Addition Reactions of Heterocyclic Compounds. Part LIX.[1] A ^{13}C Tracer Study of the Mechanism of Formation of Azepines from 2-Methylquinolines and Dimethyl Acetylenedicarboxylate

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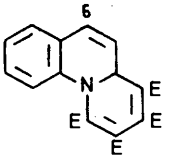
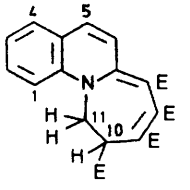
A ^{13}C label in the methyl group of 2-methylquinoline and its 6-bromo-derivative was found at position 10 or 11 of the azepino[1,2-*a*]quinolines formed in reactions with dimethyl acetylenedicarboxylate. This excludes a reaction pathway involving an ester shift but is consistent with the possibility of a spiro intermediate.

REACTIONS between 2-methylquinolines and dimethyl acetylenedicarboxylate have been studied extensively [2-4] and give many types of compound. With ether or acetonitrile as reaction medium the major adducts formed are benzo[*c*]quinolizines [*e.g.* (1)] and azepinoquinolines [*e.g.* (4)]. 6-Bromo-2-methyl- and 2,3-dimethyl-quinolines gave compounds of these types, but the isomeric azepines (8) and (9) were also formed. 1-Methylisoquinoline also gave adducts corresponding to (1) and (4), but an isomeric compound (11) was also formed.

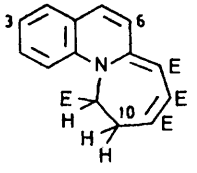
A scheme put forward [2] to accommodate these observations requires an ester shift to the 2-methyl group of the quinoline, which can behave as a nucleophilic carbon atom; there are many analogies for this. It was then found that reactions of 2-benzyl- and 2-ethyl-quinoline with the ester gave the benzo[*c*]-quinolizine (3) and the azepine (7), and the azepines (6) and (10), respectively. The formation of the last three compounds cannot be explained in terms of the original scheme, and a new one (Scheme), involving a spiro intermediate (12), was therefore proposed.[3] It accounts for the formation of azepines such as (6) and an extension involving an ester shift [5] leads to the benzo[*c*]quinolizine (11). The unattractive postulate of an unstabilised carbanion intermediate (13) appears necessary to explain the orientation of the substituents in compounds (8)—(10) and the formation of (11). In the Scheme the carbon atom of the 2-methyl group of the quinoline migrates through the spiro intermediates, whereas in the earlier proposal it does not move but receives a migrating ester group. The fate of a carbon-labelled methyl group, which should distinguish between the schemes, was therefore investigated.



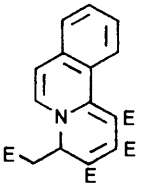
(1) 4a-Me
(2) 8-Br, 4a-Me
(3) 4a-$PhCH_2$



(4)
(5) 3-Br
(6) 11-Me
(7) 11-Ph



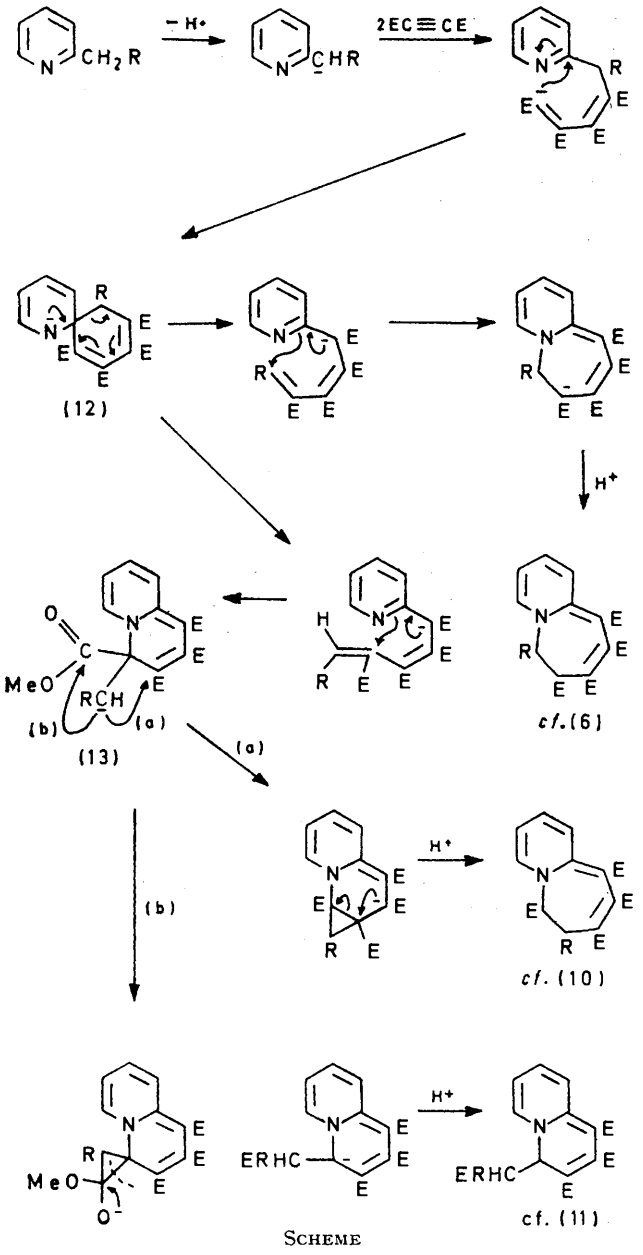
(8) 6-Me
(9) 3-Br
(10) 10-Me



(11)

E = CO_2Me

[1] Part LVIII, R. M. Acheson and J. Woollard, *J.C.S. Perkin I*, 1975, 446.
[2] R. M. Acheson, J. M. F. Gagan, and D. R. Harrison, *J. Chem. Soc.* (*C*), 1968, 362.
[3] R. M. Acheson and D. F. Nisbet, *J. Chem. Soc.* (*C*), 1971, 3291.
[4] R. M. Acheson and D. F. Nisbet, *J.C.S. Perkin I*, 1973, 1338.
[5] R. M. Acheson, *Accounts Chem. Res.*, 1971, **4**, 177.



SCHEME

The azepines (4), (5), and (9) were prepared from the corresponding 2-[^{13}C]methylquinolines and dimethyl acetylenedicarboxylate in acetonitrile. These azepines lose a methyl acrylate unit from the molecular ion in the mass spectrometer [6] to give a base peak at $(M - 86)^+$ with an appropriate natural isotope peak at $(M - 85)^+$. Comparison of the high resolution mass spectra of the enriched and unenriched azepines showed the expected enhancement of the $(M + 1)^+$ peak, within the limits of experimental error, in all three cases. The enrichments for the bromoazepines were calculated by averaging the values from the two molecular ion peaks and their successors. However, in all three cases the peak at $(M - 85)^+$ showed no enrichment relative to the base peak from the enriched samples, indicating that all the carbon-13 had been lost in the methyl acrylate unit.

Comparison of the ^{13}C n.m.r. spectra of the three enriched azepines with those of the corresponding unlabelled compounds showed that all the label was present in sp^3 carbon atoms which possessed essentially the same chemical shift (see Table). The parameters for the 60 and 100 MHz ^{1}H n.m.r. spectra of the protons at positions 10 and 11 of the bromoazepines (5) and (9) are known,[2] so the ^{13}C–^{1}H couplings for the ^{13}C-enriched samples were investigated. For the azepine (5), the resonance of one of the 11-protons (τ *ca.* 7·4) is clear of all other resonances, whereas that of the other 11-proton is superimposed on those of the 10-proton and the ester methyl groups. The 270 MHz ^{1}H spectrum showed clearly a ^{13}C–^{1}H coupling of 144 Hz for the 11-proton, so the added label must have moved to this position. For the isomeric azepine (9) separate signals due to the three aliphatic protons can be distinguished. A ^{13}C–^{1}H coupling of 145 Hz was observed for both the 10-protons, whereas no detectable coupling was observed with the 11-proton.

Off-resonance decoupling of the ^{13}C spectra for both azepines (5) and (9) caused the peaks corresponding to enriched positions to split into triplets; thus the ^{13}C atoms were present in CH_2 groups.

These data exclude the first reaction pathway proposed [2] and show that the azepines are formed by a route such as that in the Scheme, where the methyl carbon atom of the 2-methylquinoline appears in position 10 or 11 of the final azepine.

EXPERIMENTAL

The 270 MHz proton spectra were obtained with a Fourier Transform 270 MHz instrument (Bruker Spectrometer with an Oxford Instrument Co. magnet), and the ^{13}C spectra with Bruker instruments operating at 22·62 MHz.

^{13}C N.m.r. chemical shifts (p.p.m. from internal tetramethylsilane; solvent $CDCl_3$)

Compound	C-10	C-11	OCH_3	CH	C	C=O
(4)	44·7	31·1 *	50·5, 52·4, 52·7, 52·9	104·7, 118·0, 122·1, 128·5, 130·7, 136·4	123·2, 136·9	170·9
(5)	44·6	31·0 *	50·6, 52·5, 52·7, 53·1	116·5, 119·2, 120·5, 133·1, 135·0	114·6, 124·8 135·7	170·8
(9)	30·8 *	42·8	50·7, 52·1, 52·8, 53·1	114·1, 119·8, 120·6, 132·7, 134·4	124·5	170·6

* Peaks showing *ca.* 10 × enrichment over normal from labelling experiments.

The other instruments and chromatographic procedures have been noted earlier.[7] The ether used was sodium-dried.

[6] R. M. Acheson, R. T. Aplin, and D. R. Harrison, *J. Chem. Soc.* (*C*), 1968, 383.

[7] R. M. Acheson, N. D. Wright, and P. A. Tasker, *J.C.S. Perkin I*, 1972, 2918.

2-[^{13}C]*Methylquinoline*.—[^{13}C]Methyl iodide (0·5 g; *ca.* 60% enriched) and unlabelled methyl iodide (2·5 g) in ether (10 ml) were treated with lithium (0·3 g) under ether (25 ml) to give methyl-lithium. Quinoline (2·65 g) in dry ether (10 ml) was added at room temperature with stirring over 15 min, and stirring was continued for 2½ h. The mixture was poured onto ice and the organic layer was separated, dried, and evaporated to give crude 1,2-dihydro-2-[^{13}C]methylquinoline (2·45 g) [τ 8·82 (d, $J_{Me,H}$ 6 Hz, 2-Me), 6·52br (s, 1-H), 5·52—5·94 (m, 2-H), 4·62 (q, $J_{3,4}$ 9, $J_{2,3}$ 4 Hz, 3-H), and 2·92—3·92 (m, ArH_5)], which was mixed with nitrobenzene (12·4 g) and refluxed for 20 min. Ether was added and the solution was extracted with hydrochloric acid (20%). The acidic solution was basified with solid potassium hydroxide and extracted with ether. Distillation of the washed (H_2O) and dried ($MgSO_4$) ethereal extract gave 2-[^{13}C]methylquinoline (2·08 g, 73%) as a liquid, b.p. 116—122° at 15 mmHg (lit.,[8] for 2-methylquinoline, b.p. 118° at 10 mmHg), τ 7·34 (s, 2-Me), 7·34 [d, J(^{13}C,H) 125 Hz, 2-$^{13}CH_3$], and 1·8—2·93 (ArH_6), *m/e* 144 [27%, $(M + 1)^+$], 143 (100, M^+), 132 (47), 129 (13), and 128 (13).

6-*Bromo*-2-[^{13}C]*methylquinoline*.—This was prepared from 6-bromoquinoline (8·04 g; b.p. 143·5—144° at 15 mmHg), lithium (0·6 g), and [^{13}C]methyl iodide (6 g) in the same way as 2-[^{13}C]methylquinoline, and afforded needles (2·6 g, 30%), m.p. 95—99° (lit.,[9] 96—97°), τ 7·33 (s, 2-Me), 7·33 [d, J(^{13}C,H) 125 Hz, 2-$^{13}CH_3$], 2·80 (d, $J_{3,4}$ 9 Hz, 3-H), and 2·05—2·33 (m, ArH_4).

Reaction of 2-[^{13}C]*Methylquinoline with Dimethyl Acetylenedicarboxylate*.—The quinoline (1·45 g) in dried (P_2O_5) acetonitrile and the ester (3·17 g) in acetonitrile (*cf.* ref. 2) were separately cooled to 0° and mixed. After 4 days at room temperature the solvent was removed and the residue, in chloroform–toluene, was chromatographed on alumina (430 ml) made up in toluene. Elution with toluene (400 ml) gave tetramethyl 4a-[^{13}C]methyl-4a*H*-benzo[*c*]quinolizine-1,2,3,4-tetracarboxylate [as (1)] (0·2 g), m.p. 165—167° (lit.,[2] 166°), having the published n.m.r. spectrum plus τ 8·53 [d, J(^{13}C,H) 128 Hz, 4a-$^{13}CH_3$].

Elution with toluene–ether (5 : 1 v/v) gave the [11-^{13}C]-azepine [as (4)] (0·1 g), m.p. 201—203° (lit.,[2] 203—204°), showing a proton n.m.r. spectrum identical with that published apart from the ^{13}C,H couplings.

Further elution with toluene–ether gave the mixed red adducts,[2] and with ether the blue adduct [2] of m.p. 255—258°.

Reaction of 6-*Bromo*-2-[^{13}C]*methylquinoline with Dimethyl Acetylenedicarboxylate*.—The quinoline (2·6 g) in ether (35 ml) was mixed with the ester (4·5 ml) in ether (10 ml). After 1 week at room temperature the precipitated crystals were collected and the filtrate evaporated to a tar. This last was chromatographed as above; toluene eluted the 4a-[^{13}C]methylquinolizine [as (2)] (0·33 g), m.p. 182—185° (lit.,[2] 184—185°), τ 8·55 (s, 4a-Me), 8·55 [d, J(^{13}C,H) 128 Hz, 4a-$^{13}CH_3$], 6·35, 6·35, 6·30, and 6·25 (s, 4 × OMe), 3·66 (s, 5- and 6-H_2), and 2·80 (s, ArH_3).

The orange band eluted with toluene–ether (9 : 1 v/v) was collected in several fractions. T.l.c. showed that all were mixtures, except the first which yielded essentially pure tetramethyl 3-bromo-10,11-dihydro[10-^{13}C]azepino-[1,2-*a*]quinoline-7,8,9,11-tetracarboxylate (9), m.p. 220—222° (lit.,[2] 220°); n.m.r. spectrum identical with that reported apart from the ^{13}C,H couplings.

Combination of the remaining fractions with the precipitate from the reaction mixture, and slow recrystallization from methanol–acetonitrile, gave the isomeric azepine (5), m.p. 230—233° (lit.,[2] 232—233°); n.m.r. spectrum identical with that reported apart from the ^{13}C,H couplings.

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