvent[20] gave 4-bromoindan (5 g, 40%) b.p. 90°/1 mm.

5-*Bromoindan* was prepared by a modification of Baker's method,[21] using conditions for the Beckmann rearrangement developed by Roberts and Chambers.[22] Indan (100 g) was refluxed with acetyl chloride (80 g) and $AlCl_3$ (120 g) in CS_2 (800 ml) to give 5-acetylindan, b.p. 142°/15 mm (80 g, 60%), which on refluxing with hydroxylamine hydrochloride (30 g) in EtOH–water for 4 hr gave 5-indanyl-methyl-ketoxime (41 g, 94%). The oxime (30 g) was reacted with PCl_5 (20 g) in dry ether at 0°C for 2 hr to give N-acetyl-5-aminoindan, m.p. 106° (lit.[22] 106°), (18 g, 60%). Hydrolysis of the acetyl derivative in HCl gave the amine, m.p. 35° (lit.[23] 37°), which was converted to 5-bromoindan by a Sandmeyer reaction; yield 3 g (29%), b.p. 110–112°/15 mm (lit.[24] 113°/14 mm).

5-*Bromotetralin* was prepared from 5,6,7,8-tetrahydro-1-naphthylamine (L. Light and Co.) by a Sandmeyer reaction. It had b.p. 104–105°/2 mm.

6-*Bromotetralin* was prepared from 5,6,7,8-tetrahydro-2-naphthylamine (L. Light and Co.) using N_2O_3 and HBr.[25] A solution of the amine (0·1 mole), acetic acid (125 ml) and HBr (40%, 50 ml) was saturated with N_2O_3, refluxed for 10 min, and neutralized with 20% NaOH aq. The solution was extracted with ether, washed with 20% NaOH aq and water, dried ($MgSO_4$) and distilled to give 6-bromotetralin (4 g, 20%), b.p. 104°/2 mm.

3-*Nitro*-o-*xylene*, 4-*nitro*-o-*xylene* and 3,4-*dimethylphenyl acetate* were prepared as described in a previous paper.[5]

4-*Nitroindan* was prepared by nitration of indan (25 g) in fuming HNO_3 (93 ml) and glacial acetic acid (50 ml) at 20–25° for 2 hr. The reaction was quenched with water, extracted with ether, the extract dried ($MgSO_4$) and distilled to give a mixture of 4-nitro- and 5-nitroindans. The 4-nitroindan. isolated using the Megachrom preparative gas chromatograph, had m.p. 40–40·5° after one recrystallization from 50–70° pet. ether. (lit.[24] m.p. 44°).

5-*Nitroindan* was prepared by peracetic acid oxidation of the 5-aminoindan intermediate in the preparation of 5-bromoindan. A mixture of $CHCl_3$ (30 ml), H_2O_2 (95%, 7 ml) and one drop of conc. H_2SO_4 was stirred in an ice bath, and acetic anhydride (30 ml) added dropwise over 30 min. The opalescent solution, on removal from the ice, rapidly cleared and became very hot. $CHCl_3$ (20 ml) was added, the mixture heated to boiling, and 5-aminoindan (7 g) in $CHCl_3$ (15 ml) was added over 15 min; the heat of reaction maintained the solution at reflux without additional heating. The solution was refluxed for 1 hr, poured into water, and the organic layer separated, washed successively with water, 20% NaOH aq, 10% HCl, and water, dried ($MgSO_4$) and distilled to give 3·1 g (36%) 5-nitroindan, m.p. 38–39° after one recrystallization from 50°–70° pet. ether (lit.[24] 40°). The NMR spectra clearly distinguished the 4-nitro- and 5-nitroindans, which have similar m.ps.

[19] L. F. Fieser and A. M. Seligman, *J. Amer. Chem. Soc.* **57**, 2174 (1935).
[20] Pl. A. Plattner, *Helv. Chim. Acta* **27**, 801 (1944).
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[23] I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*. Eyre and Spottiswoode, London (1946).
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5-Indanyl acetate was prepared from indan-5-sulphonic acid by fusion of the sodium salt with KOH[26] and acetylation of the resulting 5-indanol. Sulphonation was carried out at 25° for 12 hr to ensure that a negligible amount of the 4-acid remained. The 5-indanol, after recrystallization from 50°–70° pet. ether had m.p. 54° (lit.[24] 55°) and showed no trace of 4-indanol (Pye Argon). The phenol was acetylated in acetic anhydride–NaOH; the acetate had b.p. 122–124°/1 mm, and contained no detectable phenol.

5-Nitrotetralin was prepared from 5,6,7,8-tetrahydro-1-naphthylamine by oxidation with peracetic acid as described for 5-nitroindan. It had m.p. 31–32° (lit.[25] 34°) after two recrystallizations from MeOH.

6-Nitrotetralin was prepared from 5,6,7,8-tetrahydro-2-naphthylamine by peracetic acid oxidation. It had m.p. 30° (lit.[25] 31·4°) after two recrystallizations from MeOH and one from pet. ether.

6-Tetralyl acetate was prepared by fusion of the sodium salt of tetralin-6-sulphonic acid with KOH.[27] The sulphonic acid, prepared from tetralin and H_2SO_4 at 100° for 8 hr, was extracted twice with cold $CHCl_3$ to remove insoluble 5-sulphonic acid. The 6-hydroxytetralin, after extraction from the fusion mixture and recrystallization from ligroin, had m.p. 59–60°, and after recrystallization from 50°–70° pet. ether had m.p. 53–55°. (Lit.[24] m.p. for the dimorphic phenol, 60–61° and 53–54°). The phenol was acetylated in acetic anhydride–NaOH; the acetate contained ca. 10% phenol which was removed on the Megachrom.

Bromination with molecular bromine. These reactions were carried out in glacial acetic acid and in 85% (V/V) acetic acid in water. To prevent the formation of lachrymatory by-products from homolytic attack of Br_2 on the side chains, reaction vessels were coated with black paint. Hydrocarbon (0·025 mole) dissolved in the appropriate solvent (25 ml) was contained in blackened flasks in a water bath at 25°. The Br_2 solution (0·025 mole in 20 ml solvent) was added dropwise over 1 hr. The reaction mixture was allowed to stand for 24 hr, quenched with distilled water, and the organic layer extracted with ether. The extract was washed with 20% NaOH aq, water, dried ($MgSO_4$) and the solvent removed under vacuum. The resulting mixture was analysed on the gas chromatograph without further treatment.

Bromination with hypobromous acid. Because of its instability, hypobromous acid was prepared *in situ*.[28] Hydrocarbon (0·025 mole) was dissolved in a mixture of glacial acetic acid (75 ml), dil. HNO_3 (33%, 36 ml) and $AgNO_3$ (4·25 g in 12·5 ml water), and the solution agitated at 25°. Br_2 (0·025 mole) dissolved in acetic acid (10 ml) was dropped into the hydrocarbon solution and the mixture allowed to stand for 24 hr at 25°, poured into water and neutralized with 20% NaOH aq. The organic material was extracted with ether, washed with 20% NaOH aq, dried ($MgSO_4$) and the solvent removed under vacuum. The resulting mixture was used for analysis without further treatment.

Nitration in acetic anhydride. The reactions were carried out as described in a previous paper.[5]

Product analysis. All reaction mixtures were analysed by gas chromatography—products of brominations on a Pye Argon instrument fitted with Sr^{90} argon detector, and nitrations on a locally-made instrument fitted with a Gow Mac 091 Gas Density Balance as detector. Both instruments were calibrated for all compounds analysed on them. Peak areas from the argon detector were found, for each of the three pairs of bromo hydrocarbons, to give mole percentages without correction. Peak areas from the Gow Mac detector, when multiplied by the appropriate correction factor[29] for each compound, gave weight percentages directly, and these were converted to molar figures. Peak areas were calculated as the product of peak height and width at half height for all analyses. The bromo compounds were analysed on a 4′ × ¼″ column packed with polyethylene glycol adipate on 80–100 mesh Celite, at temp between 75° and 125°. Nitration mixtures were analysed on a 6′ × ¼″ column, packed with 15% polyethylene glycol adipate on 80–100 mesh Chromosorb P at temp between 180° and 220°. Complete separation of all components in each mixture was achieved.

[26] A. H. Cook and R. P. Linstead, *J. Chem. Soc.* 946 (1934).
[27] V. C. E. Burnop, G. H. Elliot and R. P. Linstead, *J. Chem. Soc.* 727 (1940).
[28] D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.* 573 (1950).
[29] Gow Mac Instrument Co., *Instructions for Gow Mac Gas Density Balance Model* 091 (1963).

Identification of reaction products

Bromination reactions. The two products obtained from each bromination reaction were identified by comparison of their retention times with those of authentic materials, on at least two different columns on the Pye Argon.

Nitration reactions. Each component from nitration reactions, when isolated, was checked for purity on the Pye Argon, and shown to give one peak.

o-*Xylene.* The identification of products from the nitration of *o*-xylene in HNO_3–acetic anhydride has been described in a previous paper.[5]

Indan. The three products were isolated (Megachrom and Gas Density instrument) and identified by their IR spectra, which were identical with the spectra of authentic materials. The 4-nitro- and 5-nitroindans had m.ps identical with authentic materials. 5-Indanyl acetate was hydrolysed (MeOH–H_2SO_4) to 5-indanol, m.p. and IR spectrum identical with authentic material.

Tetralin. 5-Nitrotetralin and 6-nitrotetralin were isolated (Megachrom and Gas Density chromatograph) as solids with m.ps and IR spectra identical with those of the authentic materials. 6-tetralyl acetate was isolated (Megachrom) as an oil, with IR spectrum identical to the authentic material, and hydrolysed (MeOH–H_2SO_4) to 6-hydroxytetralin, with m.p. and IR spectrum identical to authentic 6-hydroxytetralin.

Check on extraction procedure. To ensure that no change in product composition occurred during extraction, several synthetic mixtures of the products of each reaction were analysed before and after being subjected to the extraction procedure. No significant change in composition occurred.

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