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BENZYNE CYCLISATION WITH CARBANION ACTIVATED AROMATIC RINGS[1]

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Abstract—Attempts to cyclise *o*-chlorophenyl benzyl ether, sulphide, sulphoxide and sulphone by treatment with KNH_2/NH_3 were unsuccessful. Similar reaction of 1-(*o*-chlorophenyl)-2,2-diphenylethane led to amination whereas α-(*o*-chlorobenzyl)phenylacetic acid gave a dihydrocoumarin. Reaction of 4- and 2-(*o*-chlorophenethyl)-pyridines, however, afforded products comprising benzisoquinolines and 1-pyridylbenzocyclobutenes.

Reaction of *o*-chlorobenzylanilines with KNH_2/NH_3 is a useful new route to dihydrophenanthridines. For the success of this benzyne mediated cyclisation, it is essential that the aromatic ring be rendered strongly nucleophilic by a negative charge on the adjoining N atom.[2] To find out whether carbanions can also play the requisite activating role, reactions involving intermediates of the type 2 have been investigated in the present work. It is clear that the group X and/or Y should stabilise the carbanion 2, to ensure its rapid generation, but not to an extent so that sufficient activation of the attached aromatic ring does not ensue. In view of the success in cyclisation of benzylanilines, carbon acids with similar pK_a value (~27 on McEwen's scale[3]) seemed most promising. Anyway, it was hoped that the correct balance would be struck somewhere in the series 1_a to 1_f.

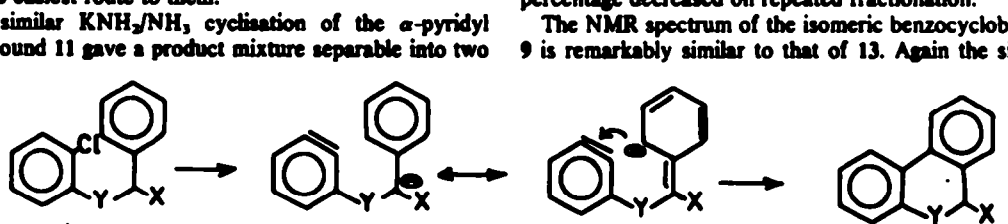
Treatment of the sulphide 1_a or the sulphoxide 1_b with excess KNH_2 in liquid ammonia led to complex mixtures from which no pure compounds could be isolated. Similarly, reaction of the sulphone 1_c, the ether 1_d and the diphenyl compound 1_e, primarily gave amination products. The acid 1_f, on the other hand, led to the dihydrocoumarin 5.

Attention was then diverted to pyridyl compounds, it being well known that α- and γ-picolines can be readily metalated. Reaction of the chloride 7 with KNH_2 in liquid ammonia (3 hr) gave a mixture containing two major products which could be separated by fractional distillation. The higher boiling fraction (~15%) corresponded to the known[4] dihydro compound 8. Its identity was confirmed by aromatisation to the known[5] benz(h)isoquinoline (10). The second fraction (~37%) obtained in the above reaction was identified as a benzocyclobutene (9) on basis of the NMR evidence discussed later. Compounds of the type 9 exhibit, as a class, many interesting reactions and this procedure seems to be the easiest route to them.

A similar KNH_2/NH_3 cyclisation of the α-pyridyl compound 11 gave a product mixture separable into two fractions. The lower boiling material (~36%) was almost pure cyclobutene 13. The TLC of the higher boiling fraction revealed it to contain at least two major products. It was treated with picric acid and two pure picrates were obtained by fractional crystallisation. M.p. (248–9°) of one of these corresponded to that of the picrate from benzo(f)quinoline.[6] The elemental analysis for the second picrate indicated it to be an amination product and it was not investigated further.

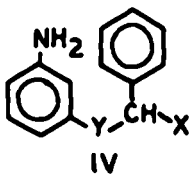
The NMR spectrum of the compound 13 exhibited three quartets centred around δ 4.89 (1H), δ 3.77 (1H) and δ 3.32 (1H) as a part of an approximate XYZ system. The quartet around δ 4.89 can be assigned to H_1, its low field position being the result of paramagnetic shielding of two adjoining aromatic rings. Among the other two quartets, assignments may be made on basis of observed coupling constants. It is known[7] that in benzocyclobutenes coupling constant between *trans* vic protons is large as compared to *cis* vic protons. The two coupling constants, which can be only approximately extracted by a first order treatment, for the quartet centred at δ 3.77 are 14.5 and 6 Hz whereas for the quartet centred at δ 3.32 the values are 14.5 and 3 Hz. The first coupling constant in each case probably represents a geminal coupling (H_2, H_3), the observed value is in fact very close to that reported for 1-bromobenzocyclobutene.[7] On comparing the other two values, the larger (6 Hz) may be assigned to H_1–H_3 coupling and the smaller to H_1–H_2 coupling. Thus the quartet at δ 3.77 may be considered to arise from H_3 and the one at 3.32 from H_2. Other features in the NMR spectrum are also in agreement with the structure 13. Besides the aromatic protons in δ 7.8–7 region, the ortho proton of the pyridine ring can be clearly discerned as a doublet at δ 8.59. The signals observed at δ 3.1 and 1.3 are considered to arise from some impurity which could not be eliminated though its percentage decreased on repeated fractionation.

The NMR spectrum of the isomeric benzocyclobutene 9 is remarkably similar to that of 13. Again the signals

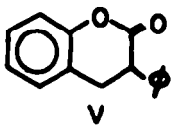


I II III

a, X = H, Y = S; b, X = H, Y = SO; c, X = H, Y = SO_2;
d, X = H, Y = O; e, X = φ, Y = CH_2; f, X = COOH, Y = CH_2



IV



V

from the three protons of the four membered ring are discernible as three quartets in δ 4.8–2.87 region. The relative intensity of the low field doublet (δ 8.4) in this case corresponds to 2H as expected for the two protons ortho to the nitrogen atom of the pyridine ring.

From the above experiments it may be concluded that although benzyne cyclisations can be effected with carbanion activated aromatic rings, the reaction is not widely applicable. Many subtle features, besides the acidity of the carbon acids, seem to influence the fate of this cyclisation.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were measured on a Perkin-Elmer 337 apparatus and mass spectra (70 e/V) were recorded on a MS-9 spectrometer. NMR spectra were recorded on a Varian Associates Model HA-100 instrument.

Procedure for reaction with potassium amide in liquid ammonia. The general procedure for reaction of various substrates with KNH_2/NH_3 was the same as described earlier.[2] To the residue obtained after evaporation of liquid NH_3, water was added followed by dil. HCl. Non basic material was then taken up in ether, dried and the solvent distilled off. In some cases amination products, obtained after basification of the HCl layer, were also examined.

o-Chlorophenyl benzyl sulphide (1_a)

A mixture of *o*-chlorothiophenol[9] (7.2 g, 49.7 mmole), benzyl chloride (6.3 g, 49.8 mmole), anhyd. K_2CO_3 (7 g, 50.7 mmole) and DMF (30 ml) was heated at 100° for 2 hr. The cooled mixture was poured into water (125 ml) and extracted with ether. The organic layer was washed with Na_2CO_3 (2%, 2 × 10 ml) followed by water (20 ml) and dried. The solvent was evaporated and the residue distilled under reduced pressure giving 1_a (8 g, 68.9%), b.p. 159–160°/3 mm. (Found: C, 67.01; H, 5.13. $C_{13}H_{11}ClS$ requires: C, 66.52; H, 4.69%).

Reaction of o-chlorophenyl benzyl sulphide (1_a) *and sulphoxide* (1_b) *with potassium amide.* Reaction of 1_a (5.2 g, 22.1 mmole) with KNH_2 (from 5.3 g, 135 mmole, K metal) and work up according to the general procedure afforded a complex mixture (1.62 g) which showed five spots on TLC. No pure material could be isolated from it or from the acid soluble fraction.

The sulphoxide 1_b was prepared from 1_a by reaction (48 hr) with monoperphthalic acid (1.1 mole) in abs. ether at room temp. Reaction of the crude material with KNH_2 (6 mole) in liquid NH_3 gave a complex mixture from which no pure products could be isolated.

o-Chlorophenyl benzyl sulphone (1_c)

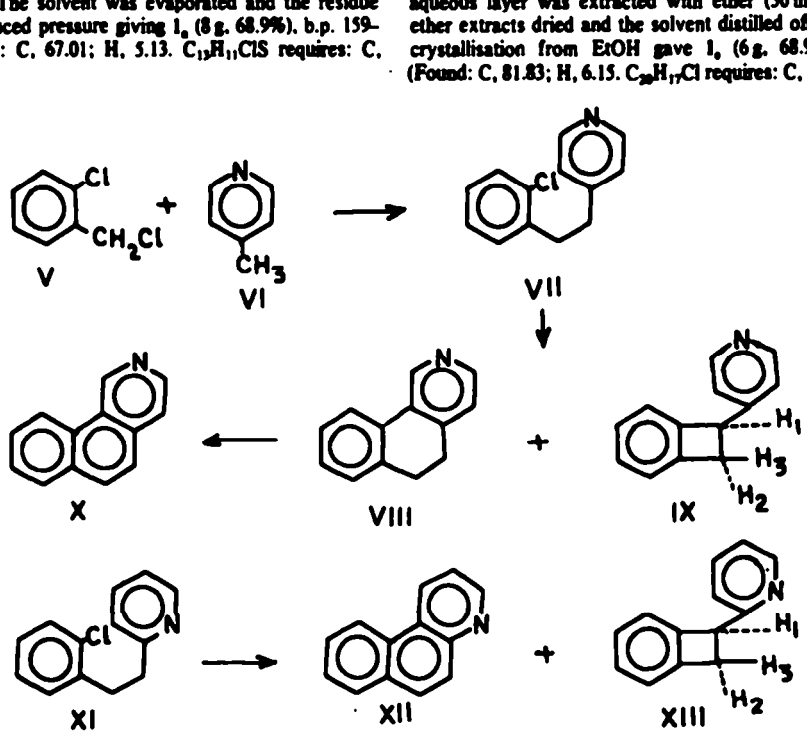
To the sulphide 1_a (7.05 g, 30 mmole) in AcOH (10 ml) was added H_2O_2 (7 g, 40%). When the reaction subsided a second portion of H_2O_2 (4 g, 30%) was added and the mixture then refluxed for 3 hr and poured into ice water (50 ml). The ppt (6 g, 74.9%) was filtered off, dried and crystallised from benzene–pet. ether to give 1_c, m.p. 102–3°. (Found: C, 58.28; H, 4.12. $C_{13}H_{11}ClO_2S$. Requires: C, 58.53; H, 4.12%).

Reaction of o-chlorophenyl benzyl sulphone (1_c) *with potassium amide.* The sulphone 1_c (1 g, 3.7 mmole) was reacted with KNH_2 (from 0.865 g, 22.2 mmole, K metal) according to the general procedure. The HCl-layer obtained on standing deposited crystals (0.8 g), m.p. 139–40° (EtOH). The mass spectrum of this material corresponded to that expected of the hydrochloride of amine 4_c, *m/e* 248 (M^+).

Reaction of o-chlorophenyl benzyl ether (1_d) *with potassium amide.* The ether 1_d[9] (1 g, 4.5 mmole) was reacted with KNH_2 (from 1.053 g, 27 mmole, K metal) in liquid NH_3. On usual work up only a small amount of non basic material was obtained. The acid soluble fraction on basification gave *m*-aminophenyl benzyl ether, m.p. 147–8° (EtOH) (lit.[10] m.p. 149°).

1-(*o-Chlorophenyl*)-2,2-*diphenylethane* (1_e)

Diphenylmethane[11] (5 g, 29.7 mmole) in abs. ether (25 ml) was added slowly to well stirred KNH_2 (from 1.16 g, 29.7 mmole, K metal) in liquid NH_3. Stirring was continued for 15 min. and *o*-chlorobenzyl chloride (5 g, 31 mmole) in abs. ether (15 ml) was added. After 1 hr additional stirring, NH_3 was allowed to escape simultaneously adding abs. ether (150 ml). When the whole of NH_3 had escaped, the mixture was refluxed for an additional 2 hr. Water (100 ml) was added and the ethereal layer separated. The aqueous layer was extracted with ether (50 ml), the combined ether extracts dried and the solvent distilled off. The residue on crystallisation from EtOH gave 1_e (6 g, 68.9%), m.p. 66–7°. (Found: C, 81.83; H, 6.15. $C_{20}H_{17}Cl$ requires: C, 82.06; H, 5.81%).



Reaction of 1 - (o - *chlorophenyl*) - 2,2 - *diphenylethane* (I_o) *with potassium amide.* Compound I_o (1 g, 3.41 mmole) was reacted with KNH_2 (from 1.335 g, 34.2 mmole, K metal) and worked up according to general procedure. The residue obtained after evaporation of the ether layer was subjected to thick layer chromatography on silica gel. The obtained major fraction was crystallised twice from acetone–pet. ether to give a solid, m.p. 121–3°, mass spectrum *m/e* 273 (M^+). (Found: C, 87.56; H, 6.78; N, 4.72. $C_{20}H_{19}N$ requires: C, 87.90; H, 6.96; N, 5.12%).

It is, presumably, an amination product whose hydrochloride is either insoluble in water or which does not easily form a hydrochloride.

Reaction of α-(o-chlorobenzyl)phenylacetic acid (I_f) *with potassium amide.* The acid I_f[12] (0.4 g, 1.5 mmole) was reacted with KNH_2 (from 0.69 g, 17.7 mmole, K metal) in liquid NH_3. After the usual work up a gummy residue (150 mg) was obtained. TLC revealed it to be a complex mixture, the major component being ~50%. Crystallisation from aqueous EtOH gave 5 (50 mg), m.p. 120–21°, IR 1800 cm^{-1} (C=O), mass spectrum *m/e* 224 (M^+). (lit.[13] m.p. 122°).

4-(o-*Chlorophenethyl)pyridine* (7). γ-Picoline (7 g, 75.2 mmole) in abs. ether (15 ml) was added to well stirred KNH_2 (from 3 g, 76.9 mmole, K metal) in liq. NH_3 (800 ml) and the whole stirred for 15 min when a dark red colour developed. *o*-Chlorobenzyl chloride (12 g, 74.5 mmole) in abs. ether (10 ml) was then added and the mixture stirred for 1.5 hr. Ammonia was allowed to escape, the residue diluted with water (50 ml) and extracted thoroughly with ether (150 ml). The organic layer was washed with water (15 ml), dried and the solvent distilled off. The residue on distillation afforded 7 (4 g, 24.8%), b.p. 104°/0.1 mm. (Found: C, 72.13; H, 5.92; N, 6.21. $C_{13}H_{12}NCl$ requires: C, 72.04; H, 5.08; N, 6.00%). With ethanolic picric acid, it gave a picrate, m.p. 171–2°. (Found: N, 12.40. $C_{19}H_{15}ClN_4O_7$ requires: N, 12.57%).

Reaction of 4 - (o - *chlorophenethyl)pyridine* (7) *with potassium amide.* The compound 7 (3.9 g, 18 mmole) was treated with KNH_2 (from 5 g, 0.128 mmole, K metal) in liquid NH_3. The residue, obtained after the usual work up, was diluted with water and extracted with ether. The ethereal layer was washed with water, dried and the solvent distilled off. On distillation of the residual oil (4 g) two fractions were collected:

Fraction (a), IX (1.20 g, 36.9%), b.p. 120–7°/0.6 mm, NMR (CCl_4) δ 8.4 (d, 2, protons *ortho* to the N atom), δ 7–8 (m, 6, aromatic protons of phenyl and pyridine rings), δ 4.57 (q, 1, H_1), δ 3.75 (q, 1, H_1), δ 3.02 (q, 1, H_2), δ 2.85 (s, impurity), δ 1.3 (s, impurity). (Found: C, 86.46; H, 5.27; N, 7.95. $C_{13}H_{11}N$ requires: C, 86.18; H, 6.07; N, 7.73%). With ethanolic solution of picric acid, it gave a picrate, m.p. 154–5° (EtOH). (Found: N, 13.63. $C_{19}H_{14}N_4O_7$ requires: N, 13.66%).

Fraction (b), 8 (0.48 g, 14.7%), b.p. 135–7°/0.6 mm (lit.[4] b.p. 140°/1 mm). With ethanolic soln of picric acid, it gave a picrate, m.p. 194–6° (EtOH) (lit.[4] m.p. 195–6°).

Benz(h)isoquinoline (10). Dehydrogenation of 8 with Pd-C, according to the procedure of Herz and Murty,[4] afforded 10, m.p. of the picrate 232–3° (lit.[5] m.p. 232°).

2-(o-*Chlorophenethyl)pyridine* (11). Reaction of α-picoline (12 g, 0.129 mole) and *o*-chloro-benzyl chloride (20 g, 0.124 mole) with KNH_2 (from 6 g, 0.153 mole, K metal) in liq. NH_3 according to the procedure afforded 11 (3 g, 10.7%), b.p. 104°/0.01 mm (lit.[14] b.p. 105–15°/8 × 10^{-3} mm). Its picrate, crystallised from benzene, had a m.p. 134–5° (lit.[14] m.p. 134–5°).

Reaction of 2-(o-*chlorophenethyl)pyridine* (11) *with potassium amide.* The compound 11 (7 g, 0.032 mole) in abs. ether (20 ml) was treated with KNH_2 (from 7.51 g, 0.192 mole, K metal) in liquid NH_3. On work up as above two fractions were obtained:

Fraction (a), 13 (1.5 g, 36%), b.p. 104–10°/0.002 mm, NMR (CCl_4) δ 8.59 (d, 1, proton *ortho* to N atom), δ 7.8–7 (m, 7, aromatic protons of phenyl and pyridine rings), δ 4.89 (q, 1, H_1), δ 3.77 (q, 1, H_1), δ 3.32 (q, 1, H_2), δ 3.1 (s, impurity), δ 1.3 (s, impurity). (Found: C, 85.90; H, 6.77; N, 7.63. $C_{13}H_{11}N$ requires: C, 86.18; H, 6.07; N, 7.73%). With ethanolic soln of picric acid, it gave a picrate, m.p. 155–6° (EtOH). (Found: N, 13.52; $C_{19}H_{14}N_4O_7$ requires: N, 13.65%).

Fraction (b), 0.5 g, b.p. 115–30°/0.002 mm. On treatment with ethanolic picric acid, it gave a mixture of picrates which was separated by fractional crystallisation from benzene. The less soluble one had a m.p. 248–9° (lit.[4] m.p. for picrate of benzo(f)quinoline 251–2°).

The more soluble picrate, on crystallisation from EtOH had m.p. 176–8°. (Found: N, 16.13. $C_{19}H_{17}N_5O_7$ requires: N, 16.40%).

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