Reaction between 3*H*-Pyrrolizines and Acetylenedicarboxylic Esters. Part II.[1] Preparation of Derivatives of Cycl[4,2,2]azine (Azepino[2,1,7-*cd*]pyrrolizine)

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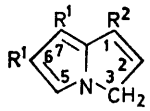
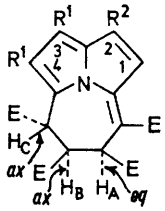
Reaction between 3*H*-pyrrolizines and an excess of dimethyl acetylenedicarboxylate gave 6,7-dihydro-5*H*-azepino[2,1,7-*cd*]pyrrolizine-5,6,7,8-tetracarboxylic esters (4)—(6); diethyl acetylenedicarboxylate gave only one analogous product (7). The 6,7-dihydro-5*H*-azepinopyrrolizine (4) was readily dehydrogenated to give the 5*H*-azepinopyrrolizinetetracarboxylate (9), which was stable towards oxidising agents. An intermediate in the production of the 3,4-dimethyldihydroazepinopyrrolizine (6) has been isolated and shown to be the pyrrolizin-3,5-diyldimaleate (11). A mechanism is proposed for the formation of the dihydroazepinopyrrolizines.

In Part I [1] we reported the production of 1 : 1 adducts from 3*H*-pyrrolizines and acetylenedicarboxylates when equimolar quantities were used. A minor product in each reaction under these conditions was an adduct from one molecule of 3*H*-pyrrolizine and two of the ester; these adducts could be made the major products if higher ratios of ester to pyrrolizine were used. In this paper the structures of this second series of adducts are discussed.



(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = Me$
(3) $R^1 = Me$, $R^2 = H$



E = CO_2Me, unless otherwise stated
(4) $R^1 = R^2 = H$
(5) $R^1 = H$, $R^2 = Me$
(6) $R^1 = Me$, $R^2 = H$
(7) $R^1 = H$, $R^2 = Me$, E = CO_2Et

From the reaction between 3*H*-pyrrolizine (1) and dimethyl acetylenedicarboxylate (ratio 1 : 5 or 1 : 10) in boiling toluene two products were isolated. The minor product (8%) was a 1 : 1 adduct (see Part I); the major product (59%) was an adduct shown by analysis and mass spectrometry (Table 1) to be made from one molecule of 3*H*-pyrrolizine (1) and two molecules of acetylenedicarboxylate. Its i.r. spectrum showed the presence of saturated and unsaturated ester systems. The chromophore was similar to that of 1 : 1 adducts.[1,2] The n.m.r. spectrum (Table 2) showed the presence of deshielded alkene protons [1,3] and a downfield broadened singlet at δ 5·85 p.p.m., eventually assigned to two equivalent pyrrole β-protons.[4] The main interest in the n.m.r. spectrum (CCl_4) centred on a three-proton system in the 3—5 p.p.m. region, partly obscured by the four methyl singlets due to the ester groups. By addition of benzene to the solution the methyl signals were sufficiently displaced to allow the identification of the couplings J_{AB} 2 and J_{BC} 12 Hz. The only satisfactory formula for the adduct is that of a reduced cycl[4,2,2]azine (azepino[2,1,7-*cd*]pyrrolizine) (4), and the coupling constants suggest the conformation shown. A similar reaction with 1-methyl-3*H*-pyrrolizine (2) gave the cyclazine (5), and 6,7-dimethyl-3*H*-pyrrolizine (3) gave the cyclazine (6). The n.m.r. spectra of the methyl-substituted cyclazines (5) and (6) proved that the exocyclic double bond is in position 3 of the original pyrrolizine (in contrast to the 1 : 1 adducts, where the double bond is at position 5), and also established that the signal at δ 5·85 p.p.m. (2H) in the cyclazine (4) represented two equivalent pyrrole protons, since the signal was absent in the spectrum of the cyclazine (6). Only one cyclazine was obtained from a 3*H*-pyrrolizine and diethyl acetylenedicarboxylate [the methyl derivative (7) from the pyrrolizine (2)]. An attempt to investigate the mechanism of the reaction by using [3-^{2}H]pyrrolizine gave a cyclazine (4) containing no deuterium; the experiment was inconclusive since column chromatography on alumina was necessary to purify the cyclazine (4). We have shown [1] that active

[1] Part I, D. Johnson and G. Jones, preceding paper.
[2] W. H. Okamura and T. J. Katz, *Tetrahedron*, 1967, **23**, 2941; W. Flitsch and R. Heidhues, *Chem. Ber.*, 1968, **101**, 3843.
[3] W. Flitsch, personal communication.
[4] R. M. Acheson and J. K. Stubbs, *J. Chem. Soc.* (*C*), 1969, 2316.

deuterium is replaced on an alumina column deactivated with water; passage of the cyclazine (4) through an alumina column deactivated by deuterium oxide caused virtually complete exchange of hydrogen atoms 5, 6, and 7 by deuterium.

didehydro-derivative indicated extended conjugation (Table 1), and the n.m.r. spectrum (Table 2) showed a sharp singlet (1H) at δ 5·93 p.p.m. in place of the ABC multiplet of compound (4). It was hoped that a hydride ion could be removed from the compound (9)

TABLE 1

U.v.–visible and mass spectra of cyclazine derivatives

Compound	$\lambda_{max.}$/nm (log ε) (95% EtOH)	*m/e* (%)
(4)	213 (4·12), 235sh, 334 (4·25), 440 (3·31)	389 (M^+, 10), 357 (27), 330 (9), 298 (13), 270 (100)
(5)	214·5 (4·12), 235 (4·06), 332 (4·24), 437 (3·33)	403 (M^+, 4), 371 (13), 344 (4), 284 (100)
(6)	214·5 (4·23), 240sh, 356 (4·29), 447 (3·25)	417 (M^+, 16), 385 (25), 358 (5), 326 (12), 298 (100)
(8)	207sh, 213 (3·95), 283 (4·33)	391 (M^+, 12), 359 (38), 332 (15), 300 (13), 272 (100)
(9)	206·5 (4·01), 220sh, 287 (4·35), 381 (3·54), 480 (3·47)	387 (M^+, 9), 328 (100)
(10)	204·5 (4·05), 258·5 (4·36), 317·5 (3·98), 355 (4·05)	389 (M^+, 11), 357 (3), 330 (100), 298 (11), 270 (12)
(11)	209·5 (4·24), 240·5 (4·27), 247sh, 382 (4·21)	417 (M^+, 37), $\left.\begin{matrix}385\\386\end{matrix}\right\}$ (22), 358 (10), 326 (22), 298 (100)

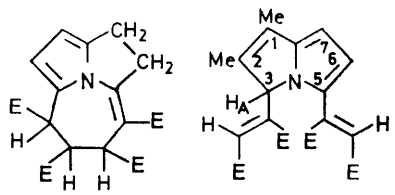
TABLE 2

N.m.r. data of cycl[4,2,2]azines

Compound	H-2	H-1	H-7	H-6	H-5	δ (p.p.m.) H-4	H-3	Ester Me	Others	*J*/Hz
(4) [a]	7·05(d)	6·55(d)	4·78(d)	3·29(q)	4·07(d)	5·85(s)		3·4—3·9(m)		$J_{1,2}$ 6, $J_{6,7}$ 2, $J_{5,6}$ 12
(5) [b]	Me, 2·06(s)	6·85(s)	4·94(d)	3·40(q)	4·25(d)	5·96(s)		3·5—3·9(m)		$J_{6,7}$ 2, $J_{5,6}$ 12
(6) [b]	7·03(d)	6·62(d)	4·95(d)	4·33(t)	4·59(d)	Me, 1·78(s)	Me, 1·92(s)	3·5—3·8(m)		$J_{1,2}$ 6, $J_{6,7}$ 4, $J_{5,6}$ 4
(7) [a]	Me, 2·05(s)	6·85(s)	4·74(d)	3·25(q)	3·8—4·6(m)	5·87(s)		1·3(m)	CH_2, 3·8—4·6(m)	$J_{6,7}$ 2, $J_{5,6}$ 12
(8) [b]	3·5—3·9(m)	2·85(t)	4·85(d)	3·55(q)	4·28(d)	6·3(m)	5·9(m)	3·5—3·9(m)		$J_{1,2}$ 6, $J_{6,7}$ 2, $J_{5,6}$ 12
(9) [a]	7·5(d)	6·95(d)			5·93(s)	6·49(d)	6·62(d)	3·85 (9H,m) 3·47 (3H,s)		$J_{1,2}$ 6, $J_{3,4}$ 3
(10) [a]	3·4—3·9(m)	2·96(t)			5·55(s)	6·45(d)	6·04(d)	3·4—3·9(m)		$J_{1,2}$ 5, $J_{3,4}$ 4

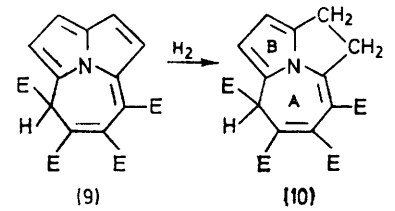
[a] In CCl_4. [b] In $CDCl_3$.

The cyclazine (4) was reduced catalytically to a dihydro-derivative (8) with loss of the principal chromophore. In the n.m.r. spectrum (Table 2) the deshielded alkene proton signals had been replaced by methylene absorptions, partly obscured by the methyl singlets.



(8)

(11)



(9) (10)

When the cyclazine (4) was treated with *N*-bromosuccinimide, or (better yield) with dicyanodichloro-*p*-benzoquinone (DDQ) in boiling benzeene, a didehydro-derivative (9) was obtained. The deeper colour of this

to give the unknown cycl[4,2,2]azinium 10 π-electron system; after treatment of compound (9) with triphenylmethyl perchlorate,[5] with phosphorus pentachloride,[6] or with DDQ and perchloric acid,[7] no identifiable products were obtained. Reduction of compound (9) to a dihydro-derivative, isomeric with the cyclazine (4), proceeded readily; the n.m.r. spectrum (Table 2) established the structure (10), illustrating the stability of the aza-azulene-type system (rings A and B). More vigorous reduction gave inseparable mixtures of products. Attempts to hydrolyse one of the ester groups in the didehydro-derivative (9) by controlled addition of base at room temperature gave mixtures of highly coloured products which were not characterised.

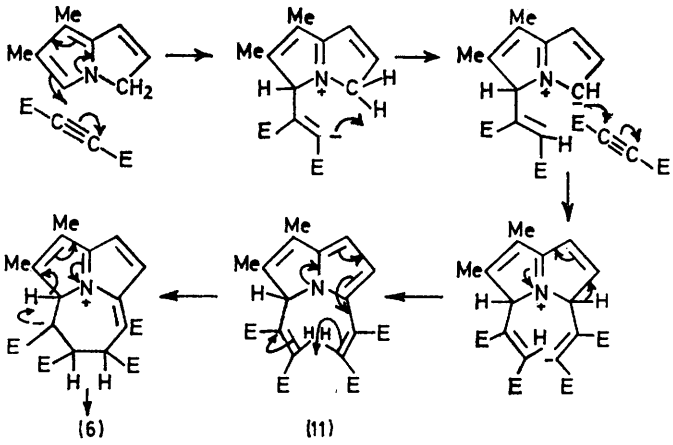
Some indication of the mechanism of formation of the reduced cyclazines (4)—(7) was provided by the reaction between the dimethylpyrrolizine (3) and dimethyl acetylenedicarboxylate. The cyclazine (6) was the minor constituent, the major product being a yellow isomer (48%). The n.m.r. absorption of this compound showed sharp singlets (each 1H) due to maleate protons, two β-pyrrole proton absorptions, and one other broadened singlet (1H), at δ 5·27 p.p.m. Double irradiation experiments confirmed that the singlet at 5·27 p.p.m. was broadened by coupling with one of the ring methyl groups; the only satisfactory

[5] H. J. Dauben, F. A. Gadecki, K. M. Harmon, and D. L. Pearson, *J. Amer. Chem. Soc.*, 1957, **79**, 4557.

[6] K. Conrow, *Org. Synth.*, 1963, **43**, 101.

[7] D. H. Reid, M. Fraser, B. B. Molloy, H. A. S. Payne, and R. G. Sutherland, *Tetrahedron Letters*, 1961, 530.

formula for the compound was (11), with H_A coupled allylically to the methyl group at position 1. The compound (11) was shown to be an intermediate in the formation of cyclazine (6), since boiling a toluene solution of the yellow compound (11) caused slow conversion into the cyclazine (6) (more rapidly achieved in a methanolic solution). Surprisingly, the 1 : 1 adducts [1] were not intermediates in the production of the cyclazines; treatment of a 1 : 1 adduct with further acetylenedicarboxylate, either with heating (with or without added base) or with irradiation, gave no cyclazine. These observations suggest a mechanism such as that shown in the Scheme; as mentioned previously no deuteriation experiments could be used to test the mechanism.



SCHEME

EXPERIMENTAL

Tetramethyl 6,7-*Dihydro*-5H-*azepino*[2,1,7-cd]*pyrrolizine*-5,6,7,8-*tetracarboxylate* (4).—A solution of 3*H*-pyrrolizine (1) (525 mg, 5 mmol) and dimethyl acetylenedicarboxylate (7·1 g, 50 mmol) in dry toluene (100 ml) was boiled (7 h), then left overnight. Evaporation (under reduced pressure) left a dark red oil, which was chromatographed on alumina (Woelm, activity 3; 200 g). Elution with petroleum (b.p. 60—80°)–toluene (1 : 1) gave the 1 : 1 adduct [1] (100 mg, 8%). Elution with toluene gave the bright red *cyclazine* (4) (1·144 g, 59%). The cyclazine was virtually pure, but could be recrystallised from carbon tetrachloride–petroleum (b.p. 60—80°); m.p. 105—112° (Found: C, 58·6; H, 5·2; N, 3·7. $C_{19}H_{19}NO_8$ requires C, 58·6; H, 4·9; N, 3·6%), $\nu_{max.}$ ($CHCl_3$) 1725 and 1695 cm^{-1}.

Tetramethyl 6,7-*Dihydro*-2-*methyl*-5H-*azepino*[2,1,7-cd]*pyrrolizine*-5,6,7,8-*tetracarboxylate* (5).—Prepared similarly from 1-methyl-3*H*-pyrrolizine (2) (357 mg), the *cyclazine* (5) (633 mg, 52%) formed red needles, m.p. 153—162° (Found: C, 59·9; H, 5·2; N, 3·4. $C_{20}H_{21}NO_8$ requires C, 59·55; H, 5·2; N, 3·45%), $\nu_{max.}$ ($CHCl_3$) 1730 and 1690 cm^{-1}.

Tetramethyl 6,7-*Dihydro*-3,4-*dimethylazepino*[2,1,7-cd]*pyrrolizine*-5,6,7,8-*tetracarboxylate* (6).—This was prepared similarly from 6,7-dimethyl-3*H*-pyrrolizine (3) (400 mg) and dimethyl acetylenedicarboxylate (4·26 g). The red oil obtained after removal of solvents was treated with a small volume of toluene; a yellow solid precipitated. Chromatographic separation of the toluene-soluble material gave the *cyclazine* (6) (191 mg, 19%) as a red solid, m.p. 151—152° (from ether) (Found: C, 60·3; H, 5·95; N, 3·4. $C_{21}H_{23}NO_8$ requires C, 60·4; H, 5·6; N, 3·35%), $\nu_{max.}$ ($CHCl_3$) 1730 and 1690 cm^{-1}. The yellow solid (600 mg, 48%) recrystallised from benzene, gave *tetramethyl* 1,2-*dimethyl*-3*H*-*pyrrolizine*-3,5-*diyldimaleate* (11), m.p. 166—171° (decomp. above 145°) (Found: C, 60·4; H, 5·5; N, 3·4. $C_{21}H_{23}NO_8$ requires C, 60·4; H, 5·6; N, 3·35%), $\nu_{max.}$ ($CHCl_3$) 1720 cm^{-1}, δ ($CDCl_3$) 1·95 (6H, s, 1- and 2-Me), 3·7 (9H, m, 3 × OMe) 3·92 (3H, s, OMe), 5·27br (1H, s, H-3), 5·74 (1H, s), 5·88 (1H, s), and 5·99 (1H, d, *J* 3 Hz), and 6·51 p.p.m. (1H, d, *J* 3 Hz) (H-6 and H-7).

Tetraethyl 6,7-*Dihydro*-2-*methyl*-5H-*azepino*[2,1,7-cd]*pyrrolizine*-5,6,7,8-*carboxylate* (7).—Prepared from 1-methyl-3*H*-pyrrolizine (357 mg) and purified as described,[1] the *cyclazine* (7) (102 mg, 7%) was obtained as a red oil which failed to crystallise. A specimen for analysis was purified by three successive p.l.c. separations [chloroform–benzene (4 : 1)] (Found: C, 62·2; H, 6·25; N, 3·1. $C_{24}H_{29}NO_8$ requires C, 62·7; H, 6·4; N, 3·1%), $\nu_{max.}$ ($CHCl_3$) 1730 and 1690 cm^{-1}.

Tetramethyl 1,2,6,7-*Tetrahydro*-5H-*azepino*[2,1,7-cd]*pyrrolizine*-5,6,7,8-*tetracarboxylate* (8).—The cyclazine (4) (396 mg) was hydrogenated in methanol (40 ml) over palladium–carbon (10%; 100 mg) at atmospheric temperature and pressure; absorption of hydrogen ceased after 2 h (1 equiv.). Removal of catalyst and evaporation left an oil, purified by p.l.c. [chloroform–benzene (3 : 1)]. The major product (200 mg, 50%) was crystallised from petroleum (b.p. 60—80°) to give the pale yellow *tetrahydrocyclazine* (8), m.p. 114—115° (Found: C, 58·4; H, 5·6; N, 3·6. $C_{19}H_{21}NO_8$ requires C, 58·3; H, 5·4; N, 3·6%), $\nu_{max.}$ ($CHCl_3$) 1730 and 1690 cm^{-1}.

Tetramethyl 5H-*Azepino*[2,1,7-cd]*pyrrolizine*-5,6,7,8-*tetracarboxylate* (9).—(*a*) A chloroform solution of the dihydrocyclazine (4) (264 mg) and *N*-bromosuccinimide (121 mg) was stirred at room temperature (3 h). The solution was washed with water (3×), dried (Na_2SO_4), and evaporated. The residual red oil was purified by p.l.c. [ether–petroleum (4 : 1)]; one band contained the cyclazine (9) (37 mg, 14%).

(*b*) A solution of the dihydrocyclazine (4) (800 mg, 2 mmol) and DDQ (940 mg, 4 mmol) in dry benzene (100 ml) was boiled (7 h) then left overnight. After filtration, the solution was evaporated, and the residual black oil was chromatographed on alumina (Woelm, activity 3; 25 g). Elution with toluene–chloroform (9 : 1) gave a deep red solution; evaporation gave the *cyclazine* (9) (515 mg, 64%) as a red oil, slowly solidifying and crystallising from carbon tetrachloride; m.p. 150° (Found: C, 59·0; H, 4·8; N, 3·7. $C_{19}H_{17}NO_8$ requires C, 58·9; H, 4·45; N, 3·6%), $\nu_{max.}$ ($CHCl_3$) 1735 and 1705 cm^{-1}.

Tetramethyl 1,2-*Dihydro*-5H-*azepino*[2,1,7-cd]*indolizine*-5,6,7,8-*tetracarboxylate* (10).—A solution of the cyclazine (9) (315 mg) in 95% ethanol (50 ml) containing palladium–carbon (10%; 100 mg) was hydrogenated at atmospheric temperature and pressure until the colour was discharged and uptake of hydrogen had slowed considerably (4 h). Filtration and evaporation gave a brown oil; p.l.c. [chloroform–benzene (1 : 1)] gave red, yellow, and colourless bands. The yellow band gave the *dihydrocyclazine* (10) (180 mg, 57%) as almost colourless needles, m.p. 112—113° [from petroleum (b.p. 60—80°)] (Found: C, 58·9; H, 4·6; N, 3·8. $C_{19}H_{19}NO_8$ requires C, 58·6; H, 4·9; N, 3·6%), $\nu_{max.}$ ($CHCl_3$) 1725 and 1697 cm^{-1}.

Isomerisation of Compound (11).—(*a*) A methanolic solution of compound (11) (62 mg) was left overnight and then evaporated to give a red oil; p.l.c. [chloroform–benzene (3 : 1)] gave the dihydrocyclazine (6), identical (i.r. and mass spectra; mixed m.p.) with the dihydrocyclazine (6) prepared directly.

(*b*) A solution of compound (11) in toluene was boiled (3 days); t.l.c. and the n.m.r. spectrum of the mixture obtained showed the presence of the dihydrocyclazine (6).

We thank the S.R.C. for a maintenance grant (to D. J.) and the P.C.M.U. (Harwell) for spin-decoupling experiments.

[1/2178 *Received*, 17*th November*, 1971]