Acid-promoted Behaviour of 1a,7b-Dihydro-1*H*-cyclopropa[*c*]cinnolines

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Compounds (1a—c) undergo in boiling acetic acid a fast reaction to afford 1,4-dihydrocinnolines or 4,5-dihydro-1*H*-1,2-benzodiazepines, which arise from a skeleton rearrangement involving cleavage of the cyclopropane ring. Fragmentation products are also obtained in the case of (1c).

WE have reported [1] a synthetic route leading to 1a,7b-dihydro-1*H*-cyclopropa[*c*]cinnolines a new class of strained molecules structurally related to the well studied diazanorcaradienes. Since the latter compounds are known to undergo interesting thermal and acid-catalysed rearrangements,[2-6] we have undertaken an analogous investigation on the tricyclic substrates (1a—c). While their thermal reactions in an inert solvent have been the object of a recent communication,[7] the present report deals with the results obtained by heating (1a—c) in a protic solvent such as acetic acid. Experiments under different acidic conditions have been also carried out with the aim of providing support to structures and mechanisms.

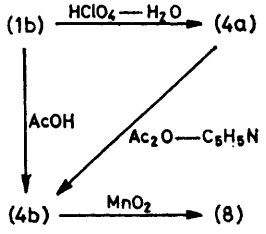
It is worthwhile to anticipate that the results here described reveal an intriguing variability of chemical behaviour within the series of the investigated substrates.

RESULTS AND DISCUSSION

In boiling acetic acid, compounds (1a—c) underwent a fast reaction which was complete in all cases within 30 min. However, different kinds of products were obtained from the different substrates. In fact, while the reaction of (1a) led to (2) and (3) in 55 and 20% yield respectively, compound (1b) gave only the acetoxy-derivative (4b), which was isolated as one pure isomer of undetermined stereochemistry in 60% yield.† On the other hand, when starting from (1c), the reaction resulted in a complex mixture from which the chromatographic separation gave ethyl phenylglyoxylate (5) (25%), a 2 : 1 diastereoisomeric mixture of (6) (39%), the acetoxy-compound (4c) (6%, one isomer), and ethyl cinnoline-3-carboxylate (7) (9%). Both diastereoisomers of formula (6) were obtained pure after several recrystallizations.

With the idea of depressing the fragmentation process observed in the case of (1c), the reaction of this substrate was repeated under milder conditions. Actually, when (1c) was treated with acetic acid at 70 °C (5 h), the yield of (4c) rose to 30% at the expense of the other products. It was then ascertained that (4c) is unstable in boiling acetic acid, decomposing completely within 2 h to give (5), (6), and (7).

While (2),[7] (5),[8] and (7) [9] were recognized by comparison of their physical and spectral properties with those of authentic samples, the structures of the new compounds (3), (4b, c), and (6) were assigned on the basis of the following evidence. All gave correct elemental analyses, molecular weights (from mass spectra), and i.r. and ^{1}H n.m.r. data (see Experimental section). Further support to the structures (4b, c) came from ^{13}C n.m.r. spectroscopy; in fact, diagnostic signals in the off-resonance spectra were a doublet at 73.3 and 77.3 p.p.m. for (4b) and (4c) respectively and a singlet at 53.7 and 62.7 p.p.m. for (4b) and (4c) respectively. In the case of (4b), structural confirmation was obtained through the set of reactions outlined in Scheme 1. Such chemical evidence is lacking for (4c); in fact, while the treatment of (1b) with perchloric acid gave (4a) in a fair yield, the reaction of (1c) under the same conditions resulted in a very complex mixture including (5), (6), and (7).‡



SCHEME 1

The diastereoisomers of formula (6) both showed in the ^{1}H n.m.r. spectrum an AB-type signal, due to the CH–CH group, with J = 11 and 7.5 Hz. By analogy with the vicinal coupling constants reported for pairs of diastereoisomers,[10] these values may tentatively be attributed to the *erythro*- and *threo*-configurations respectively. It is noteworthy that (6) was formed in high yield upon hydrogenation of (1c) in the presence of palladium catalyst. In this case, however, the diastereoisomeric ratio was different from that given above (*ca.* 1 : 2 rather than 2 : 1).

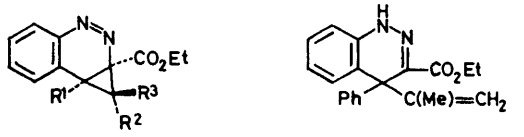
The most striking feature of the above results is the dramatic change in chemical behaviour on going from one substrate to another. The following is aimed at rationalizing this pattern of behaviour.

Since the reported thermal reactions of (1a—c) in boiling xylene [7] were much slower than those described

† The ^{1}H n.m.r. analysis of the crude product arising from (1b) showed the presence of a small quantity (roughly 10%) of a by-product which, however, was not obtained pure either by fractional crystallization or by column chromatography. The spectrum of the mixture suggests that the minor product might have a stereoisomeric structure with respect to the major one.

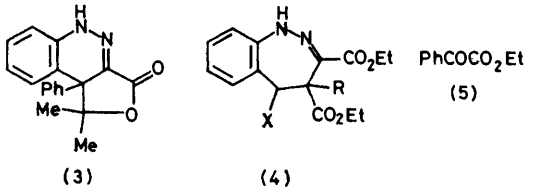
‡ For the sake of comparison, the behaviour of (1a) in the presence of perchloric acid was also studied. The product was a mixture of (2) and (3), the latter being the predominant component.

here, it is reasonable to attribute the great reactivity of (1a—c) in an acid medium to a preliminary protonation which facilitates the heterolytic opening of the three-membered ring. In view of previous reports on the



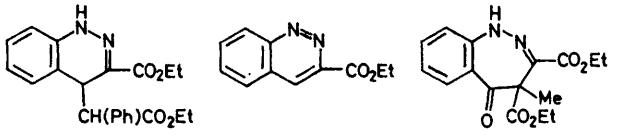
(1) (2)

a; R^1 = Ph, R^2 = R^3 = Me
b; R^1 = H, R^2 = CO_2Et, R^3 = Me
c; R^1 = H, R^2 = CO_2Et, R^3 = Ph



(3) (4) (5)

a; R = Me, X = OH
b; R = Me, X = OAc
c; R = Ph, X = OAc



(6) (7) (8)

electrophilic cleavage of fused-ring cyclopropanes,[11-13] competition is conceivable between internal and external bond rupture to give the isomeric carbocation intermediates (9) and (10), which are interconvertible *via* a 1,2-sigmatropic shift (see Scheme 2). The intermediacy of (9; R^1 = Ph, R^2 = R^3 = Me) well accounts for both the products arising from (1a); the formation of (3) is probably due to a nucleophilic attack by the moisture present in the reaction medium followed by lactonization.*

The preference for the path B by the substrates (1b, c) is not surprising because of the electron-withdrawing nature of the R^2 substituent, which should destabilize the carbocation intermediate (9) with respect to the isomeric one (10). However, a full rationalization of the experimental findings is not easy for (1c). A possible explanation is that, in the case of (1c), the formation of (10) might be preferred on kinetic, but not thermodynamic grounds. Thus, the first-formed acetoxy-compound (4c) may well undergo re-ionization to (10) followed by isomerization to (9), which then evolves to the other products.† A mechanistic proposal for the formation of (5), (6), and (7) is illustrated within Scheme 2.

* Alternatively, the formation of (3) can be formulated as occurring *via* (9) through nucleophilic participation of the neighbouring ethoxycarbonyl group, somewhat similar to that involved in the formation of phthalides from 2-phenoxycarbonyl- and 2-methoxycarbonyl-benzyl bromides.[14]

EXPERIMENTAL

Spectra were obtained on the following instruments: Varian HA-100 (^{1}H n.m.r.) and XL-100 (^{13}C n.m.r.) apparatus with $SiMe_4$ as an internal standard, Perkin-Elmer 377 i.r. spectrophotometer, and Hitachi RMU-6L mass spectrometer operating at 70 eV (direct insertion). M.p.s were taken on a Büchi apparatus and are uncorrected. Organic solutions were dried over anhydrous sodium sulphate.

Treatment of (1a) *with Acetic Acid.*—A solution of (1a) [1] (0.60 g) in acetic acid (90 ml) was refluxed for 30 min. After cooling, the mixture was poured in water and extracted with tetrachloromethane. The organic solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was chromatographed on silica gel (50 g) with diethyl ether as eluant to give (2) [7] (0.33 g) followed by 5,9b-*dihydro*-1,1-*dimethyl*-9b-*phenylfuro*[3,4-c]-*cinnolin*-3(1H)-*one* (3) (0.11 g), m.p. 125 °C (from di-isopropyl ether) (Found: C, 73.6; H, 5.3; N, 9.7. $C_{18}H_{16}N_2O_2$ requires C, 73.9; H, 5.5; N, 9.6%); $\nu_{max.}$ (Nujol) 3 340 (NH) and 1 750 cm^{-1} (CO); δ($CDCl_3$) 1.39 (3 H, s, Me), 1.59 (3 H, s, Me), 6.9—7.5 (9 H, m, Ar), and 8.7br (1 H, s, NH); *m/e* 292 (3.5%), 234 (18), 206 (54), and 205 (100).

Treatment of (1a) *with Perchloric Acid.*—Compound (1a) (0.40 g) in tetrahydrofuran (15 ml) was treated with 60% aqueous perchloric acid (0.2 ml). After 10 min at room temperature, the mixture was neutralized with sodium hydrogen carbonate, the solvent was partly removed under reduced pressure, and the residue was taken up with water and extracted with ether. The organic solution was dried and evaporated and the residue was chromatographed on silica gel as in the preceding preparation to give (2) (0.04 g) and (3) (0.25 g).

Treatment of (1b) *with Acetic Acid.*—A solution of (1b) [1] (1.0 g) in acetic acid (150 ml) was refluxed for 30 min, after which it was treated as described for (1a). Recrystallization of the crude product from di-isopropyl ether gave *diethyl* 5-*acetoxy*-4,5-*dihydro*-4-*methyl*-1H-1,2-*benzodiazepine*-3,4-*dicarboxylate* (4b) (0.72 g), one isomer, m.p. 152—153 °C (Found: C, 59.9; H, 6.1; N, 7.5. $C_{18}H_{22}N_2O_6$ requires C, 59.7; H, 6.1; N, 7.7%); $\nu_{max.}$ (Nujol) 3 300 (NH), 1 750 (CO), and 1 725 cm^{-1} (CO); δ($CDCl_3$) 1.20, 1.30 (6 H, two t, CH_2*Me*), 1.32 (3 H, s, Me), 2.18 (3 H, s, COMe), 4.13, 4.25 (4 H, two q, *CH_2*Me), 6.40 (1 H, s, CH), 6.9—7.4 (4 H, m, Ar), and 8.9br (1 H, s, NH); ^{13}C δ (25.2 MHz, $CDCl_3$) 14.0 (q), 14.1 (q), 19.9 (q), 20.6 (q), 53.7 (s), 61.2 (t), 61.5 (t), 73.3 (d), 118.2 (d), 123.9 (d), 125.1 (d), 126.7 (s), 128.4 (d), 133.9 (s), 137.9 (s), 164.1 (s), 168.6 (s), and 169.9 (s); *m/e* 362 (27%), 317 (1.5), 302 (8), 289 (1.5), 273 (11), 256 (14), 247 (15), 229 (33), 203 (27), 202 (22), and 201 (100). In addition to the above signals, the ^{1}H n.m.r. spectrum of the crude product before recrystallization showed two singlets at δ 1.95 and 6.00 of relative intensity 3 : 1.

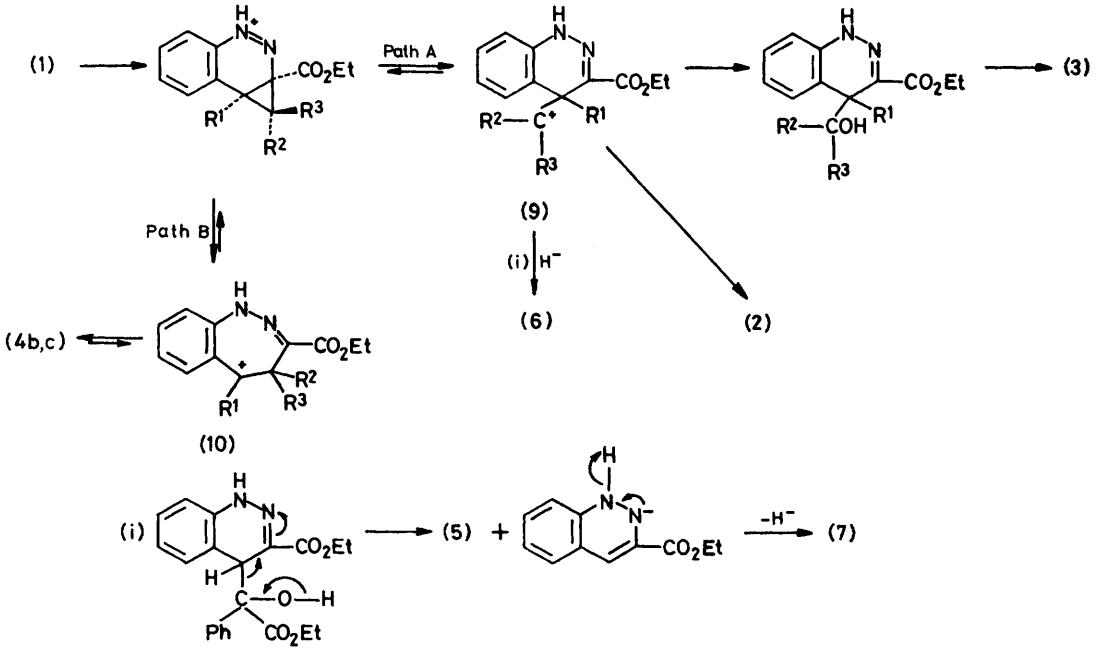
A sample of (4b) (one isomer) was refluxed in acetic acid for 8 h. After the standard work-up, a *ca.* 1 : 1 isomeric mixture was obtained, m.p. 105—108 °C (n.m.r. analysis). The composition of the mixture was unchanged after 24 h in refluxing acetic acid.

Treatment of (1b) *with Perchloric Acid.*—A solution of (1b)

† The reversibility of the pathway (4c) ⇌ (10) is reasonable in view of the good ionizing power of the solvent. In this context, it is interesting that (4b), obtained as a pure isomer from (1b), gave an equilibrium stereoisomeric mixture after prolonged heating in acetic acid.

(0.80 g) in tetrahydrofuran (30 ml) was treated with 60% aqueous perchloric acid (0.4 ml). After 20 min at room temperature, the mixture was worked up as described for (1a). Chromatography of the crude product on silica gel (80 g) with diethyl ether as eluant gave a solid material which was recrystallized from di-isopropyl ether to afford *diethyl 4,5-dihydro-5-hydroxy-4-methyl-1H-1,2-benzodiazepine-3,4-dicarboxylate* (4a) (0.32 g), one isomer, m.p. 164—165° (Found: C, 59.7; H, 6.3; N, 8.5. $C_{16}H_{20}N_2O_5$ requires C, 60.0; H, 6.3; N, 8.7%); $\nu_{max.}$ (Nujol) 3 450 (OH), 3 300 (NH), and 1 730 cm^{-1} (CO); $\delta(CDCl_3)$ 1.20 (3 H, s, Me), 1.22, 1.28 (6 H, two t, CH_2Me), 3.9br (1 H, s, OH), 4.22, 4.24 (4 H, two q, CH_2Me), 5.38 (1 H, s, CH), 6.9—7.8 (4 H, m, Ar), and 8.9br (1 H, s, NH); *m/e* 320 (43%), 302 (54), 273 (30), 256 (48), 247 (15), 229 (59), 201 (93), and 200 (100).

Treatment of (1c) *with Acetic Acid.*—Compound (1c) [1] (0.87 g) in acetic acid (110 ml) was refluxed for 30 min. After the standard work-up, the product mixture was chromatographed on silica gel (190 g). Elution with diethyl ether gave (5) [8] (0.17 g) followed by *ethyl 4-(α-ethoxycarbonylbenzyl)-1,4-dihydrocinnoline-3-carboxylate* (6) (0.34 g) as a diastereoisomeric mixture, m.p. 105—110°. After two recrystallizations from di-isopropyl ether, compound (6) was obtained as the pure *threo*-form, m.p. 125 °C (Found: C, 68.9; H, 5.9; N, 7.7. $C_{21}H_{22}N_2O_4$ requires C, 68.8; H, 6.0; N, 7.6%); $\nu_{max.}$ (Nujol) 3 300 (NH) and 1 730—1 740 cm^{-1} (CO); $\delta(CDCl_3)$ 1.20, 1.40 (6 H, two t, CH_2Me), 3.70 (1 H, d, *J* 7.5 Hz, CH), 4.12, 4.38 (4 H, two q, CH_2Me), 4.93 (1 H, d, *J* 7.5 Hz, CH), 6.6—7.4 (9 H, m, Ar), and 8.2br (1 H, s, NH).



SCHEME 2

Acetylation of (4a).—Compound (4a) (0.10 g) in acetic anhydride (10 ml) was treated with pyridine (1 ml) and heated at 60 °C for 4 h. The solvent was partly removed under reduced pressure and the remaining mixture was poured into cold water and extracted with tetrachloromethane. The organic layer was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was taken up with di-isopropyl ether and filtered to afford (4b) (0.060 g) (n.m.r. analysis).

Oxidation of (4a).—A solution of (4a) (0.080 g) in acetone (10 ml) was stirred with active MnO_2 (0.5 g) at room temperature for 30 h. The solid was filtered off and the solution was evaporated. The residue was chromatographed on silica gel (20 g) with benzene–diethyl ether (1 : 1 v/v) as eluant to give *diethyl 4,5-dihydro-4-methyl-5-oxo-1H-1,2-benzodiazepine-3,4-dicarboxylate* (8) (0.042 g), m.p. 88—89 °C (from n-pentane–di-isopropyl ether) (Found: C, 60.6; H, 5.6; N, 8.7. $C_{16}H_{18}N_2O_5$ requires C, 60.4; H, 5.7; N, 8.8%); $\nu_{max.}$ (Nujol) 3 320 (NH), 1 730 (CO), and 1 670 cm^{-1} (CO); $\delta(CDCl_3)$ 1.05, 1.33 (6 H, two t, CH_2Me), 1.82 (3 H, s, Me), 4.10, 4.35 (4 H, two q, CH_2Me), 6.9—7.7 (3 H, m, Ar), 8.0—8.2 (1 H, m, Ar), and 9.3br (1 H, s, NH); *m/e* 318 (24%), 272 (38), 244 (26), 218 (29), 203 (38), and 199 (100).

Further elution gave *diethyl 5-acetoxy-4,5-dihydro-4-phenyl-1H-1,2-benzodiazepine-3,4-dicarboxylate* (4c) (0.060 g), m.p. 188—190 °C (from methanol) (Found: C, 65.3; H, 5.7; N, 6.4. $C_{23}H_{24}N_2O_6$ requires C, 65.1; H, 5.7; N, 6.6%); $\nu_{max.}$ (Nujol) 3 300 (NH), 1 750 (CO), and 1 730 cm^{-1} (CO); $\delta(CD_3COCD_3)$ 1.16, 1.28 (6 H, two t, CH_2Me), 1.93 (3 H, s, COMe), 3.9—4.4 (4 H, m, CH_2Me), 6.88 (1 H, s, CH), 6.7—7.3 (9 H, m, Ar), and 10.1br (1 H, s, NH); ^{13}C δ (25.2 MHz, $CDCl_3$) 13.8 (q), 14.1 (q), 20.1 (q), 61.4 (t), 61.9 (t), 62.7 (s), 77.3 (d), 117.5 (d), 122.0 (d), 124.2 (d), 126.9, 127.2, 127.8 (overlapping signals), 128.8, 132.1 (d), 137.8 (s), 140.4 (s), 166.5 (s), 170.5 (s), and 170.8 (s); *m/e* 424 (24%), 423 (100), 363 (78), 362 (74), 318 (35), 291 (80), 263 (80), and 203 (31). Subsequent fractions contained (7) [9] (0.045 g).

Hydrogenation of (1c).—Compound (1c) (0.36 g) in ethyl acetate (40 ml) was hydrogenated over 5% palladium–charcoal (50 mg) at 23 °C and 1 atm (uptake 25 ml). After filtration of the catalyst and evaporation of the solvent, the residue was taken up with di-isopropyl ether to give (6)

(0.27 g) as a diastereoisomeric mixture, m.p. 110—112 °C; *m/e* 366 (0.1%), 365 (0.2), 364 (0.5), 293 (1), 247 (2), 219 (5.5), and 203 (100). Two recrystallizations from methanol afforded (6) as the pure *erythro*-form, m.p. 129—130 °C (Found: C, 68.9; H, 5.8; N, 7.6. $C_{21}H_{22}N_2O_4$ requires C, 68.8; H, 6.0; N, 7.6%); $\nu_{max.}$ (Nujol) 3 300 (NH) and 1 725—1 735 cm^{-1} (CO); $\delta(CDCl_3)$ 1.02, 1.10 (6 H, two t, CH_2Me), 3.58 (1 H, d, *J* 11 Hz, CH), 3.7—4.2 (4 H, m, CH_2Me), 4.98 (1 H, d, *J* 11 Hz, CH), 6.6—7.4 (9 H, m, Ar), and 8.6br (1 H, s, NH).

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