Reactions of Spiro-indazoles containing Keto-groups. Part 2.[1] Evidence for a Spiro-benzocyclopropene Intermediate in the Thermolysis of Anthrone-10-spiro-3'-3'*H*-indazoles to Benz[*a*]aceanthrylenes

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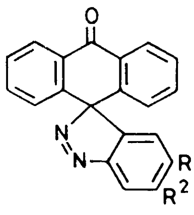
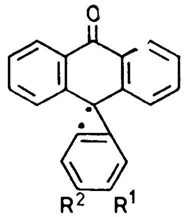
The reaction of 10-diazoanthrone (4) with 4-methylbenzyne gave the spiro-indazole regioisomers (1b) and (1c), both of which thermolyzed to give the hydroxybenz[*a*]aceanthrylenes (8b) and (8c). Thermolysis is interpretable on the basis of formation of the corresponding biradicals (2b) and (2c) which isomerize to one another, followed by the cyclization to the benzaceanthrylenes. The intramolecular radical isomerization provides strong evidence for a spiro-benzocyclopropene intermediate (3b) in this reaction.

We have previously shown that the spiro-indazoles [*e.g.* (1a)] containing keto-groups are converted thermally and photochemically into fused polycyclic compounds *via* the formation and intramolecular cyclization of the biradical (2a).[1] Other spiro-indazoles, such as fluorene-9-spiro-3'-3'*H*-indazole and 3*H*-indazole-3-spiro-1'-indene, also undergo an analogous reaction.[2,3] Not only are these rearrangements of synthetic interest but also mechanistically because both of the light they shed on the thermal rearrangements of highly strained spirocyclopropanes and spiro-cyclopropenes[4] and the possibility that biradicals and highly strained spiro-benzocyclopropenes might be formed from spiro-indazoles. Although the reactions previously investigated have been postulated to involve the spiro-benzocyclopropenes [*e.g.* (3a)] besides the biradicals as intermediates, there is little concrete evidence to support the possibility of spirobenzocyclopropene participation except in the formation of spiro-naphtho[*a*]cyclopropene from anthrone-10-spiro-1'-1'*H*-benz[*e*]indazole.[1-3,5] To confirm the formation of spiro-benzocyclopropenes as intermediates in the rearrangement of spiro-indazoles, the spiro-indazoles (1b) and (1c) have been prepared and subjected to decomposition.



(1)



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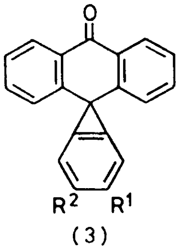
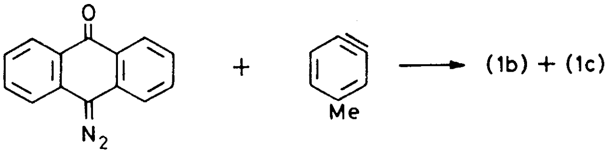


(3)

a; $R^1 = R^2 = H$
b; $R^1 = Me, R^2 = H$
c; $R^1 = H, R^2 = Me$

RESULTS AND DISCUSSION

The diazoketone (4) reacted with 4-methylbenzyne (5) generated by aprotic diazotization of 2-amino-5-methylbenzoic acid to give, on fractional crystallization of the product from ethanol, the spiro-indazoles (1b) and (1c) in 53 and 29% yields, respectively. The structural assignment of (1b) and (1c) rests on their n.m.r. spectra [(1b) methyl singlet, H-4' singlet, and H-7' doublet at δ 2.39, 7.09, and 8.27 ($J_{6',7'}$ 8.1 Hz), respectively; (1c) methyl singlet, H-4' doublet, and H-7' singlet at δ 2.50, 7.18, ($J_{4',5'}$ 7.9 Hz), and 8.18, respectively].† This cycloaddition is regioselective, the diazo-bearing carbon of the diazoketone (4) predominantly attacking the 2-position of 4-methylbenzyne (5). The predominance of (1b) and (1c) formation in the cycloaddition may be satisfactorily explained in terms of (i) a *para*/*meta* ratio of 40 : 60 in the addition of base to 4-methylbenzyne (5)[6] and (ii) a major contribution of (6) to the structure of diazoketones,



(4) (5)

(6)

The spiro-indazole (1b) when heated in anhydride resulted in loss of nitrogen to yield a mixture of the acetoxybenz[*a*]aceanthrylenes (7b) and (7c). Similarly, the spiro-indazole (1c) on thermolysis gave the acetates (7b) and (7c). These runs were carried out at thermolysis temperatures of 110 and 135 °C, and the results obtained by n.m.r. analyses [(7b) a singlet for 2'-Me at δ 2.57; (7c) a singlet for 3'-Me at δ 2.51] are

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† The n.m.r. spectrum of the spiro-indazole (1a) showed a one-proton signal (multiplet, δ 8.22—8.35) for H-7'.

shown in the Table. The acetates (7b) and (7c) although readily separated by preparative h.p.l.c. presented problems of structural differentiation; the latter was achieved on the basis of i.r. and n.m.r. spectral evidence. The structural assignments are supported by the fact that in the thermolysis of the spiro-indazoles the ratio of (7b) to (7c) formed indicates that the relative yields of the latter obtained from (1c) are much greater than those from (1b) (see mechanistic section). These structures were not pursued further.

TABLE

Thermolysis of the spiro-indazoles (1b) and (1c) in acetic anhydride

	Reaction conditions		
Indazole	Temp. (°C)	Reaction period (h)	Estimated (7c)/(7b) (by n.m.r.)
(1b)	110	4	1.7
(1b)	135	2	1.6
(1c)	110	4	2.5
(1c)	135	2	3.7

Total yields of the acetates (7b) and (7c): *ca.* 96%.

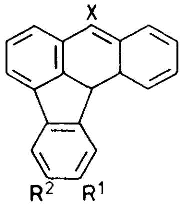
Thermolysis of both the spiro-indazoles (1b) and (1c) in inert solvent such as toluene gave a mixture of the hydroxybenz[*a*]aceanthrylenes (8b) and (8c) as the major products, along with a trace amount of a product thought to be 10-(*p*- and *m*-tolyl)anthrones (by t.l.c.). The hydroxyaceanthrylenes (8b) and (8c) were too unstable to be isolated, so that they were identified as (7b) and (7c) (total yield *ca.* 53—55%) after conversion of them into the isolable acetates. The products distribution by n.m.r. was comparable with that of the thermolysis of (1b) and (1c) in acetic anhydride.

$$\begin{tikzcd}
(1b) \arrow[r, "heat", "-N_2"'] & (2b) \arrow[r, "k_1", "cyclization"'] \arrow[d, shift right, "k_3"'] & (9b) \arrow[r] & (8b) \arrow[r, "acetylation"'] & (7b) \\
(1c) \arrow[r, "heat", "-N_2"'] & (2c) \arrow[r, "k_2"] \arrow[u, shift right, "k_{-3}\ isomerization"'] & (9c) \arrow[r] & (8c) \arrow[r] & (7c)
\end{tikzcd}$$

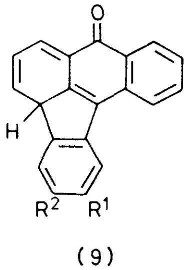
SCHEME

These results can readily be rationalized as shown in the Scheme[1] in which the spiro-indazoles (1b) and (1c) lose nitrogen either *via* direct extrusion or *via* an electrocyclic ring-opening to give the biradicals (2b) and (2c) respectively,[7] both of which undergo two competitive reactions: isomerization to one another and intramolecular cyclization to give the respective hydroxybenzaceanthrylene (8b) and (8c) *via* the formation and enolization of (9b) and (9c).[1] The intramolecular radical isomerization of (2b) and (2c) strongly suggest the spiro-benzocyclopropeneanthrone (3b) [= (3c)] as an intermediate formed from either (2b) or (2c). Further, the production of some benzocyclopropenes supports this suggestion.[5] The second conceivable mechanism, a concerted process from (2b) [(2c)] to (2c) [(2b)] may be excluded, since the concerted reaction in the radical isomerization must require much more activation energy than the reaction of (2b) [(2c)] to give (3b).*

In the analysis of the Scheme, the intramolecular cyclizations both of (2b) to (9b) and of (2c) to (9c) are


(7) : X = OAc

(8) : X = OH


(9)

assumed to be irreversible. Therefore, the ratio of the rate of formation of (7c) over (7b) is expressed as: (7c)/(7c) = $k_2[(2c)]/k_1[(2b)]$. The ratio for the thermolysis of the spiro-indazole (1b), according to the usual steady-state approximation for the biradical (2c) (working with $d[(2c)]/dt \cong 0$), is expressed by equation (1):

$$(7c)/(7b) = \frac{k_2k_3}{k_1(k_2 + k_{-3})} \text{ for (1b)} \qquad (1)$$

where k_1, k_2, k_3, and k_{-3} are rate constants for the respective steps, as shown in the Scheme. Similarly, the (7c)/(7b) ratio for the spiro-indazole (1c) is expressed by equation (2).

$$(7c)/(7b) = \frac{k_2(k_1 + k_3)}{k_1k_{-3}} \text{ for (1c)} \qquad (2)$$

By means of equations (1) and (2) and the values of the observed (7c)/(7b) ratio for (1b) and (1c) respectively, at each reaction temperature (see Table), the relative values of the rate constants, k_1/k_3 and k_2/k_{-3}, may be estimated. These values are as follows: at 110 °C, $k_1/k_3 = 0.14$ and $k_2/k_{-3} = 0.31$; at 135 °C, $k_1/k_3 = 0.28$ and $k_2/k_{-3} = 0.81$. This result demonstrates that the rate of radical isomerization is faster than that of intramolecular cyclization. If it is assumed that k_1 is approximately equivalent to k_2, the values of k_{-3}/k_3 are 0.45 and 0.35 at 110 and 135 °C, respectively, *i.e.* the biradical (2b) may be less stable than the biradical (2c). At present however, there is no firm evidence to substantiate this.

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* Usually activation energies for combination of two radicals to nonradical products are nearly zero.[8]

Finally, it appears that the thermal rearrangements of other spiro-indazoles, such as 3*H*-indazole-3-spiro-1′-naphthalen-4′(1′*H*)-one,[1] fluorene-9-spiro-3′-3′*H*-indazole,[2] and 3*H*-indazole-3-spiro-1′-indene, also involve the formation of spiro-benzocyclopropenes as an intermediate.

EXPERIMENTAL

M.p.s were determined on a Yanagimoto hot-stage apparatus. I.r. spectra were recorded with a JASCO IRA-1 spectrophotometer (KBr disc), n.m.r. spectra with JEOL JNH-3H-60 (60 MHz) and JNH-FX90 (90 MHz) spectrometers for solutions in deuteriochloroform ($SiMe_4$ as internal standard), and mass spectra with a JEOL JMS-01SG-2 spectrometer (at 75 eV). Elemental analyses were performed on a Perkin-Elmer model 240 elemental analyzer. Preparative h.p.l.c. separations were carried out with a 250 mm × 8 mm LiChrosorb RP-18 column. For analytical t.l.c., Wakogel B-10 was used. Components were detected by staining with iodine vapour. Purity of products was checked by spectral, t.l.c., and h.p.l.c. analyses.

5- *and* 6-*Methylanthrone*-10-*spiro*-3′-3′H-*indazoles* (1b) *and* (1c).—A solution of 2-amino-5-methylbenzoic acid (3.32 g, 22 mmol) in acetone (70 ml) was added dropwise during 3.5 h to a refluxing solution of 10-diazoanthrone (4) [9] (4.40 g, 20 mmol) and isopentyl nitrite (2.81 g, 24 mmol) in dichloromethane (200 ml). After an additional 1 h of refluxing, the red solution was concentrated under reduced pressure at 20—30 °C. The oily crystalline residue was washed with ethanol and filtered off to give a mixture of spiro-indazoles (1b) and 1c) (5.08 g, 82%). N.m.r. analysis indicated (1b) and (1c) in a 65 : 35 ratio. Fractional recrystallizations of the mixture from ethanol gave the slightly more-soluble *spiro-indazole* (1b) as colourless needles, m.p. 200—202 °C (decomp.) (Found: C, 81.2; H, 4.6; N, 9.1. $C_{21}H_{14}N_2O$ requires C, 81.3; H, 4.55; N, 9.0%); $\nu_{max.}$ 1 660 cm (CO); δ 2.39 (3 H, s, Me), 6.20—6.50 (2 H, m, H-4 and -5), 7.09 (1 H, s, H-4′), 7.20—7.82 (5 H, m, H-2, -3, -6, -7, and -6′), 8.27 (1 H, d, *J* 8.1 Hz, H-7′), and 8.40—8.72 (2 H, m, H-1 and -8); *m/e* 282 ($M^+ - 28$, 100%), 267 (41), 253 (16), 252 (23), 239 (51), 126 (21), and 113 (18): and then the *spiro-indazole* (1c) as pale yellow microcrystals, m.p. 198—200 °C (decomp.) (Found: C, 81.15; H, 4.6; N, 9.2. $C_{21}H_{14}N_2O$ requires C, 81.3; H, 4.55; N, 9.0%); $\nu_{max.}$ 1 660 cm^{-1} (CO); δ 2.50 (3 H, s, Me), 6.20—6.50 (2 H, m, H-4 and -5), 7.18 (1 H, d, *J* 7.9 Hz, H-4′), 7.20—7.80 (5 H, m, H-2, -3, -6, -7, and -5′), 8.18 (1 H, s, H-7′), and 8.40—8.70 (2 H, m, H-1 and -8); *m/e* 282 ($M^+ - 28$, 100%), 267 (27), 253 (25), 252 (23), 239 (35), 141 (21) 126 (30), 125 (30), and 113 (20).

Separation of the mixture of the spiroindazoles (1b) and (1c) by chromatography on silica (benzene as eluant) was not particularly effective.

Thermolysis of the Spiro-indazoles (1b) *and* (1c).—(a) *In acetic anhydride.* A solution of a spiro-indazole (0.31 g, 1 mmol) in acetic anhydride (10 ml) was heated until t.l.c. showed the absence of the starting material. After cooling, the resulting mixture was poured into water. The crystals which had separated were collected and washed with water to give a mixture (*ca.* 0.31 g, 96%) whose n.m.r. analysis indicated 8-acetoxy-2-methylbenz[*a*]aceanthrylene (7b) and the 3-methyl compound (7c). Results were summarized in the Table.

Preparative h.p.l.c. of the acetates (7b) and (7c) was completed using water–methanol (1 : 9) as eluant at a flow rate of 1.5 ml min^{-1}. The efficiency of separation was checked by n.m.r. spectroscopy. The first eluate gave the *acetate* (7b) as yellow microcrystals, m.p. 215—216 °C (Found: C, 85.1; H, 5.0. $C_{23}H_{16}O_2$ requires C, 85.2; H, 5.0%); $\nu_{max.}$ 1 760 cm^{-1} (CO); δ 2.57 (3 H, s, Me), 2.65 (3 H, s, COMe), 7.10—8.20 (8 H, m, Ar-H), and 8.65—8.85 (2 H, m, H-7 and -9); *m/e* 324 (M^+, 13), 282 (100), 281 (18), 267 (10), 252 (14), 250 (9), 239 (11), and 43 (9). The second fraction consisted of the *acetate* (7c) as orange microcrystals, m.p. 193—195 °C (Found: C, 85.0; H, 5.0. $C_{23}H_{16}O_2$ requires C, 85.2; H, 5.0%); $\nu_{max.}$ 1 760 cm^{-1} (CO); δ 2.51 (3 H, s, Me), 2.65 (3 H, s, COMe), 6.80—8.25 (8 H, m, Ar-H), and 8.55—8.80 (2 H, m, H-7 and -9); *m/e* 324 (M^+, 12%), 282 (100), 281 (24), 267 (8), 252 (19), 250 (12), 239 (11), and 43 (10).

(b) *In toluene.* A solution of a spiro-indazole (0.31 g, 1 mmol) in toluene (20 ml) was refluxed under nitrogen until t.l.c. showed the absence of the starting material (*ca.* 4 h). T.l.c. analysis of the resulting mixture showed the presence of the hydroxybenz[*a*]aceanthrylenes (8b) and (8c) and a trace amount of a product thought to be 10-(*p*- and *m*-tolyl)anthrones. Because the hydroxyaceanthrylenes (8b) and (8c) were unstable to air, light, and prolonged heating, they were separated as a mixture of the respective acetates (7b) and (7c). In a parallel experiment, acetic anhydride (5 ml) was added to the reaction mixture. After the mixture had been stirred at 90 °C for 30 min and worked up, the products were examined by n.m.r. analysis: (1b), (7b) : (7c) = 37 : 63, total yield 53%; (1c), (7b) : (7c) = 27 : 73, total yield 55%.

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