Studies on Intramolecular Cycloaddition Reactions of Some Isoquinolinium Salts

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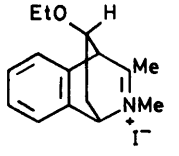
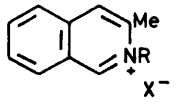
Thermally-induced intramolecular addition reactions of isoquinolinium derivatives bearing an alkenyl side-chain have been studied. Cycloadditions can occur across the isolated olefinic bond and the 1,4-positions of the isoquinolinium system to produce tetracyclic adducts. The chemistry of these adducts is compared with that of cycloadducts produced in intermolecular additions. Preparation of some of the isoquinoline derivatives involved alkylation of the parent base; 3-methylisoquinoline can be substituted either at the methyl group, upon reaction with aromatic nitriles or at C-4, using alkyl halides.

INTERMOLECULAR cycloaddition reactions of isoquinolinium salts have been the subject of several recent studies by Bradsher and his co-workers.[1] As part of a general programme aimed at a study of intramolecular cycloaddition reactions across heterocyclic systems[2] some reactions involving isoquinolinium salts have been examined.

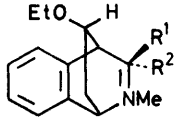
In order to have available a series of suitable reference compounds, the chemistry of the cycloadduct (1), formed from 2,3-dimethylisoquinolinium iodide (2) and ethyl vinyl ether, was studied.[3] This cycloaddition proceeded only poorly in the absence of hydroquinone. Duplication of the literature method,[4] in which hydroquinone was added to the reaction mixture, produced a slow reaction with disappearance of the starting isoquinolinium salt over a period of 5 d. Hydroquinone



(1)

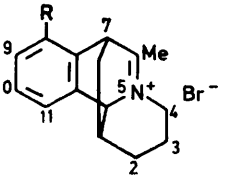


(2) R = Me, X = I
(6) R = -[CH$_2$]$_3$CH=CH$_2$, X = Br

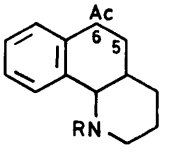


(3) R^1 = Me, R^2 = CN
(4) R^1 = CN, R^2 = Me
(5) R^1 = H, R^2 = Me

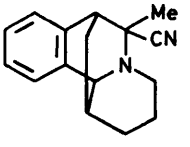
forms a complex with the isoquinolinium salt (2) (1 : 2 ratio, respectively); use of the complex in place of the free isoquinolinium salt effected a more rapid cycloaddition to ethyl vinyl ether, formation of the cycloadduct (1) being complete within 18 h. Treatment of the primary adduct (1) with 2M sodium hydroxide solution at room temperature rapidly afforded 1-acetylnaphthalene, whilst addition of cyanide in dimethylformamide (DMF) produced the adduct (3), m.p. 115—118 °C. When left in chloroform solution the nitrile (3) equilibrated to give a 1 : 1 mixture with its epimer (4).[1c,3] Reduction of either the nitrile (3) or the initial cycloadduct (1) with lithium aluminium hydride in diethyl ether gave mainly one tertiary amine. This amine showed a highfield secondary methyl resonance in its ^{1}H n.m.r. spectrum, consistent only with shielding by the aromatic ring and, hence, this compound was assigned structure (5).



(7) R = H
(12) R = NHAc



(8) R = H
(9) R = Ac



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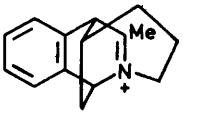
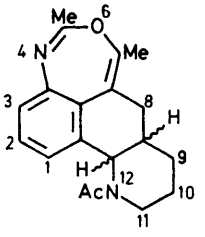


(11)

Investigation of intramolecular counterparts of the above reactions commenced with the preparation of the pentenyl bromide derivative (6). Whereas intermolecular cycloaddition reactions between isoquinolinium salts and olefins are sensitive to electronic and steric effects,[5] thermolysis of the salt (6), in acetonitrile at 145 °C, smoothly produced the cycloadduct (7). Mild, basic hydrolysis of the adduct hydrolysed the iminium bridge to form the keto-amine (8), although this material was unstable and was best obtained as its acetylated derivative (9) as a mixture of isomers about the acetyl junction. Cyanide addition occurs across the iminium double bond of the adduct (7), although the product (10) was itself very unstable, apparently equilibrating with the iminium system. On treatment with strong base the adduct (7) did not behave as the ethyl vinyl ether adduct (1) and a complex mixture of products was formed.

Formulation of the structure of the cycloadduct as (7), rather than as its regioisomer (11), was mainly based on a study of molecular models, which indicate considerable strain and steric hindrance between the 3-methyl group and the nitrogen substituent in the process leading to the latter, but not to the former, species. Attempts to extend the reaction to isoquinolinium salts not bearing the 3-methyl group failed; Bradsher *et al.* have previously noted the favourable effect of the 3-methyl substituent in intermolecular counterparts to this reaction.[6]

8-Substituted isoquinolinium salts have also been reported to undergo cycloadditions and electronegative substituents enhance the rates of such reactions.[6] Although 3-methyl-5-nitroisoquinoline failed to quaternise with pent-4-enyl bromide, heating this halide with the derivative 5-acetamido-3-methylisoquinoline, did produce the expected cycloadduct (12) as an unstable salt. Basic hydrolysis, followed by acetylation, produced one major product. This was not the expected, substituted analogue of the amide (9) but, instead, an anhydro-derivative. Examination of its ^{1}H n.m.r. spectrum indicated no amide proton associated with the starting material and one less non-aromatic ring proton. Furthermore, the i.r. spectrum showed absence of the amide II band, both changes indicating an interaction between the 8-acetamido-substituent and the acetyl group, resulting in formation of the fused oxazepine ring system (13). 4,5-



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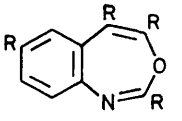

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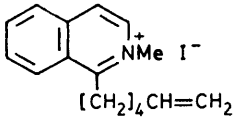
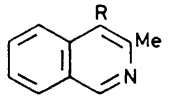


(15)

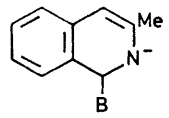
Benzo-fused oxazepines of the type (14) have been reported.[7] Although the ^{1}H n.m.r. spectrum indicated that compound (13) was isolated as a mixture of stereoisomers about the positions indicated, these isomers could not be separated by thin layer chromatography (t.l.c.).

Introduction of a substituent into C-1 of the isoquinoline nucleus was achieved by direct alkylation of the anion from 1-methylisoquinoline[8] with pent-4-enyl bromide. Quaternisation of the resulting derivative with iodomethane gave the salt (15), but thermolysis of this, under a variety of conditions, gave no identifiable cycloaddition products.

When the direct alkylation of 3-methylisoquinoline with pent-4-enyl bromide was attempted the product was not the hex-3-enyl derivative but, instead, 3-methyl-4-pent-4-enylisoquinoline (16). This reaction was unexpected and was hence briefly studied. The base used in the latter alkylation was the hindered base, lithium cyclohexylisopropylamide, suggesting that the known



(16) R = $[CH_2]_3CH=CH_2$
(18) R = Et
(19) R = $Ph[CH_2]_3$
(21) R = $PhCH_2$



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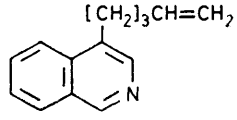


(20)

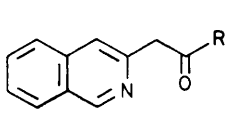
process[9] of addition of the amine to C-1 of the isoquinoline nucleus and alkylation of the resulting enamide species, *e.g.* (17), was *not* occurring under our reaction conditions. In order to check this point the more nucleophilic, but less basic species, lithium piperidide was used; no alkylation was observed. Alkylation of 3-methylisoquinoline at C-4 was also observed, using lithium cyclohexylisopropylamide as base, in moderate yields with bromoethane and 3-bromo-1-phenylpropane to give the products (18) and (19), respectively.

Isoquinoline itself could also be alkylated using strong base systems and the reaction with pentenyl bromide afforded the alkylated derivative (20) in 33% yield. The temperature used in these alkylations was critical. For example, upon reaction of benzyl chloride with the anion obtained from 3-methylisoquinoline at −78 °C the principal product was 1-chloro-1,2-diphenylethane, with only traces of the benzyl-substituted isoquinoline (21). At −10 °C a 21% yield of the expected product (21) was formed whilst, at higher temperatures, yields of the alkylation product again fell away.

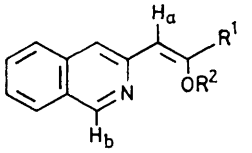
In trying to extend the range of these substitutions, some reactions using aromatic nitriles were attempted. With *p*-toluonitrile a mixture of products formed from which only a low yield (11%) of one new compound could be isolated. This was analysed as $C_{18}H_{15}NO$ and showed only one aromatic methyl group in its ^{1}H n.m.r. spectrum. The i.r. spectrum indicated a carbonyl resonance at ν 1 678 cm^{-1}. The structure (22) fits these data; some evidence for the presence of small amounts of the tautomer (23) was obtained from its ^{1}H n.m.r. spectrum, in which two small singlets, at δ 6.17 and 9.03 were present, assigned to H_a and H_b respectively. A similar reaction was observed with 4-cyanopyridine, from which the ketone (24) and its corresponding enol (25) were

obtained in 34% yield; in this case the enol tautomer predominated. A strong, intramolecular hydrogen bond ing was noted in the enol. Treatment of the mixture of tautomers with an excess of diazomethane produced the enol ether (26). When isoquinoline itself was subjected to the same reaction conditions the red solution, initially formed, rapidly changed to black upon addition of 4-cyanopyridine and no discrete products could be isolated.

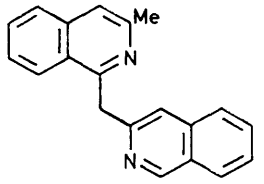
An attempt to react the anion obtained from 3-methylisoquinoline with either bromine or benzophenone did not produce substitution products but, instead, afforded a dimer which was assigned structure (27).



(22) R = C_6H_4Me-*p*
(24) R = 4-C_5H_4N



(23) R^1 = C_6H_4Me-*p*, R^2 = H
(25) R^1 = 4-C_5H_4N, R^2 = H
(26) R^1 = 4-C_5H_4N, R^2 = Me



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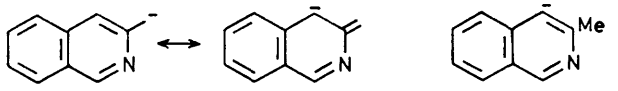
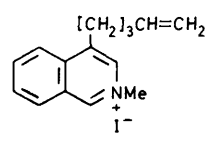


(28a) (28b) (29)

The different courses followed by the above reactions require explanation. Assuming that addition–elimination processes of the type leading to the species (17) are not involved, the products leading to substitution at either the 3-methyl group or C-4 demand transient formation of intermediate carbanions. Loss of a proton from the methyl group produces the anion (28a), in resonance with the species (28b), whilst abstraction of a proton from C-4 would lead to the anion (29). As judged by the rate of disappearance of the red anion colour the nitriles react rapidly at −78 °C, indicating that anions of the type (28) are initially formed and react preferentially at the methyl group in order to produce the observed products (22)—(25). Alkylation with alkyl halides is a slower process and takes place during the extended periods allowed for the reaction mixture to reach ambient temperatures. Since products of alkylation at the methyl group itself were not observed it is tempting to suggest that the kinetically formed anion (28) slowly rearranges to the more stable vinyl anion (29), and that it is the latter species which undergoes alkylation.* The alternative explanation, that the site of substitution, (28a) or (28b), depends on the hard or soft nature of the attacking electrophile cannot be ruled out from our studies, although there appears to be no reason why alkylation at the methyl group is not observed. Furthermore, alkylation of species related to the anion (29) has been achieved, by starting with 4-bromoisoquinolines and generating the anion by exchange reactions with butyl-lithium.[10] Formation of the dimer (27) probably proceeds by a redox reaction,[11] the free radical corresponding to the anion (28) coupling by addition to the imine bond of another molecule.

The net result of these studies on the alkylation of 3-methylisoquinoline was a simple method for the formation of the 4-alkylated derivative (16), which was suitable for further examination of the cycloaddition reac-



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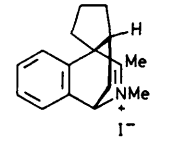

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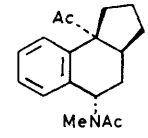

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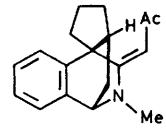

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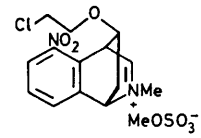

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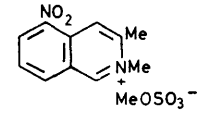

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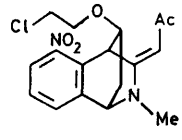

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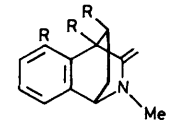

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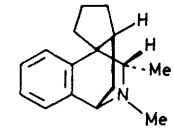

(38)

tion. The methiodide salt (30) could be easily prepared and, on heating this at 145 °C, the cycloadduct (31) was formed. The presence of only one highfield proton from the ethano-bridge, caused by aromatic ring shielding, led to the tentative assignment of the stereochemistry indicated. Treatment of this product with base gave an oil which afforded a single compound upon acetylation with acetic anhydride in pyridine. The product was not, however, the expected ring-opened keto-amide (32), since only two methyl groups were apparent in its ^1H n.m.r. spectrum. The presence of an extra vinylic hydrogen atom points to the vinylic amide structure (33). A similar acetylation product, compound (36), formed from the cycloadduct (34), was produced from the 5-nitroisoquinolinium salt (35) and 2-chloroethyl

* An alternative example, when a vinylic anion equilibrates with an ethyl anion has been reported in the chromone series, see A. M. B. S. R. C. Costa, F. M. Dean, M. A. Jones, D. A. Smith, and R. S. Varma, *J. Chem. Soc., Chem. Commun.*, 1980, 1224.

vinyl ether. Steric factors disfavour the ring-opening of the iminium bond in the cycloadducts (31) and (34) and base causes initial formation of the enamine structure (37), which is then acetylated.

Reduction of the cycloadduct (31) with sodium borohydride gave a mixture of tertiary amines from which the major product was identified as compound (38). As for the product (5), the amine (38) showed a highfield doublet resonance at δ 0.79, attributed to the methyl group shielded by the aromatic ring; the methyl group in the minor isomer was detected at δ 1.16 in the crude reaction product.

The contrast between the behaviour of the isoquinolinium salts (6), (15), and (30) requires some comment. The failure of the salts (15) or the methiodide obtained from compound (20) to undergo cycloaddition was unexpected, since one would expect similar electronic effects to be operating in this case as for the salts (6) and (30). Notwithstanding the electronic effects of the different methylation patterns it appears that the cycloadditions of the salts (6) and (30) are aided by steric buttressing effects.[12] A similar effect has recently been reported with respect to cycloadditions across substituted pyridones.[13]

EXPERIMENTAL

M.p.s were determined on a hot-stage apparatus and are uncorrected. I.r. spectra were determined with a Perkin-Elmer 157G spectrometer on chloroform solutions, unless otherwise stated, and u.v. spectra were measured on a Pye-Unicam SP800 spectrometer for solutions in ethanol. Mass spectra were determined on an A.E.I. MS30 double-beam instrument and accurate mass measurements were obtained from the Physical and Chemical Measurements Unit, Harwell. ^{1}H N.m.r. spectra were obtained on a Jeol MH100 instrument using deuteriochloroform as solvent and tetramethylsilane as internal reference; chemical shifts are measured in p.p.m. and observed coupling constants in Hz. Solvents were dried and distilled before use. Thin layer chromatography (t.l.c.) was carried out on Merck SiO_2 GF_{254}, using plates 0.2 mm thick for analytical purposes and 1.0 mm thick for preparative work (p.l.c.). Thermolyses were carried out in sealed thick-walled Pyrex-glass tubes, *ca.* one-third filled, with the solution under nitrogen.

2,3-*Dimethylisoquinolinium Iodide–Hydroquinone Complex*.—2,3-Dimethylisoquinolinium iodide (0.71 g, 2.5 mmol) and hydroquinone (0.275 g, 2.5 mmol) were stirred in acetonitrile (10 ml) at room temperature for 48 h. The precipitated solid was collected, washed with acetonitrile, and dried to give the 2 : 1 complex $(C_{11}H_{12}IN)_2 \cdot C_6H_6O_2$ (0.68 g, 78%), m.p. 166—168 °C; $\nu_{max.}$ 3 215, 1 656, 1 608, 1 520, 1 460, 1 403, 1 346, 1 300, 1 245, 1 195, 900, 840, and 761 cm^{-1} (Found: C, 49.4; H, 4.4; N, 4.1. $C_{28}H_{30}I_2N_2O_2$ requires C, 49.4; H, 4.4; N, 4.1%).

Reaction of the complex with ethyl vinyl ether in acetonitrile at room temperature for 18 h, followed by diethyl ether precipitation, gave the adduct 9-ethoxy-1,4-tetrahydro-2,3-dimethyl-1,4-ethanoisoquinolinium iodide (1), m.p. 220—224 °C, identical (mixed m.p. and i.r.) with a sample prepared according to the literature procedure.[4] Treatment of the adduct (1) with 2M NaOH at 0 °C afforded 1-acetylnaphthalene (60%).

Reactions of the Adduct (1).—(a) *With cyanide*. The salt (1) (0.85 g) was treated with potassium cyanide (0.18 g) in dry dimethylformamide (DMF) (15 ml) at room temperature for 3 h before the addition of water (20 ml) and extraction of the organic material with diethyl ether. The extract was washed with water, dried, and evaporated to afford crystals of exo-3-*cyano*-9-*ethoxy*-1,2,3,4-*tetrahydro*-2,3-*dimethyl*-1,4-*ethanoisoquinoline* (3) (0.50 g, 78%), as needles, m.p. 115—118 °C (light petroleum–diethyl ether); $\nu_{max.}$ 2 800, 2 230, 1 599, 1 280, 1 099, 1 080, 1 050, 1 000, and 700 cm^{-1}; δ 1.07 (3 H, t, *J* 7 Hz), 1.00—1.60 (1 H, m), 1.65 (3 H, s), 2.31 (3 H, s), 2.20—3.00 (1 H, m), 3.20—3.75 (4 H, m), 4.08 (1 H, dt), and 7.00—7.50 (1 H, m) (Found: C, 75.0; H, 7.9; N, 10.9. $C_{16}H_{20}N_2O$ requires C, 74.7; H, 8.0; N, 11.0%).

On leaving the sample of compound (3) in deuteriochloroform the spectrum gradually changed,[1a] eventually showing a new set of peaks, indicating a highfield methyl singlet at δ 1.11 and a separate *N*-methyl signal at δ 2.47. Attempted isolation of the new isomer failed.

(b) *Reduction*. The adduct (1) (178 mg) was added to a slurry of lithium aluminium hydride (76 mg) in dry diethyl ether (10 ml) at 0 °C under nitrogen before the mixture was stirred for 15 min and then worked up in the usual manner. Diethyl ether extraction of the products afforded 3,4-trans-9-*ethoxy*-1,2,3,4-*tetrahydro*-2,3-*dimethyl*-1,4-*ethanoisoquinoline* (5) as an oil (101 mg, 93%); $\nu_{max.}$ (film) 2 930, 2 850, 2 795, 1 495, 1 460, 1 380, 1 355, 1 097, and 758 cm^{-1}; δ 0.80 (3 H, d, *J* 6 Hz), 0.95 (3 H, t, *J* 7 Hz), 1.22 (1 H, m), 2.20 (3 H, s), 1.80—2.70 (2 H, m), 2.80—4.00 (5 H, m), and 6.90—7.30 (4 H, m). The amine was characterised as its tetraphenylborate *salt*, m.p. 234—236 °C (decomp.) (Found: C, 84.7; H, 7.0; N, 2.5. $C_{40}H_{40}BNO$ requires C, 84.9; H, 7.8; N, 2.5%).

Preparation and Thermolysis of 3-*Methyl*-2-*pent*-4-*enylisoquinolinium Bromide* (6a).—3-Methylisoquinoline (0.29 g) in dry acetonitrile (0.5 ml) was boiled under reflux for 20 h in the presence of 5-bromopentene (0.29 g). Removal of the solvent afforded the *salt* (6) (0.54 g, 93%) as orange needles, m.p. 158—159 °C (ethyl acetate–acetonitrile); $\nu_{max.}$ 1 649, 1 611, 1 580, 1 507, 1 456, 1 429, 1 395, 1 350, 1 165, 1 151, 940, 775, and 769 cm^{-1}; $\lambda_{max.}$ 240 (39 000), 269 (2 600), 279 (2 500), 336 (2 900), and 346 nm (4 100); δ 2.04—2 60 (4 H, m), 3.03 (3 H, s), 4.9—5.3 (4 H, m), 5.3—(1 H, m), 787 6.4 (1 H, dd, *J* 3, 8 Hz), 8.17 (2 H, m), 8.27 (1 H, s), 8.62br (1 H, d, *J* 8 Hz), and 11.25 (1 H, s) (Found: C, 61.65; H, 6.2; N, 4.8. $C_{15}H_{18}BrN$ requires C, 61.50; H, 5.9; N, 4.8%.)

A sample of the salt (6) (50 mg) was heated in acetonitrile (0.1 ml) in a sealed tube for 3 h at 145 °C. On being cooled the contents were triturated with diethyl ether to give 1,2,3,4,7,11b-hexahydro-6-methyl-1,7-ethanobenzo[*a*]quinolizinium bromide (7) (23 mg, 46%) as an orange, amorphous, hygroscopic solid, m.p. 245—255 °C (ethyl acetate–acetonitrile).

The primary adduct (7) (39 mg) was dissolved in water (0.5 ml) containing sodium hydrogencarbonate (1 equiv.) and then extracted into ethyl acetate to afford, after drying and evaporation, a pale yellow oil which was unstable when stored. The oil was dissolved in pyridine (0.05 ml) and acetylated with acetic anhydride (20 mg) at room temperature for 18 h. Evaporation of the solvent and separation of the major product by preparative t.l.c. afforded 1,6-*diacetyl*-1,2,3,4,4a,5,6,10b-*octahydrobenzo*[h]*quinoline* (9) (20.3 mg, 56%) as a oil; $\nu_{max.}$ 2 938, 1 710, 1 639, 1 430, 1 361, 1 165, 989, and 760 cm^{-1}; δ 1.30—2.95 (9 H, m), 2.04 (3 H,

s), 2.34 (3 H, s), 3.83 (1 H, m), 6.08 (1 H, m), and 6.95—7.50 (4 H, m); *m/e* 271, 143, 228, 226, 200, and 187 (Found: C, 70.9; H, 7.6; N, 4.95. $C_{17}H_{21}NO_2 \cdot H_2O$ requires C, 70.6; H, 8.0; N, 4.8%. Found: M^+, 271.1 571. $C_{17}H_{21}NO_2$ requires M, 271.1572.)

Reactions between 5-Acetamido-3-methylisoquinoline and 5-Bromopent-1-ene.—The isoquinoline[6] (0.54 g) was heated with 5-bromopent-1-ene (0.48 g) in acetonitrile at reflux for 9 h to produce a black, solid precipitate. The supernatant liquor was decanted off and the solid triturated with diethyl ether to give a microcrystalline solid, m.p. 208—212 °C. Further heating of the supernatant liquor gave a second crop of the black solid which was harvested in a similar manner. The combined solids (110 mg) were treated with 2M sodium hydrogencarbonate solution (1 ml) and the oil produced was extracted with dichloromethane (3 × 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated to afford a brown oil. This was immediately acetylated with acetic anhydride–pyridine (0.5 ml; 1 : 2) at room temperature overnight. Evaporation, followed by preparative t.l.c., afforded, as the major reaction product, 12-*acetyl*-8a,9,10,11,12,12a-*hexahydro*-5,7-*dimethyl*-8H-*quino*[6,7,8-ef]-3,1-*benzoxazepine* (13) (0.121 g, 14%) which was isolated as a pale yellow viscous oil; $\nu_{max.}$ 2 982, 2 930, 2 860, 1 702, 1 624, 1 424, 1 355, 1 157, and 997 cm^{-1}; δ 1.32—1.78 (4 H, m), 2.31 (3 H, s), 2.59 (3 H, s), 2.76 (3 H, s), 2.10—3.24 (4 H, m), 3.8—4.6 (1 H, m), 5.3—6.3 (1 H, m), 6.94 (1 H, t, *J* 7 Hz), 7.18—7.42 (1 H, m), and 7.70 (1 H, dd, *J* 5, 7 Hz) (Found: M^+, 310.1699. $C_{19}H_{22}N_2O_2$ requires M^+, 310.1681).

1-*Hex*-5-*enyl*-2-*methylisoquinolinium Iodide* (15).—A solution of 1-methylisoquinoline (1.00 g) in tetrahydrofuran (THF) (20 ml) was added slowly, under nitrogen, to a freshly prepared solution of lithium isopropylcyclohexylamide (from the amine, 0.99 g and butyl-lithium) in THF (20 ml) (acetone–solid CO_2). The solution turned black over 40 min, after which time 5-bromopent-1-ene (1.04 g) was added. The mixture was stirred overnight, the temperature being allowed to rise to ambient after 2 h. Water (30 ml) was added and the separated oil was extracted into dichloromethane (3 × 30 ml). The organic extract was washed with water, dried ($MgSO_4$), and then evaporated. After preparative t.l.c., 1-hex-5-enylisoquinoline was isolated as a pale yellow oil (1.30 g, 88%); $\nu_{max.}$ (film) 3 048, 2 921, 2 853, 1 638, 1 622, 1 585, 1 561, 1 499, 909, and 801 cm^{-1}; δ 1.39—2.29 (6 H, m), 3.27 (2 H, t, *J* 7 Hz), 4.80—5.16 (2 H, m), 5.57—6.03 (1 H, m), 7.29—7.78 (4 H, m), 7.89—8.19 (1 H, m), and 8.38 (1 H, d, *J* 6 Hz). The *methiodide salt* (15) was prepared almost quantitatively from the base and methyl iodide in acetonitrile; $\nu_{max.}$ 1 639, 1 618, 1 572, 1 148, 998, 923, 818, and 763 cm^{-1}; $\lambda_{max.}$ (ε) 230 (49 600), 269 (2 850), 278 (2 950), 288 (1 550), 340 (5 250), and 341 nm (5 450) (Found: M^+, 226.1594. $C_{16}H_{20}N^+$ requires M^+, 226.1596.)

Little change occurred when the methoidide (15) was heated in acetonitrile at 145 °C for 3 h; after 3 h at 160 °C most of the salt had been consumed, but work-up only afforded intractable tars.

Preparation of 3-Methyl-4-pent-4-enylisoquinoline (16).—3-Methylisoquinoline (1.00 g) in THF (20 ml) was added as drops to a solution of lithium isopropylcyclohexylamide, prepared from the amine (0.99 g) and n-butyl-lithium in THF (40 ml), and kept under nitrogen at −78 °C. After 1 h, 5-bromopent-1-ene (1.04 g) was added and the stirred mixture was allowed to warm to room temperature overnight; it was then worked up by the addition of water and extraction with dichloromethane. The product, 3-*methyl*-4-*pent*-4-*enylisoquinoline* (16), was isolated by short-column chromatography through silica gel as a pale yellow liquid (0.69 g, 47%). The isoquinoline was characterised as its N-*methiodide* (30), prepared almost quantitatively as yellow crystals, m.p. 146—148 °C; $\nu_{max.}$ (Nujol) 3 090, 1 638, 1 607, 1 503, 1 398, 928, and 783 cm^{-1}; $\lambda_{max.}$ (ε) 224 sh (43 200), 248 (58 300), 272 (2 650), 281 (2 800), 292 (1 600), 340sh (5 750), and 349 nm (6 600); δ 1.55—1.94 (2 H, m), 2.11—2.42 (2 H, m), 2.93 (3 H, s), 3.04—3.30 (2 H, m), 4.70 (3 H, s), 4.97—5.26 (2 H, m), 5.60—6.10 (1 H, m), 7.67—8.09 (3 H, m), 8.52 (1 H, d, *J* 9 Hz), and 10.61 (1 H, s) (Found: C, 54.4; H, 5.5; N, 3.9. $C_{16}H_{20}IN$ requires C, 54.4; H, 5.7; N, 4.0%).

Other Alkylations of 3-Methylisoquinoline.—(a) *With bromoethane.* Prepared from isopropylcyclohexylamine (1.04 g), butyl-lithium (0.47 g), 3-methylisoquinoline (1.00 g) and the bromide (0.80 g) in the above manner, the product, 4-ethyl-3-methylisoquinoline (18), could only be obtained as a mixture, contaminated by the starting isoquinoline. Estimations by ^1H n.m.r. spectroscopy indicated a yield of 0.49 g (41%); δ 1.20 (3 H, t, *J* 8 Hz), 2.68 (3 H, s), 2.97 (2 H, q, *J* 8 Hz), 7.36—7.94 (4 H, m), and 8.96 (1 H, s). The methiodide of the mixture was prepared as a yellow crystalline solid (Found: M^+, 186.1276. $C_{13}H_{16}N^+$ requires M^+, 186.1283).

(b) *With 1-bromo-3-phenylpropane.* Prepared from isopropylcyclohexylamine (0.25 g), butyl-lithium (0.11 g), 3-methylisoquinoline (0.25 g), and the bromide (0.35 g) the 3-*methyl*-4-(3-*phenylpropyl*)*isoquinoline* (19) was isolated as a viscous oil (0.16 g, 34%); δ 1.70—2.09 (2 H, m), 2.68 (3 H, s), 2.46—3.13 (4 H, m), 6.98—7.79 (9 H, m), and 8.87 (1 H, s). The methoidide showed M^+, 261.1516; $C_{19}H_{19}N^+$ requires M^+, 261.1518.

(c) *With benzyl chloride.* In a similar manner to the above, 3-methylisoquinoline (1.00 g) was treated with benzyl chloride (0.93 g) at −20 °C to give 4-*benzyl*-3-*methylisoquinoline* (21) (0.24 g, 21%); δ 2.69 (3 H, s), 4.38 (2 H, s), 6.99—7.98 (9 H, m), and 9.17 (1 H, s) (Found: M^+, 233.1214; $C_{17}H_{15}N$ requires M, 233.1204). 1-Chloro-1,2-diphenylethane, formed by self-condensation of benzyl chloride, was isolated from this reaction in increasing yield as the temperature of the reaction was lowered. Thus, at −78 °C only this product was obtained from the reaction mixture with none of the alkylation product (21).

Reaction of 3-Methylisoquinoline with Aromatic Nitriles.—(a) With p-*methylbenzonitrile.* Reaction of the anion from 3-methylisoquinoline (0.25 g, 1.8 mmol), prepared as described above using n-butyl-lithium (0.11 g) and isopropylcyclohexylamine (0.25 g), with *p*-methylbenzonitrile (0.21 g, 1.8 mmol) afforded, after work-up and isolation by preparative t.l.c., 3-*isoquinolylmethyl* p-*tolyl ketone* (22) (50 mg, 11%) as a solid, m.p. 106—110 °C; $\nu_{max.}$ 1 678, 1 622, 1 589, 1 486, 1 451, 1 322, 1 263, 996, and 879 cm^{-1}; δ 2.38 (3 H, s), 4.60 (2 H, s), 7.11—8.07 (9 H, m), and 9.17 (1 H, s) (Found: $M^+ - 1$, 260.1066. $C_{18}H_{15}NO$ requires $M - 1$, 260.1075).

(b) With 4-*Cyanopyridine.* In a similar manner, 3-methylisoquinoline (1.02 g) was treated with 4-cyanopyridine (0.78 g) to give, as yellow crystals from chloroform, 2-(3-*isoquinolyl*)-1-(4-*pyridyl*)*ethenol* (25) (0.60 g, 34%), m.p. 137—138 °C; $\nu_{max.}$ 3 450—3 090, 2 944, 1 621, 1 596, 1 485, 1 451, 1 308, 956, and 879 cm^{-1}; $\lambda_{max.}$ (ε) 232 (87 000), 224.5 (66 000), 274 (46 500), 285 (42 500), and 348 nm (115 000); δ 6.35 (1 H, s), 7.40—8.04 (7 H, m), 8.68 (2 H, d,

J 6 Hz), 9.12 (1 H, s), and 14.20—14.50br (1 H, s, exchanged with D_2O) (Found: C, 77.6; H, 4.7; N, 11.3%; M^+, 248.0949. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%; *M*, 248.0949).

An excess of diethyl ether–diazomethane solution was added to the enol (25) which caused the loss of the exchangeable proton at lowfield and the formation of a three-proton singlet at δ 3.78. The product, an oil, was assigned as the methyl ether (26) (Found: M^+, 262.1087. $C_{17}H_{14}N_2O$ requires *M*, 262.1106).

3-Isoquinolyl-(3-methyl-1-isoquinolyl)methane (27).—Treatment of the lithium salt, prepared from 3-methylisoquinoline (1.07 g) in the manner described above, with benzophenone (1.36 g) gave, after preparative t.l.c., the *title compound* (0.62 g, 61%) as an oil, $\nu_{max.}$ 3 045, 2 914, 1 625, 1 589, 1 580, 1 562, 950, and 873 cm^{-1}; $\lambda_{max.}$ (ε) 220 (82 600), 264 (8 000), 272 (8 050), 280 (6 350), 319 (6 300), and 328 nm (7 250); δ 2.75 (3 H, s), 5.00 (2 H, s), 7.19—7.93 (9 H, m), 8.20 (1 H, d, *J* 9 Hz), and 9.14 (1 H, s) (Found: M^+, 284.1292. $C_{20}H_{16}N_2$ requires *M*, 284.1313).

Thermolysis of 2,3-Dimethyl-4-pent-4-enylisoquinolinium Iodide (30).—The iodide (0.16 g) in degassed acetonitrile (1 ml) was heated for 3 h at 145 °C in a sealed tube. Evaporation of the solvent afforded a foam which was hygroscopic and unstable upon storage. A ^1H n.m.r. spectrum on the crude product showed δ 1.32 (1 H, m), 2.84 (3 H, s), 4.00 (3 H, s), and 5.98br (1 H, s) as well as a broad multiplet for the remaining aliphatic hydrogens at δ 1.4—2.5 (8 H) and the aromatic protons at δ 7.4—78 (4 H, m); the characteristic resonance pattern for the olefinic group in the starting material was absent. The salt dissolved in 2M sodium hydrogencarbonate solution. Neutralisation with acid (1 equiv.) afforded an oil which was extracted into dichloromethane, washed with water, dried ($MgSO_4$), and then evaporated to dryness and acetylated using acetic anhydride–pyridine (1 : 2) at room temperature overnight. After removal of the reagents the residue was purified by preparative t.l.c. to afford *1,2,3,4-tetrahydro-2-methyl-3-(2-oxopropylidene)-1,2′-methanoisoquinoline-4-spirocyclopentane* (33) (101 mg, 84%) as an oil; $\nu_{max.}$ 2 915, 1 672, 1 618, 1 603, 1 311, 954, and 878 cm^{-1}; δ 1.16br (1 H, d, *J* 13 Hz), 1.48—2.66 (8 H, m), 2.05 (3 H, s), 3.06 (3 H, s), 4.37br (1 H, d, *J* 4 Hz), 5.07 (1 H, s), and 6.98—7.35 (4 H, m) (Found: M^+, 267.1619. $C_{18}H_{21}NO$ requires M^+, 267.1623).

Another sample of the iodide (30) (0.25 g) was thermolysed in a similar fashion to obtain quantitative conversion into the adduct. This was dissolved in THF (5 ml) and solid sodium borohydride (27 mg) was added. The orange solution turned yellow and, after being stirred at room temperature overnight, was poured into water and the precipitated oil extracted into dichloromethane. After washing with water the organic extract was dried ($MgSO_4$) and evaporated to dryness to afford an oil. Silica-gel chromatography gave, as the major product, *1,2,3,4-tetrahydro-2,3-dimethyl-1,2′-methanoisoquinoline-4-spirocyclopentane* (38) (0.143 g, 89%), an amorphous solid, m.p. 56—88 °C; $\nu_{max.}$ 3 023, 2 950, 2 864, 1 475, 1 466, 1 453, 1 377, 1 181, 1 170, 1 148, and 1 064 cm^{-1}; δ 0.79 (3 H, d, *J* 8 Hz), 1.08 (1 H, dd, *J* 13, 6 Hz), 1.40—2.08 (6 H, m), 2.24 (3 H, s), 2.10—2.50 (1 H, m), 3.24 (1 H, ddd, *J* 12, 9, 4 Hz), 3.63 (1 H, 1, *J* 8 Hz), 3.88br (1 H, d, *J* 4 Hz), and 7.16—7.46 (4 H, m) [Found: $(M - 15)^+$, 212.1439. $C_{16}H_{21}N$ requires $(M - 15)$, 212.1438].

Alkylation of Isoquinoline.—Isoquinoline (0.90 g) was treated with lithium cyclohexylisopropylamide, obtained from butyl-lithium (0.45 g) and the amine (0.99 g), in THF (60 ml) at −78 °C for 1 h before adding 5-bromopent-1-ene (1.04 g) as drops over 15 min. The reaction mixture was allowed to warm to 0 °C overnight and worked-up by the addition of water and extraction with dichloromethane. After drying and removal of the solvent the residue was purified by p.l.c. to obtain 4-pent-4-enylisoquinoline (20) (0.45 g, 33%) as a pale yellow oil. This was characterised as its N-*methiodide*, m.p. 104—105 °C; $\nu_{max.}$ (Nujol) 1 638, 1 607, 1 399, 1 184, and 1 155 cm^{-1}; $\lambda_{max.}$ (ε) 232 (44 350), 273 (2 250), 280 (2 600), 290 (2 000), 329 (4 450), and 340 nm (5 050); δ 1.73—2.40 (4 H, m), 3.22 (2 H, t, *J* 8 Hz), 4.79 (3 H, s), 4.94—5.22 (2 H, m), 5.63—6.09 (1 H, m), 7.82—8.30 (3 H, m), 8.68 (1 H, d, *J* 9 Hz), 8.74 (1 H, s), and 10.58 (1 H, s) (Found: C, 53.0; H, 5.4; N, 4.4%; M^+, 212.1439. $C_{15}H_{18}N^+I^-$ requires C, 53.1; H, 5.35; N, 4.1%; M^+, 212.1433).

When the methiodide salt of compound (20) was heated at 145 °C for 3 h in acetonitrile no reaction occurred. On increasing the thermolysis temperature to 160 °C extensive decomposition occurred, but no discrete products could be isolated.

Syn-1,4-Dihydro-9-(2-chloroethoxy)-2,3-dimethyl-5-nitro-1,4-ethanoisoquinolinium Methoxysulphonate (34).—2,3-Dimethyl-5-nitrosoisoquinolinium methoxysulphonate (35) (0.40 g), 2-chloroethyl vinyl ether (0.68 g), and a catalytic amount of hydroquinone (10 mg) were stirred in dry methanol (10 ml) at room temperature for 3 d, before the solvent was evaporated off under reduced pressure to give a solid. After trituration with ethyl acetate the title salt was obtained (0.58 g, 95%).

Basic Hydrolysis and Acetylation of Compound (34).—The salt (34) (0.30 g) in methanol (5 ml) was added as drops to 2M sodium hydroxide solution [obtained from NaOH (0.04 g)]. The oil that formed was extracted into dichloromethane, dried ($MgSO_4$), filtered, and then evaporated to yield a brown oil. The oil was acetylated with acetic anhydride–pyridine (1 : 2) at room temperature overnight. Work-up, followed by purification by p.l.c., gave *syn-2-chloroethoxy-1,2,3,4-tetrahydro-2-methyl-5-nitro-3-(2-oxopropylidene)-1,4-ethanoisoquinoline* (36) (0.20 g, 83%); $\nu_{max.}$ 2 932, 2 878, 1 638, 1 548, 1 405, 1 352, 1 168, 1 107, and 966 cm^{-1}; δ 1.45br (1 H, d, *J* 13 Hz), 2.12 (3 H, s), 2.67 (1 H, ddd, *J* 13, 9, 4, Hz), 3.01 (3 H, s), 7.80 (1 H, d, *J* 4 Hz), 3.36—4.32 (5 H, m), 4.64—4.79 (1 H, m), 5.03 (1 H, s), 7.32—7.72 (2 H, m), and 8.04 (1 H, d, *J* 8 Hz) (Found: M^+, 350.1010. $C_{17}H_{19}{}^{35}ClN_2O_4$ requires M^+, 350.1033).

We thank the S.R.C. and Glaxo Research Ltd., Ware, for support of this work through C.A.S.E. Studentships (to G. P. G. and R. A. W.)

[1/866 *Received*, 28*th May*, 1981]

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