143. *Addition Reactions of Heterocyclic Compounds. Part IX.* Benzoquinolizines from Isoquinoline and Dimethyl Acetylenedicarboxylate.*

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Isoquinoline and dimethyl acetylenedicarboxylate gave trimethyl benzo[*g*]indolizine-1,2,3-tricarboxylate or tetramethyl 11b*H*-benzo[*a*]quinolizine-1,2,3,4-tetracarboxylate according to the conditions, and various derivatives of the quinolizine are described. The infrared absorption spectra of the quinolizine, its 4*H*-isomer, and related compounds fall into a regular pattern in the 5—7 μ region.

Diels and Harms [1] investigated the products obtained from isoquinoline with dimethyl acetylenedicarboxylate, and largely on analogy with formulations they believed pertained to corresponding compounds from quinoline and pyridine with this ester, they suggested structures for the isoquinoline derivatives. Recent work has necessitated a review of the structures allocated to the pyridine [2] and quinoline [3] derivatives, and a parallel study of the products from isoquinoline has now been made.

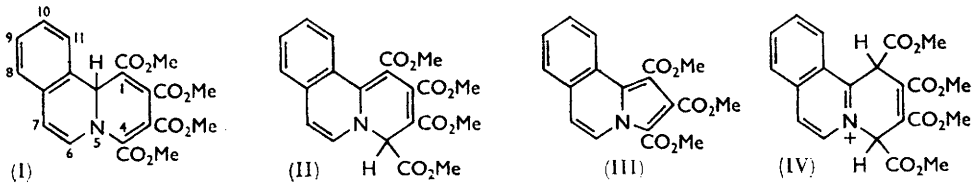
Freshly distilled isoquinoline and dimethyl acetylenedicarboxylate, as found by Diels and Harms, gave largely a 1 : 2 molar "labile" adduct which is now formulated as (I). If the isoquinoline was not freshly distilled the product was a tar from which none of the adduct (I) could be isolated, but only a small quantity of an indolizine (III) which was also obtained by Diels and Harms from the labile adduct (I) and later isolated by Wiley and Knabeschuh [4] as the only crystalline product when the reaction was carried out in ether at −80°. We have obtained the indolizine when using methanol as solvent at room temperature and at −50°.

Rearrangement of the "labile" adduct (I) to the "stable" isomer (II) has been effected in boiling xylene,[1] but other compounds can be formed [1] and in our hands sulphuric–acetic acid gave a cleaner isomerisation product. Diels and Harms's "second

* Part VIII, *J.*, 1961, 457.

[1] Diels and Harms, *Annalen*, 1936, **525**, 73.
[2] Acheson and Taylor, *Proc. Chem. Soc.*, 1959, 186; *J.*, 1960, 1691.
[3] Acheson, Earl, Higham, Richards, Taylor, and Vernon, *Proc. Chem. Soc.*, 1960, 281.
[4] Wiley and Knabeschuh, *J. Org. Chem.*, 1953, **18**, 836.

stable adduct," claimed as a by-product of the isomerisation, was never found by us; its description is suspiciously similar to that of the initial adduct (I). This type of rearrangement with an increase in conjugation (Table 1) parallels the isomerisation of 9a*H*- to 4*H*-quinolizines;[2] the greater difficulty observed in effecting the isomerisation compared with that of tetramethyl 7,9-dimethyl-9a*H*-quinolizine-1,2,3,4-tetracarboxylate [2]



is consistent with the greater steric hindrance in the region of the hydrogen atom initially at the ring junction. The ultraviolet absorption spectrum of the " labile " adduct (I) is unaltered by 35% perchloric acid, and as in the quinoline series [3] this strength of acid is needed before the " stable " adduct (II) is converted completely into the cation (IV). This structure (IV) for the cation is preferred to the isomeric one where the proton is added at position 3 on analogy with the protonation of similarly hindered 9-methyl-4*H*-quinolizines and because of the general similarity of its absorption spectrum to that of 2-methylisoquinolinium salts.[5]

The infrared absorption spectra (Table 2) of the " labile " pyridine [2] and quinoline adducts of known constitution, in chloroform, show maxima at *ca.* 5·87 and at 6·18—6·22 μ not present for the adducts of the " stable " series which have themselves maxima at 5·97—6·01 and 6·33—6·37 μ that are absent in the spectra of the labile adducts; paraffin pastes and potassium bromide discs [6] gave distorted spectra in this region. The spectra of the two " labile " and " stable " isoquinoline adducts fit well in this general pattern.

Diels and Harms oxidised the " labile " adduct (I) with an excess of bromine in methanol to tetramethyl 6-*o*-methoxycarbonylphenylpyridine-2,3,4,5-tetracarboxylate which they degraded to 2-phenylpyridine. This oxidation has been confirmed, but if less bromine is used an intermediate product, tentatively formulated as (V), can be isolated. It can be further oxidised to the pyridine derivative, and does not react with 2,4-dinitrophenylhydrazine. One hydrogen atom is probably at position 11b, as oxidation of the " stable " adduct (II) with an excess of bromine in methanol gave only the quinolizinium perbromide (VI), neither an intermediate product nor the phenylpyridine ester being detected. The quinolizinium perchlorate (VI), also prepared [1] from the tribromide with perchloric acid, was obtained from the " labile " adduct (I) with bromine and perchloric acid, but it is possible that the acid caused isomerisation to (II) before oxidation took place. The ultraviolet absorption spectra of the perchlorate and perbromide were very similar and resembled that of 7-methylbenzo[*a*]quinolizinium bromide [7] where the maxima were at somewhat lower wavelengths; the lower extinction coefficients obtained with the perbromide are probably related to its instability. Adding sodium methoxide to solutions of both these quinolizinium salts altered the spectrum to one which closely resembled that of the " stable " adduct (II), suggesting that addition of a methoxyl anion occurred at position 4, as in the pyridine-adduct series,[2] yielding the base (VII).

Hydrogenation of the " labile " adduct (I) over palladium on charcoal gave, as described,[1] a dihydro-derivative. This probably has structure (VIII) as its ultraviolet absorption spectrum is closely similar to that of tetramethyl 6,7,8,9-tetrahydro-9-methyl-

[5] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832.
[6] Jackman, Johnson, and Tebby, *J.*, 1960, 1507.
[7] Bradsher and Beavers, *J. Amer. Chem. Soc.*, 1955, **77**, 453.

TABLE 1.

Absorption spectra of the adducts and derivatives.

Compound	Solvent	Absorption maxima (Å) ($10^{-4}\varepsilon$)					
(I)	M	4380 (0·59)	3000 (1·78)	2920 (2·01) *	2660 (1·48)	2380 (1·59)	
6-Me deriv. of (I) †	M	4200 (0·53)	2880 (1·51)	2390 (2·28)			
(II)	M	4640 (1·66)	3380 (1·29) *	3220 (1·51)	2600 (1·12)	2290 (4·47)	
(IV)	P	3470 (0·47)	2750 (0·58)	2420 (3·60)			
6-Me deriv. of (II) †	M	4690 (1·40)	3250 (1·36)	2620 (0·99)	2310 (4·26)		
	P	3530 (0·40)	2750 (0·40)	2400 (3·80)			
(VIII)	M	4000 (0·71)	2835 (1·53)	2265 (1·54)			
(IX or X), m. p. 217°	M	2950 (2·01)	2100 (1·10)				
(IX or X), m. p. 124—126°	M	2905 (1·88)	2020 (1·20)				
(VI) perbromide	M	3845 (0·84)	3700 (0·68) *	3000 (1·74)	2290 (3·40)		
(VI) perchlorate	M	3850 (1·11)	3710 (0·86) *	3020 (2·12)	2310 (3·30)		
(VII)	B	4770 (1·65)	3160 (1·31)	2600 (0·98) *	2290 (3·20)		
(V)	M	4440 (0·54)	3900 (1·21)	3100 (0·78)	2730 (1·81)	2400 (1·31)	
	A	5150 (0·54)	3800 (1·54)	3620 (1·21)	3100 (1·34)	2790 (2·14)	
		2400 (0·97)					
trans-Cinnamic acid [10]	E	2730 (2·00)	2150 (1·50)	2040 (1·50)			
cis-Cinnamic acid [10]	E	2640 (0·95)	2140 (1·05)	2000 (1·55)			
Et *trans*-β-diethylamino-crotonate [11]	E	2880 (3·05)	2850 (3·05)				
1-Benzyl-1,4,5,6-tetrahydro-5-hydroxynicotinamide [12]	W	2920 (1·04)					

* = Inflexion. † Prepared according to ref. 6.

A = Methanol containing a trace of sulphuric acid; B = methanol basified with sodium methoxide; E = ethanol; M = methanol; P = methanol (2 vol.) and 72% perchloric acid (1 vol.); W = water.

TABLE 2.

Infrared absorption spectra of the adducts (tetramethyl quinolizine-1,2,3,4-tetracarboxylates) and related compounds in the 5·5—7·0 μ region in chloroform.

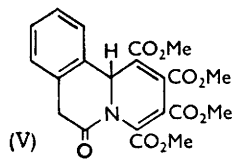
" Labile " series								
11b*H*-Benzo[*a*]- (I)	5·75	5·88	6·21	6·63	6·86	6·98		
6-Methyl-11b*H*-benzo[*a*]- †	5·76	5·87	5·91 *	6·22	6·68	7·00		
11a*H*-Benzo[*c*]- ‡	5·75	5·89	6·18	6·40	6·63	6·75	6·98	
" Stable " series								
4H-Benzo[*a*]- (II)	5·75	5·98	6·15	6·33	6·50	6·70	6·99	
6-Methyl-4*H*-benzo[*a*]- †	5·75	5·98	6·12	6·33	6·45	6·72	6·99	
4*H*-Benzo[*c*]- ‡	5·75	5·97	6·17	6·34	6·41	6·64	6·86	6·97
7-Methyl-4*H*-	5·74	6·01	6·37	6·56	6·72	6·99		
Isoquinoline derivatives								
Dihydro- (VIII)	5·75	5·94	6·24	6·63	6·76	6·88 *	6·98	
Tetrahydro- (IX or X), m. p. 217°	5·73	5·92	6·29	6·34	6·71	6·92	6·99	
Tetrahydro- (IX or X), m. p. 124—126°	5·74	5·92	6·29	6·36	6·72	6·91	6·99	

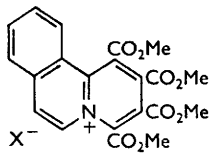
* Inflexion. † Prepared according to ref. 6. ‡ Prepared according to ref. 3.

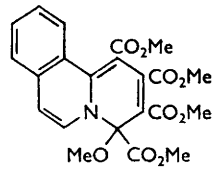
9a*H*-quinolizine-1,2,3,4-tetracarboxylate;[2] neither spectrum is altered by the addition of acid. When Raney nickel was used as catalyst two tetrahydro-derivatives of similar infrared and ultraviolet absorption spectra were obtained. One of these was identical with the products obtained by hydrogenation of the " stable " adduct (II) over platinum oxide and of the dihydro-derivative (VIII) over Raney nickel. If we assume that the carbocyclic ring is not reduced [8] there are five positions for the remaining double bond. The ultraviolet absorption spectra show too much conjugation for the bond to be between positions 1,2 or 2,3, and differ considerably from that of 2-n-butyl-1,2-dihydroisoquinoline,[9]

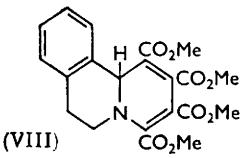
[8] Acheson, " Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publ., Inc., New York, 1960, p. 177.
[9] Schmidt and Karrer, *Helv. Chim. Acta*, 1949, **32**, 960.
[10] Braude, *Ann. Reports*, 1945, **42**, 105.
[11] Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45.
[12] Segal and Stein, *J.*, 1960, 5254.

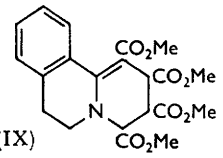
thereby excluding the 6,7-position. The remaining structural possibilities are the isomers associated with (IX) and (X). Similar comparisons (Table 1) with the ultraviolet absorption spectra of the nearest model compounds found in the literature, ethyl *trans*-β-diethylaminocrotonate, 1-benzyl-1,4,5,6-tetrahydro-5-hydroxynicotinamide, and *cis*- and

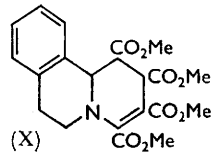

(V)


(VI)


(VII)


(VIII)


(IX)


(X)

trans-cinnamic acid suggest that the tetrahydro-derivatives are derived from (X). Structure (X) is also stereochemically the more probable as it is the much less strained in the 1-methoxycarbonyl–11*H* region.

Experimental

Tetramethyl 11bH-*Benzo*[a]*quinolizine*-1,2,3,4-*tetracarboxylate* (I).—Diels and Harms's " first labile isoquinoline *adduct* " (ascribed a different structure) was obtained as described, from freshly distilled isoquinoline, in 77% yield as golden needles, m. p. 167° (Found: C, 60·8; H, 4·7; N, 3·6; OMe, 29·8. $C_{21}H_{19}NO_8$ requires C, 61·0; H, 4·6; N, 3·4; 4OMe, 30·0%) (lit., m. p. 167—169°). The sole crystalline product, obtained in about 5% yield when the isoquinoline had not been freshly distilled, was the benzo[*g*]indolizine, described below.

Trimethyl Benzo[g]*indolizine*-1,2,3-*tricarboxylate* (III).—(i) Isoquinoline (1 g.) in methanol (5 ml.) was mixed with dimethyl acetylenedicarboxylate (2 ml.) in methanol (3 ml.) at room temperature, and after 2 days the yellow precipitate was collected. After chromatography on alumina the indolizine separated from methanol as colourless needles, m. p. 154—155° (Found: C, 63·3; H, 4·4; N, 4·3; OMe, 26·6%; *M*, 331. Calc. for $C_{18}H_{15}NO_6$: C, 63·3; H, 4·4; N, 4·1; 4OMe, 27·2%; *M*, 344). Wiley and Knabeschuh [4] give m. p. 150—151°, and record an absorption spectrum which was reproduced by our compound in methanol.

(ii) Isoquinoline (8 ml.) in methanol (10 ml.) at −32° was added dropwise to the acetylenic ester (11 ml.) in methanol (30 ml.) also at −32°. The temperature was allowed to rise to 0° and after 2 days at 0° the solid was collected. Crystallisation from methanol gave the indolizine (2·5 g.), identical in m. p., mixed m. p., and infrared absorption spectrum with a specimen from expt. (i).

Tetramethyl 4H-*Benzo*[a]*quinolizine*-1,2,3,4-*tetracarboxylate* (II).—The isomeric 11*bH*-benzo[*a*]quinolizine (1 g.) in glacial acetic acid (15 ml.) and concentrated sulphuric acid (5 ml.) was kept at 0° for 24 hr. Treatment with an excess of solid sodium carbonate, followed by water, precipitated the *product* which separated from glacial acetic acid in vermilion needles, m. p. 229—231° (Found: C, 60·6; H, 4·7; N, 3·7. $C_{21}H_{19}NO_8$ requires C, 61·0; H, 4·6; N, 3·4%) (lit.,[1] for the same product, given a different structure, m. p. 231°).

1,2,3,4-*Tetramethoxycarbonylbenzo*[a]*quinolizinium Perchlorate* (VI).—(i) The 11*bH*-benzo[*a*]quinolizine (I; 0·5 g.) in glacial acetic acid (5 ml.) containing 60% aqueous perchloric acid (0·5 ml.) was treated with bromine (0·19 g.) in acetic acid (1·9 ml.). After 16 hr. the crystalline *perchlorate* was collected and separated from acetic acid in pale yellow prisms, m. p. 212° (decomp.; varies with rate of heating) (Found: C, 48·4; H, 3·4; N, 3·1; Cl, 7·6. $C_{21}H_{18}NO_8,ClO_4$ requires C, 48·4; H, 3·5; N, 2·7; Cl, 6·8%). Diels and Harms [1] give m. p. 215° (decomp.) and an analysis for the hemihydrate.

(ii) The 4*H*-benzo[*a*]quinolizine (II) (0·1 g.) was suspended in 1 : 1 aqueous methanol (5 ml.), and bromine (2 g.) was added. After 5 minutes' refluxing, the excess of bromine and solvent were removed *in vacuo*, and crystallisation of the residue from aqueous methanol gave the benzo[*a*]quinolizinium perbromide as pale yellow plates, m. p. 140° (decomp.) [lit.,[1] m. p. 140° (decomp.)].

Tetramethyl 6,7-*Dihydro*-6-*oxo*-11b*H*-*benzo*[a]*quinolizine*-1,2,3,4-*tetracarboxylate* (V).—The 11*bH*-benzo[*a*]quinolizine (I, 4 g.) was suspended in 1 : 1 aqueous methanol (30 ml.), and bromine (2 g.) was rapidly added. After refluxing for 1 min. the mixture was allowed to cool. The *quinolizine* which separated (2·2 g.) crystallised from methanol in bright red needles, m. p. 207° (Found: C, 58·8; H, 4·1; N, 3·7; OMe, 28·3. $C_{21}H_{19}NO_9$ requires C, 58·6; H, 4·4; N, 3·3; 4OMe, 29·0%).

Tetramethyl 6-o-*Methoxycarbonylphenylpyridine*-2,3,4,5-*tetracarboxylate*.—(i) The 11*bH*-benzo[*a*]quinolizine (I) (4 g.), suspended in 1 : 1 aqueous methanol (30 ml.), was treated with bromine (6 g.) and refluxed for 1 min. On cooling, the pyridine derivative (1·7 g.) separated and after crystallisation from methanol had m. p. 149—150° (Found: C, 56·3; H, 4·4; OMe, 34·9. Calc. for $C_{21}H_{19}NO_{10}$: C, 56·6; H, 4·3; 5OMe, 34·9%) (lit.,[1] m. p. 152°). In methanol it had $\lambda_{max.}$ 2800 Å (ε 5800).

(ii) The 6-oxo-11*bH*-benzo[*a*]quinolizine (V) (0·5 g.) in 1 : 1 aqueous methanol (10 ml.) was refluxed with bromine (2 g.) and then evaporated to dryness *in vacuo*. The residue, after crystallisation from methanol, had m. p. and mixed m. p. with the product from expt. (i), 149—150°.

Tetramethyl x,x,6,7-*Tetrahydro*-11bH-*benzo*[a]*quinolizine*-1,2,3,4-*tetracarboxylate* (X).—(i) The 11*bH*-benzo[*a*]quinolizine (I) (1 g.) in methanol (25 ml.) was hydrogenated over Raney nickel at 4 atm. for 14 hr. After filtration the solvent was removed *in vacuo* and the residue shaken with cold methanol (20 ml.). The insoluble material crystallised from methanol, giving the *tetrahydro-compound* as colourless needles, m. p. 217° (Found: C, 60·5; H, 5·4; N, 4·0. $C_{21}H_{23}NO_8$ requires C, 60·4; H, 5·5; N, 3·4%). The cold-methanol-soluble material, obtained by evaporation, separated from aqueous methanol (50%) and was an isomeric *tetrahydro-derivative*, m. p. 124—126° (Found: C, 59·9; H, 5·5; N, 3·8.

(ii) The 4*H*-benzo[*a*]quinolizine (II, 0·2 g.) on hydrogenation in glacial acetic acid (25 ml.) over platinum oxide for 14 hr. at 4 atm. gave a product which was identical in m. p., mixed m. p., and infrared absorption spectrum with the tetrahydro-derivative, m. p. 217°, described above (lit.,[1] m. p. 217°). Raney nickel did not catalyse this hydrogenation and palladium–charcoal gave an oil.

(iii) The 6,7-dihydroquinolizine (VIII) (0·2 g.) in methanol (20 ml.) was hydrogenated over Raney nickel for 2 hr. Filtration and evaporation gave an almost quantitative yield of the tetrahydro-derivative (X), identical in infrared absorption spectrum and m. p. and mixed m. p. with a specimen of m. p. 217° from expt. (i).

Tetramethyl 6,7-*Dihydro*-11bH-*benzo*[a]*quinolizine*-1,2,3,4-*tetracarboxylate* (VIII).—Hydrogenation of the 11*bH*-benzo[*a*]quinolizine (I) (0·5 g.) in methanol (25 ml.) over 5% palladium–charcoal at 4 atm. gave the *dihydro-derivative* (VIII) which separated from methanol as a yellow-green solid, m. p. 179—180° (Found: C, 60·8; H, 5·0; N, 3·5. $C_{21}H_{21}NO_8$ requires C, 60·7; H, 5·1; N, 3·4%) (lit.,[1] m. p. 180°).

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