

Homolytic Substitution of Heteroaromatic Compounds. Part I. Homolytic Benzylolation of Pyridine, Quinoline, and Isoquinoline in Acidic and Non-acidic Media

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The effect of *N*-protonation on the homolytic benzylolation of pyridine, quinoline, and isoquinoline has been studied. Pyridine is not benzylated in non-acidic solution, but 2- and 4-benzylpyridine are formed in acidic media. Benzylolation of quinoline at positions 2 and 4, and isoquinoline at positions 1, 3, and 4, occurs to a small extent in non-acidic solution, and the reactivities of positions 2 and 4 in quinoline and position 1 in isoquinoline are enhanced in acidic media.

RECENT work has shown the effect of *N*-protonation on the reactivity of pyridine and its mono- and di-methyl derivatives towards homolytic substitution by phenyl and substituted phenyl radicals.¹⁻⁴ In general, the total reactivities of the heterocyclic compounds are increased and the proportions of isomeric phenylation products formed in acid solution are different from those obtained when an excess of the appropriate heteroaromatic compound is used as solvent.

The present work is a study of the effect of *N*-protonation on the homolytic benzylolation of pyridine, quinoline and isoquinoline. The reactions of benzyl radicals with several heterocyclic compounds have been extensively investigated.⁵⁻⁸ The thermal decomposition of di-*t*-butyl peroxide in toluene has been used as a source of benzyl radicals in solution for studies of their reactions with acridine,^{5a} benzacridines,^{5b} phenazine,^{5c} indole,⁶ and thiophen.⁷ Homolytic benzylolation of thiophen has also been effected with benzyl radicals produced by the thermal decomposition of di-(9-benzyl-9-fluorenyl) peroxide.⁸ In the present investigation, the following radical sources have been used: (a) the thermal⁹ and photochemical¹⁰ decomposition of dibenzylmercury and (b) the thermal decomposition of lead tetraphenylacetate¹¹ (prepared *in situ* from red lead and an excess of phenylacetic acid).

Pyridine.—Both the thermolysis and the photolysis of dibenzylmercury in pyridine gave bibenzyl (91% from the photolytic reaction) as the sole organic product, in agreement with the work of Cadogan, Hey, and Sanderson,⁸ who found that benzyl radicals generated from di-(9-benzyl-9-fluorenyl) peroxide did not react with pyridine. In contrast, the thermal decomposition of dibenzylmercury in a solution of pyridine in glacial acetic acid gave 2- and 4-benzylpyridine, together with the other products given in Table 1. The same organic products were formed from the thermal decomposition of lead tetraphenylacetate in pyridine in the presence of a large excess of phenylacetic acid. These

results indicate the enhanced reactivity of the pyridinium ion towards homolytic attack, compared with that of the free base, as predicted by molecular orbital calculations of radical localisation energies for the pyridinium ion.¹² The absence of any attack by benzyl radicals at

TABLE 1
Products of reaction of dibenzylmercury with pyridine in acetic acid ^a

Mercury (%)	97.6
Bibenzyl	18.9
Toluene	43.1
2-Benzylpyridine	26.8
4-Benzylpyridine	8.2
Total benzyl (%)	97.0

^a Yields of organic products calculated as % benzyl from dibenzylmercury.

position 3 in pyridine is in accord with the work of Bonnier and Court,² who found that although the reactivities of positions 2 and 4 towards phenyl radicals were increased in acidic media, that of position 3 was unchanged.

Quinoline and Isoquinoline.—Elkobaisi and Hickinbottom¹³ have shown that benzyl radicals produced in the thermal rearrangement of benzyl phenyl ether react with quinoline to give 2- and 4-benzylquinoline and 2,2'-biquinolyl. In isoquinoline the products of the rearrangement included 1-benzylisoquinoline. The thermal decomposition of dibenzylmercury in quinoline and isoquinoline gave the products whose yields are given in Table 2, together with the dimers, 2,2'- and 4,4'-biquinolyl, and 1,1'-bi-isoquinolyl. 3-Benzylquinoline was shown to be absent from the products of the reaction with quinoline.

The formation of the hydrocarbons, 1,2,3-triphenylpropane, 1,2,3-triphenylpropene, and 1,2,3,4-tetraphenylbutane may be accounted for by α -hydrogen abstraction from the primary product, bibenzyl, by benzyl radicals to give toluene and 1,2-diphenylethyl

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TABLE 2
Products of pyrolysis of dibenzylmercury in quinoline
and isoquinoline ^a

Solvent	Quinoline	Isoquinoline
Mercury (%)	96.8	97.6
Bibenzyl	78.4	80.6
Toluene	9.2	8.2
1,2,3-Triphenylpropane	3.6	3.9
1,2,3-Triphenylpropene	1.3	1.5
1,2,3,4-Tetraphenylbutane	0.7	0.7
1-Benzylisoquinoline	—	0.7
2-Benzylquinoline	0.6	—
3-Benzylisoquinoline	—	0.4
4-Benzyl-quinoline or -isoquinoline...	0.8	0.2
2,4-Dibenzylquinoline	0.4	—
Total benzyl (%)	95.0	96.2

^a Yields of organic products calculated as % benzyl from dibenzylmercury.

radicals.^{10,14} The latter may then combine with benzyl radicals to give 1,2,3-triphenylpropane or dimerise to 1,2,3,4-tetraphenylbutane. Further α -hydrogen abstraction from 1,2,3-triphenylpropane would give 1,2,3-triphenylpropyl radicals, which may combine with benzyl radicals to give 1,2,3,4-tetraphenylbutane, or disproportionate to 1,2,3-triphenylpropene and 1,2,3-triphenylpropane. The amounts of benzylated quinolines and isoquinolines formed were of the same order as those of the hydrocarbons discussed previously, and hence the low reactivities of quinoline and isoquinoline in a non-acidic medium towards benzyl radicals are comparable with that of bibenzyl under the same conditions.

The yields of products from the thermal decomposition of dibenzylmercury in solutions of quinoline and isoquinoline in glacial acetic acid are given in Table 3.

TABLE 3
Products of reaction of dibenzylmercury with quinoline
and isoquinoline in acetic acid ^a

Solvent	Quinoline	Isoquinoline
Mercury (%)	98.4	99.2
Bibenzyl	5.2	5.0
Toluene	53.5	42.7
1-Benzylisoquinoline	—	48.6
2-Benzylquinoline	17.5	—
3-Benzylisoquinoline	—	0.5
4-Benzyl-quinoline or -isoquinoline...	15.7	0.5
2,4-Dibenzylquinoline	1.5	—
Total benzyl (%)	93.4	97.3

^a Yields of organic products calculated as % benzyl from dibenzylmercury.

Dimers of quinolyl and isoquinolyl radicals were not formed, and there was no attack of bibenzyl by benzyl radicals under these conditions. Also, 3-benzylquinoline was again shown to be absent from the products of the quinoline reaction. The same organic products were

formed from the thermal decomposition of lead tetraphenylacetate in quinoline and isoquinoline in the presence of a large excess of phenylacetic acid, but the ratio of 2- to 4-benzylquinoline was greater. The yields of benzylated quinolines and isoquinolines given in Tables 2 and 3 show the greatly enhanced reactivities of the quinolinium and isoquinolinium ions towards homolytic attack, compared with those of the free bases.

Brown and Harcourt¹⁵ have calculated the radical localisation energies of quinoline and isoquinoline and the corresponding ions. Their values indicate the orders of reactivities for homolytic substitution in the heterocyclic ring of quinoline and the quinolinium ion to be $4 > 2 > 3$ and $2 > 4 > 3$, respectively.^{15a} For both isoquinoline and the isoquinolinium ion, position 1 should be the most reactive.^{15b} The results obtained in the present work are in agreement with the predicted positional reactivities. The order of reactivities for the quinolinium ion, $2 > 4$, was the reverse of that for the same positions in quinoline, and there was no radical attack at position 3 of either the free base or the ion. Also, position 1 was the most reactive for both isoquinoline and the isoquinolinium ion.

EXPERIMENTAL

Reagents.—Dibenzylmercury¹⁶ (m.p. 111°), 1,2,3-triphenylpropane¹⁷ (b.p. 220–230°/10 mm.), 1,2,3-triphenylpropene¹⁸ (m.p. 62–63°), 1,2,3,4-tetraphenylbutane¹⁹ (racemic modification,²⁰ m.p. 88–89°), 3-benzylquinoline²¹ (b.p. 175–190°/4 mm.), 1-benzylisoquinoline²² (b.p. 206–210°/10 mm.), 3-benzylisoquinoline²³ (m.p. 104°), 4-benzylisoquinoline²¹ (m.p. 118–120°), 4,4'-biquinolyl²⁴ (m.p. 166°), and 1,1'-bi-isoquinolyl²⁵ (m.p. 160–162°) were prepared by established methods. 2-Benzylquinoline (b.p. 210–215°/10 mm.), a mixture of 2- and 4-benzylquinoline (b.p. 200–220°/10 mm.), and 2,4-dibenzylquinoline (b.p. 230–245°/3 mm.) were prepared by the method of Bergmann and Rosenthal.²² 2-Benzylpyridine, 4-benzylpyridine, 2,2'-bipyridyl, 4,4'-bipyridyl, and 2,2'-biquinolyl were commercially available compounds. They were purified by standard methods, and their purity was confirmed by gas chromatography.

Pyridine (AnalaR) was dried (KOH) and redistilled from barium monoxide (b.p. 114–115°/760 mm.). Quinoline was dried (KOH) and, as for isoquinoline, was redistilled immediately before use (b.p. 236–238°/760 mm. and 242–243°/760 mm., respectively).

Gas Chromatography.—The Microtek G.C. 2000-R Chromatograph, fitted with a flame ionisation detector, was employed with the following columns on Chromosorb W (60–80 mesh): (a) 20% Carbowax 20M, for the detection of pyridine bases, and (b) 5% silicone elastomer,

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for the detection of hydrocarbons and quinoline and isoquinoline bases. Compounds were identified by comparison of retention times with those of authentic samples.

Photolysis and Pyrolysis of Dibenzylmercury in Pyridine.—

(i) A solution of dibenzylmercury (3.0 g.) in pyridine (75 ml.) was irradiated under nitrogen for 12 hr. with ultraviolet light from a Hanovia low-pressure mercury arc tube. The bright yellow solution remaining was extracted with ether to leave mercury (1.48 g., 94%).

(ii) Dibenzylmercury (1.0 g.) and pyridine (2.5 ml.) were heated together in a sealed tube at 200° for 15 min. The residue was extracted with ether to leave mercury (0.51 g., 97%).

Gas chromatography of the ether solutions from reactions (i) and (ii) indicated the presence of bibenzyl [91%, based on dibenzylmercury, from reaction (i)]. Benzylpyridines and bipyridyls were shown to be absent from both solutions.

Pyrolysis of Dibenzylmercury in Quinoline and Isoquinoline.—Dibenzylmercury (2.5 g.) and quinoline or isoquinoline (25.8 g., 0.2 mole) were heated together under reflux at 190–195° for 5 min. The solutions were extracted with ether to leave mercury in almost quantitative yield. The ether extracts were shaken several times with dilute hydrochloric acid to remove the amines and leave ethereal solutions of the neutral products. The acid extracts were made alkaline with dilute sodium hydroxide, and the amines liberated were extracted with ether. Gas chromatography of the separate ether solutions of neutral and basic products from each reaction indicated the presence of the hydrocarbons and amines whose yields are given in Table 2, together with the dimers, 2,2'- and 4,4'-biquinolyl, and 1,1'-bi-isoquinolyl. 3-Benzylquinoline was shown to be absent.

Reaction of Dibenzylmercury with Pyridine, Quinoline, and Isoquinoline in Acetic Acid.—Solutions of dibenzylmercury (2.5 g.) and pyridine, quinoline, or isoquinoline (0.2 mole) in glacial acetic acid (1.0 mole) were boiled under

reflux for 12 hr. The solutions were removed to leave mercury in almost quantitative yield, and then made alkaline with sodium hydroxide, and extracted with ether. The neutral products in the ether extracts were separated from the amines as described above. Gas chromatography of the separate ether solutions of neutral and basic products from each reaction indicated the presence of the hydrocarbons and amines whose yields are given in Tables 1 and 3. 3-Benzylquinoline and dimers of pyridine, quinoline, and isoquinoline were shown to be absent.

Reaction of Lead Tetraphenylacetate with Pyridine, Quinoline, and Isoquinoline.—Red lead (17 g., 0.025 mole) was added in small portions during 1 hr. to stirred mixtures of phenylacetic acid (68 g., 0.5 mole) and pyridine, quinoline, or isoquinoline (0.1 mole), which were heated under reflux (water-bath). Stirring and heating were continued for a further 4 hr. The reaction mixtures were made alkaline with sodium hydroxide, filtered, and the residues and filtrates washed or extracted with ether. The combined ether washings and extracts from each reaction were treated as described above to separate the neutral products from the amines. Gas chromatography of all the neutral ether solutions indicated the presence of bibenzyl and toluene. The basic products identified by gas chromatography from the reaction with pyridine were 2- and 4-benzylpyridine (0.5 and 0.1%). The reaction with quinoline gave 2- and 4-benzylquinoline (2.4 and 1.8%) and 2,4-dibenzylquinoline (0.1%). Isoquinoline gave 1-benzylisoquinoline (6.4%) and small amounts of 3- and 4-benzylisoquinoline (>0.1%).

The yields of products are based on pyridine, quinoline, and isoquinoline.

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