319. *The Reaction of β-Picoline and Dimethyl Acetylenedicarboxylate.*

By L. M. Jackman, A. W. Johnson, and J. C. Tebby.

One of the five adducts obtained from β-picoline and dimethyl acetylenedicarboxylate in ether has been formulated as a derivative of the non-basic 9a*H*-quinolizine and two of the others as derivatives of the basic 4*H*-quinolizine. The fourth adduct, which decomposed spontaneously at room temperature, may possess an " ylid " structure, and the fifth is an analogue of " Kashimoto's compound " described earlier by Diels.[1] Reactions of the quinolizine adducts are described, including dehydrogenation to a dehydroquinolizinium perchlorate and a base-exchange reaction of the 4*H*-quinolizine. Adducts from dimethyl acetylenedicarboxylate with γ-picoline and 3-methylisoquinoline are also described.

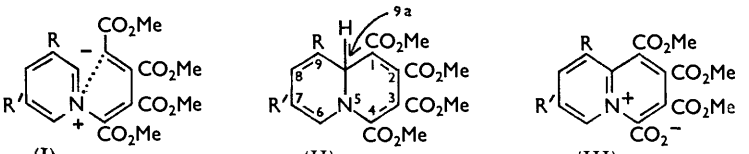
In a series of papers dating from 1932, Diels and his associates [1] investigated the structure and reactions of an interesting group of adducts formed from dimethyl acetylenedicarboxylate and pyridine. Similar reactions were also observed with α-picoline, quinoline, stilbazole, isoquinoline, acridine, and other heterocyclic bases.[2]

In ethereal solution at room temperature three products were isolated from pyridine, the first-formed being a red, relatively unstable compound formulated by Diels as the " ylid " (I; R = R′ = H). This so-called " labile adduct " (I; R = R′ = H) was easily transformed into a yellow stable adduct, formulated as the quinolizine derivative (II; R = R′ = H), and a third product, known as " Kashimoto's compound " and formulated as

[1] Diels *et al.*, *Annalen*, 1932, **498**, 16; 1933, **505**, 103; 1934, **510**, 87; **513**, 129; 1937, **530**, 68; 1944, **556**, 38; *Ber.*, 1942, **75**, 1452.

[2] Diels *et al.*, *Annalen*, 1935, **516**, 45; **519**, 140; 1936, **525**, 73; 1937, **530**, 87; 1939, **543**, 79; *J. prakt. Chem.*, 1940, **156**, 195.

(III; R = R′ = H). Our interest in these reactions originated from Diels's view of the mechanism; he believed that a dimer of the acetylenic ester was an intermediate and he

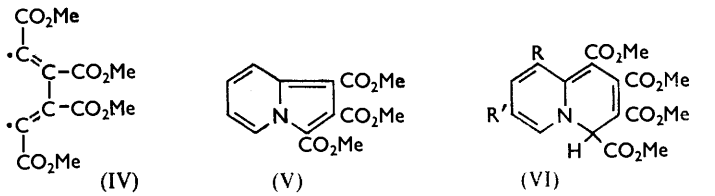


(I) (II) (III)

formulated the dimer at various times as the diradical (IV) and the corresponding zwitterion. If this view is correct, the intermediate could be regarded as a derivative of cyclobutadiene, a substance of current theoretical interest.[3]

We have carried out the condensation of dimethyl acetylenedicarboxylate with β-picoline in ether at room temperature, as we found that the adducts are easier to isolate and purify than those from pyridine. Measurement of the ultraviolet absorption of the reaction mixture at intervals by means of a self-recording spectrophotometer gave no evidence for the existence of an intermediate corresponding to (IV). The product was a mixture of an orange compound, m. p. 120—121°, corresponding to the red pyridine " labile adduct," and two yellow compounds, the first, m. p. 224°, corresponding to the yellow pyridine " stable adduct " and the second, m. p. 175—176°, corresponding to " Kashimoto's compound." When a benzene solution of the orange adduct was heated, there was formed a second yellow " stable adduct," m. p. 207°, which was isomeric with the first (m. p. 224°) and differed from it only in the position of the methyl group, as will be shown below.

Two other groups of investigators recently have examined the reaction of β-picoline and dimethyl acetylenedicarboxylate. Wiley and Knabeschuh [4] obtained only a yellow adduct, m. p. 117—119·5°, for the structure of which they reserved a final decision but suggested tentatively the indolizine formulation (V). More recently, Acheson and Taylor [5] have prepared the same " labile " and " stable " adducts from β-picoline as ourselves; they do not accept the Diels formulations and regard the labile orange adduct as (II; R = Me, R′ = H), the stable adduct of m. p. 224° as (VI; R = H, R′ = Me) or (VII; R = H,

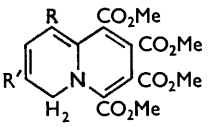


(IV) (V) (VI)

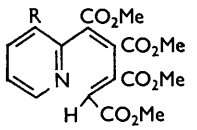
R′ = Me), and the stable adduct, m. p. 207° as (VI; R = Me, R′ = H) or (VII; R = Me, R′ = H). There are thus two suggested structures, (I) and (II), to be considered for the orange labile adduct from β-picoline apart from the precise position of the methyl group and three, (II), (VI), and (VII), for the yellow stable adducts. Our experiments, and particularly the interpretation of the nuclear magnetic resonance spectra of these compounds (see below), have led us to accept structure (VI) for the stable adducts and structure (II; R = Me, R′ = H) for the labile adduct as suggested by Acheson and Taylor.[5] van Tamelen *et al.*[6] recently have studied the nuclear magnetic resonance spectra of the quinoline–dimethyl acetylenedicarboxylate adducts and, like ourselves, explained the results in terms of the analogues of structures (II) and (VI) respectively for the labile and

[3] Baker and McOmie, *Chem. Soc. Spec. Publ.*, 1958, No. 12, p. 49.
[4] Wiley and Knabeschuh, *J. Org. Chem.*, 1953, **18**, 836.
[5] Acheson and Taylor, *Proc. Chem. Soc.*, 1959, 186; *J.*, 1960, 1691.
[6] van Tamelen, Aldrich, Bender, and Miller, *Proc. Chem. Soc.*, 1959, 309.

the stable adduct, the latter being regarded as a ring-chain tautomer of the monocyclic structure (VIII; R = H) which is stated to accommodate the nuclear magnetic resonance results more simply. We are very grateful to Professor van Tamelen for informing us of his results before their publication.



(VII)



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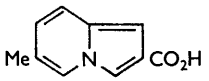
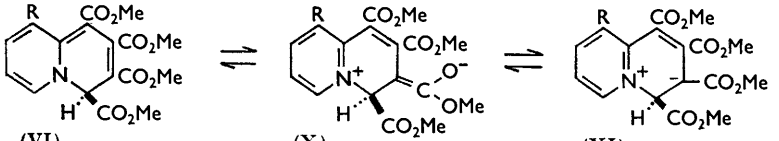


(IX)

Theoretically, two labile β-picoline adducts should exist, but the isomer corresponding to the stable adduct, m. p. 224°, has not been isolated in the present work. The two series, *i.e.*, the labile adduct, m. p. 121°, and the corresponding stable adduct, m. p. 207°, on the one hand, and the stable adduct, m. p. 224°, on the other, differed by the position of the methyl group on the nucleus and this has been determined as follows. Oxidation of the stable adduct, m. p. 224°, with dilute nitric acid gave trimethyl 6-methylindolizine-1,2,3-tricarboxylate, the structure of which was proved by hydrolysis and decarboxylation to 6-methylindolizine-2-carboxylic acid which was synthesised by condensation of 2,5-lutidine and bromopyruvic ester by the method of Burrows and Holland.[7] Hence the methyl group in the quinolizine ring of the yellow stable adduct is in the 7-position, if we accept the existence of the quinolizine ring in these compounds on the degradative evidence of Diels [1] and Acheson and Taylor.[5]

Similar oxidation of the stable adduct, m. p. 207°, gave trimethyl 8-methylindolizine-1,2,3-tricarboxylate which was converted by alkaline hydrolysis into 8-methylindolizine-2-carboxylic acid. The structure of this acid was proved in the same way as before, by its synthesis from 2,3-lutidine and bromopyruvic ester. Thus if we assume structure (II; R = Me, R′ = H) for the labile β-picoline adduct, the reason that it can be isolated so easily is the steric hindrance caused by the 9-methyl and the 1-methoxycarbonyl groups to the detachment of the angular proton. When the methyl group is in the 7- or 8-position (the adduct from γ-picoline) or is absent (the adduct from pyridine), the labile adducts can be isolated only with difficulty, if at all.

The nuclear magnetic resonance spectra of the stable pyridine adduct, and of both the stable adduct, m. p. 224°, and the labile adduct from β-picoline have been examined and



(VI) (X) (XI)

the relevant band positions are given in the Table. The positions of the C–CH_3 and olefinic protons in the spectrum of the labile adduct are consistent with structure (II) in so far as they accord with the positions of the absorptions of analogous protons in simple olefinic systems. Further, a band of intensity equivalent to one proton is found at 5·0 which may be assigned to the proton at the ring junction. The fact that this proton is not involved in spin-coupling confirms the orientation of the methyl group.

The related bands in the spectra of the two stable adducts exhibit a marked paramagnetic shift relative to the labile β-picoline adduct. Shifts of this order can reasonably be ascribed to the operation of long-range shielding arising from an induced ring current in a cyclic conjugated system.[8] This evidence allows formulation of the stable adducts as

[7] Burrows and Holland, *J.*, 1947, 673.
[8] Schneider, Bernstein, and Pople, *J. Chem. Phys.*, 1958, **28**, 601.

(VIII) or (VI). The structure (VIII) contains a pyridine ring and can obviously give rise to a ring current. It is possible that structure (VI) can likewise develop a ring current since ring A contains a complete cyclic π-orbital system which may be rather similar to that of pyridine if canonical structures such as (X) and (XI) make a significant contribution to the ground state of the molecule. The basicity of the stable adducts can also be explained in terms of such canonical structures. We believe that the nuclear magnetic resonance evidence quoted here does not at present distinguish between structures (VI) and (VIII), and that as the chemical evidence favours (VI) this structure is the more acceptable.

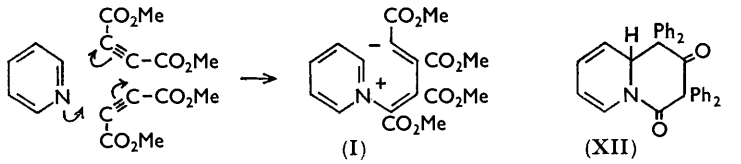
Proton chemical shifts for adducts and model compounds.

Measurements were made at 40 Mc./sec. on 4—5% solutions of the adducts in deuterochloroform, with tetramethylsilane as the internal reference. Band positions are quoted as τ-values (cf. Tiers [9]).

	C–Me	$\geqslant$CH	=CH–
β-Picoline adducts { labile	8·22	5·00	3·6—4·5
β-Picoline adducts { stable	7·77	3·99	2·4—3·4; 1·45 [a]
Pyridine adduct (stable)	—	3·96	2·3—3·7; 1·40 [a]
Isoprene	8·17		
β-Picoline	7·70		2·4—3·1; 1·6—1·8
Pyridine			3·01,[b] 2·64,[b] 1·50 [b]

[a] Doublet (J ~7·5 c./sec.). [b] The τ-values of the three types of protons which give rise to the complex spectrum of pyridine. These values are based on the detailed analysis by Schneider, Bernstein, and Pople.[10]

The genesis of the acetylenic ester–pyridine adducts is visualised as follows with " ylid " structure (I) as the first-formed adduct. The reaction is related to the addition of diphenylketen and pyridine [11] to give the adduct (XII). With regard to the Diels formulation [1] (I) of the labile adducts, it should be stressed that the stability of the orange adduct is much greater than that expected of an " ylid," [12] *e.g.*, it can be crystallised from hot methanol. When β-picoline was treated with the acetylenic ester in ether or in toluene at −10°, another adduct, a very unstable pale cream-coloured solid, was obtained in high yield. Similar unstable products have been obtained from β-picoline and diethyl acetylenedicarboxylate as well as from pyridine and dimethyl acetylenedicarboxylate. Because of the instability of these adducts, satisfactory analytical results were not obtained but the observed figures suggested that two molecules of the acetylenic esters had reacted with each molecule of β-picoline. It is possible that these compounds are the true ylids (I). When kept at room temperature the unstable adduct from β-picoline and dimethyl acetylenedicarboxylate rapidly decomposed to a dark resin with the evolution of β-picoline and one mol. of carbon dioxide. Both the orange labile adduct and the yellow stable



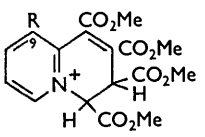
(I) (XII)

adduct, m. p. 224°, were isolated, albeit in small yield, from the resinous decomposition product, and in addition dimethyl fumarate and a small quantity of another unsaturated ester which has not yet been identified. It is clear that these unstable picoline–acetylenic ester adducts can rearrange or decompose by more than one mechanism. The formation of fumaric esters and free β-picoline suggests a decomposition approximating to the reverse

[9] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.
[10] Schneider, Bernstein, and Pople, *Ann. New York Acad. Sci.*, 1958, **70**, 806.
[11] Staudinger, Klever, and Kober, *Annalen*, 1910, **374**, 1; Berson and Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 1625.
[12] Wittig, *Angew. Chem.*, 1951, **63**, 15.

of the mode of formation, although the cause of the evolution of carbon dioxide is still not clear. The rearrangement to the labile and stable isomers is an alternative reaction.

The structures of the labile and the stable adducts thus differ only in the position of the hydrogen atom and the extent of the conjugated system. It was thus somewhat surprising to find that when the adducts were titrated against perchloric acid in acetic acid solution, the yellow stable adducts behaved as monoacid bases whereas the orange labile adduct was non-basic. Warming the labile adducts with perchloric acid caused isomerisation to the stable adducts and formation of the corresponding salts. The basic character of the



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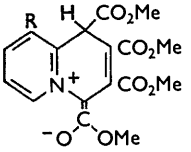

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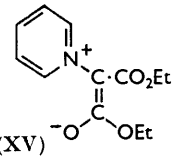

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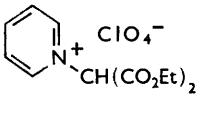


(XVI)

yellow stable adducts was also revealed by the effect of acid on the ultraviolet absorption spectra and by the isolation of crystalline perchlorates. A possible explanation for this difference in basic character is that the conjugate acid (XIII) derived from the stable adduct is a pyridinium salt when the proton is added in the manner established for cyclic enamines,[13] whereas protonation of the labile adduct in a similar manner can give rise only to non-basic dihydropyridine structures. In this connection, certain dihydropyridines [14] were prepared for comparison. Zwitterion structures (*e.g.*, XIV) were considered for the labile adduct but these were rejected as they did not accord with the nuclear magnetic resonance spectra; moreover, the dipole moment (4·05 D) of the labile adduct from β-picoline was actually less than that (4·80 D) of the corresponding stable adduct. These measurements were made by Dr. J. Chatt, to whom we are very grateful. A structure (XV) somewhat related to (XIV) has been proposed [15] for the yellow adduct derived from pyridine and bromomalonic ester after treatment with sodium carbonate, and the adduct readily forms the perchlorate (XVI). In this respect, it differs from the labile β-picoline adduct (II; R = Me, R′ = H).

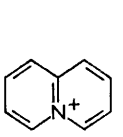
Another consequence of the position of the methyl group on the nucleus was revealed in the properties of the perchlorates (XIII) of the stable adducts. In most cases, these salts were easily hydrolysed in the absence of excess of perchloric acid, but a methyl group in the 9-position (XIII; R = Me) presumably hindered the approach of the base and consequently the perchlorate of the stable adduct, m. p. 207°, was relatively stable compared with that derived from the adduct, m. p. 224°. These labile and stable adducts are derivatives of the quinolizine ring systems [16] and are almost the sole representative of this class. The parent compounds 9a*H*-quinolizine and 4*H*-quinolizine are unknown [17] although several methods now are available for the preparation of the corresponding aromatic series, the dehydroquinolizinium salts [18] (XVII). Diels [1] has already shown that such compounds can be prepared from the stable adducts by treatment of the corresponding perbromides with perchloric acid and this has been confirmed in the β-picoline series. The same dehydroquinolizinium perchlorate was obtained from the " Kashimoto compound " after treatment with methanolic sodium methoxide and then perchloric acid.

When the β-picoline labile adduct (II; R = Me, R′ = H) was heated in methanol with

[13] Leonard, Fulmer, and Hay, *J. Amer. Chem. Soc.*, 1956, **78**, 1984, 3457.
[14] Traber and Karrer, *Helv. Chim. Acta*, 1958, **41**, 2066; Karrer, " Festschrift A. Stoll," Basle, 1957, p. 294.
[15] Kröhnke, *Ber.*, 1937, **70**, 543.
[16] Thyagarajan, *Chem. Rev.*, 1954, **54**, 1019.
[17] Boekelheide *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 3681; 1954, **76**, 1832.
[18] Woodward and McLamore, *J. Amer. Chem. Soc.*, 1949, **71**, 379; Bradsher and Beavers, *ibid.*, 1955, **77**, 453; Boekelheide *et al.*, *ibid.*, 1954, **76**, 1832; 1955, **77**, 5691; Richards and Stevens, *J.*, 1958, 3067; Glover and Jones, *J.*, 1958, 1750, 3021.

another pyridine base it was observed that the product was the stable adduct of the new base. Thus pyridine and γ-picoline gave the corresponding stable adducts and, when the β-picoline labile adduct was heated with methanolic β-picoline, the stable adduct, m. p. 224° (VI; R = H, R′ = Me), was formed, *i.e.*, the isomer of the stable adduct, m. p. 207°, corresponding to the labile adduct.

With α-picoline the adducts are more difficult to form, and the product from the β-picoline labile adduct and methanolic α-picoline was the stable β-picoline adduct, m. p.



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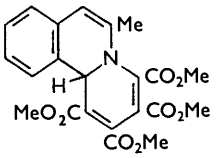
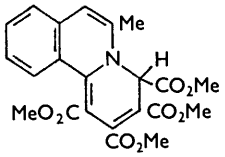


(XVIII)



(XIX)

207° (VI; R = Me, R′ = H) *i.e.*, only a prototropic rearrangement had occurred. These reactions, which involve the fission and re-forming of both bonds to the pyridine ring, stress the lability of the 9a*H*-quinolizine system. Similar rearrangements did not occur with the isomeric 4*H*-quinolizines, *i.e.*, the stable adducts.

In another series, 3-methylisoquinoline was treated with dimethyl acetylenedicarboxylate in ether: the sole product was the labile adduct (XVIII). When this was heated with methanolic β-picoline, it was converted into the corresponding stable adduct (XIX) by a straightforward prototropic shift, although in this case the rearrangement could not be brought about by heating a benzene solution as in the β-picoline series.

Experimental

Ultraviolet absorption spectra refer to ethanolic solutions except where otherwise stated.

Reaction of β-Picoline and Dimethyl Acetylenedicarboxylate.—Purified β-picoline (20 c.c.) was added with stirring to a solution of dimethyl acetylenedicarboxylate (50 c.c.) in dry ether (280 c.c.), and the mixture was kept in an open conical flask for 3 days. Methanol (50 c.c.) was added to dissolve the precipitated solid, and the solution was then cooled in the refrigerator for 1 hr. The precipitated solid was separated, washed with a little methanol, and dried in air. This crude product (33 g.) was dissolved in the minimum quantity of hot methanol (100 c.c.), ether (500 c.c.) was added, and the solution stirred while cooling. The crystallised solid was separated and the filtrate (A) treated separately (see below). The solid (16·5 g.), m. p. 196—210°, was washed with a little methanol, dried, and then crystallised twice from methanol (650 c.c.), to yield the *tetramethyl 7-methyl-*4H*-quinolizine-1,2,3,4-tetracarboxylate* (VI; R = H, R′ = Me) as dark yellow needles (7·5 g.), m. p. 224—225° (Found: C, 57·1; H, 5·35; N, 4·0. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·1; N, 3·7%), $\lambda_{max.}$ 266, 308, 352, and 448 mμ (log ε 3·97, 4·17, 4·06, and 4·04 respectively), $\lambda_{max.}$ (in 8% methanolic perchloric acid) 226 and 319 mμ (log ε 4·22 and 4·13), $\nu_{max.}$ (KBr disc) 797, 848, 960, 992, 1038, 1072, 1121, 1143, 1158, 1210, 1237, 1297, 1340, 1361, 1383, 1426, 1438, 1495, 1532, 1569, 1640, 1682s, 1690s, 1731s, 1747s, 2955, and 3465 cm.$^{-1}$.

The *perchlorate* formed colourless needles, m. p. 163—164° (Found: C, 45·3; H, 4·45; N, 3·0; Cl, 7·8. $C_{18}H_{20}ClNO_{12}$ requires C, 45·2; H, 4·2; N, 2·9; Cl, 7·4%), which were unstable and decomposed slowly in presence of methanol and more rapidly with water to generate the free base. It had $\nu_{max.}$ (KBr disc) 767, 790, 829, 849, 868, 978, 1007, 1099s, 1143, 1166, 1202, 1222, 1347, 1398, 1433, 1476, 1520, 1541, 1623, 1647s, 1657s, 2960, and 3078 cm.$^{-1}$.

The methanolic mother-liquors from the quinolizine crystallisations were evaporated and the residue (4·5 g.) crystallised from methanol. The labile isomer, m. p. 120°, was then removed by extraction with cold 1 : 4 methanol–ether (250 c.c.), and the residue crystallised twice from methanol to give the β-picoline *analogue* of Kashimoto's compound [19] as small bright yellow crystals (0·7 g.), m. p. 175—176° (Found: C, 56·8; H, 3·9; N, 3·7. $C_{17}H_{15}NO_8$ requires C, 56·6; H, 4·2; N, 3·9%), $\lambda_{max.}$ 223, 273, 343, and 435 mμ (log ε 4·32, 4·16, 3·85, and 4·36 respectively), $\nu_{max.}$ (KBr disc) 689, 801, 839, 858, 922, 932, 951, 1001, 1047, 1096, 1157, 1193, 1214, 1246, 1279,

[19] Diels, Alder, Kashimoto, Friedrichsen, Eckardt, and Klare, *Annalen*, 1932, **498**, 16.

1289, 1309, 1338, 1375, 1391, 1427, 1445, 1489, 1527, 1564, 1632, 1648s, 1691s, 1715s, 1744s, 2600, 3480, and 3620 cm.$^{-1}$.

The ether–methanol filtrate (A) from the above purification was evaporated to remove the ether, and then further methanol (total volume, 150 c.c.) was added. The solution was heated to dissolve any precipitated solid and, after cooling, orange needles were obtained which were recrystallised from methanol. The labile adduct, *tetramethyl 9-methyl-9aH-quinolizine-1,2,3,4-tetracarboxylate* (II; R = Me, R′ = H) (10·25 g.), m. p. 121—122°, was washed with a little methanol and dried (Found: C, 57·1; H, 5·25; N, 3·85. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·1; N, 3·7%). It had $\lambda_{max.}$ 234, 291, and 441 mμ (log ε 4·17, 4·19, and 3·67 respectively) $\lambda_{max.}$ (in 8% methanolic perchloric acid) 233, 289, and 403 mμ (log ε 4·15, 4·15, and 3·65 respectively), $\nu_{max.}$ (KBr disc) 730, 781, 817, 856, 880, 933, 993, 1013, 1033, 1090, 1140, 1179, 1211, 1237, 1252, 1320, 1332, 1364, 1444, 1525, 1578, 1619, 1707s (infl.), 1721s, 1738s, 2958, and 3600 cm.$^{-1}$. Addition of the labile adduct to 60% perchloric acid did not cause decolorisation, and crystallisation of the salt could be induced only by warming, presumably by causing a preliminary rearrangement to tetramethyl 9-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (see below). Recrystallisation gave a perchlorate, m. p. 197—198°, identical with that obtained from the stable adduct, m. p. 207° (see below).

Tetramethyl 9-Methyl-4H-quinolizine-1,2,3,4-tetracarboxylate (VI; R = Me, R′ = H).—The labile adduct (5 g.) from the previous experiment was dissolved in benzene (100 c.c.) and heated under reflux for 16 hr. After removal of the solvent the residue was crystallised twice from methanol, to give the *product* as yellow rods (3·2 g.), m. p. 207° (Found: C, 57·1; H, 5·45; N, 4·0. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·1; N, 3·7%), $\lambda_{max.}$ 265, 313, 360, and 441 mμ (log ε 3·90, 4·03, 4·12, and 4·00 respectively), $\lambda_{max.}$ (in 8% methanolic perchloric acid) 276 and 316 mμ (log ε 3·82 and 2·80 respectively), $\nu_{max.}$ (KBr disc) 790, 825, 976, 999, 1024, 1073, 1122, 1187. 1207, 1247, 1270, 1382, 1440, 1476, 1551, 1570, 1661s, 1687s, 1733m, 1749s, and 3460 cm.$^{-1}$. The *perchlorate* (XIII; R = Me) formed colourless needles, m. p. 197—198° from methanol containing a small quantity of perchloric acid (Found: C, 45·0; H, 4·1; N, 3·2; Cl, 7·45. $C_{18}H_{20}ClNO_{12}$ requires C, 45·2; H, 4·2; N, 2·95; Cl, 7·4%).

Tetramethyl 7-Methyldehydroquinolizinium-1,2,3,4-tetracarboxylate Perchlorate.—(i) Tetramethyl 7-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (0·5 g.) was dissolved in boiling acetic acid (3 c.c.), and a solution of bromine (0·5 g.) in acetic acid (1·5 c.c.) was added. Crystalline material began to separate after 1 hr. and next morning the brick-red crystals of the perbromide (0·5 g.), m. p. 104—105° (decomp.), were separated and washed with a little acetic acid. The perbromide (0·3 g.) was heated with 60% aqueous perchloric acid (1 c.c.) on the steam-bath for 5 min. and a current of air passed through the solution in order to remove the bromine. The hot solution was filtered and then diluted with water to bring about separation of the *perchlorate*. The colourless crystals were removed, washed with aqueous methanol, and then crystallised from aqueous methanol to yield colourless needles, m. p. 165—166° (Found: C, 45·9; H, 4·2; N, 3·4; Cl, 7·7. $C_{18}H_{18}ClNO_{12}$ requires C, 45·5; H, 3·8; N, 3·0; Cl, 7·45%), $\lambda_{max.}$ 231, 252, 300, 335, 346, and 458 mμ (log ε 4·32, 4·31, 3·77, 3·98, 4·06, and 3·43 respectively), $\nu_{max.}$ (KBr disc) 760, 813, 837, 876, 889, 945, 957, 989, 1001, 1105s, 1163, 1178, 1226, 1260s, 1287s, 1325, 1343, 1378, 1411, 1449, 1530, 1589, 1638, 1753, 2371, 2968, and 3115 cm.$^{-1}$.

(ii) The β-picoline analogue of Kashimoto's compound (0·5 g.) was dissolved in methanol (5 c.c.), and a concentrated solution of sodium methoxide (3 g.) in methanol was added. After 10 min., the product was acidified with 10% perchloric acid; the crystalline perchlorate was separated, washed with aqueous methanol, and crystallised from methanol, forming colourless needles, m. p. 165—166°, not depressed on admixture with the product from the previous experiment (Found: C, 45·2; H, 3·8; N, 3·05; Cl, 7·65%).

Trimethyl 8-Methylindolizine-1,2,3-tricarboxylate.—Tetramethyl 9-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (1·6 g.) was dissolved in 2N-nitric acid (5 c.c.) by gentle warming. Reaction occurred rapidly with evolution of carbon dioxide and nitrous fumes. The volume of the solution was reduced to one-half by evaporation and then, on cooling, the *product* separated as colourless rods (0·6 g.) which after crystallisation from methanol had m. p. 106—108° (Found: C, 59·2; H, 5·0; N, 4·9. $C_{15}H_{15}O_6N$ requires C, 59·0; H, 4·95; N, 4·6%), $\lambda_{max.}$ 241, 274, 321, and 336 mμ (log ε 4·58, 3·96, 4·18, and 4·18 respectively), inflection at 265 mμ (log ε 3·91), $\nu_{max.}$ (KBr disc) 694, 735, 760, 777, 794, 862, 910, 945, 978, 1000, 1022, 1073, 1103, 1208, 1247s, 1280s, 1320, 1357, 1380, 1392, 1414, 1450, 1490, 1540, 1559, 1712s, 1748s, and 2860 cm.$^{-1}$.

Trimethyl 6-Methylindolizine-1,2,3-tricarboxylate (V).—By a similar oxidation, tetramethyl

7-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate (3 g.) gave *trimethyl 6-methylindolizine-1,2,3-tricarboxylate* as colourless rods, m. p. 146—147° (from methanol; charcoal) (Found: C, 59·3; H, 5·3; N, 4·9%), $\lambda_{max.}$ 246, 265, 275, and 326 mμ (log ε 4·53, 4·11, 4·17, and 4·21 respectively), inflection 220 mμ (log ε 4·26), $\nu_{max.}$ (KBr disc) 659, 700, 762, 775, 787, 819, 886, 947, 1009, 1027, 1048, 1084, 1142, 1173, 1240s, 1327, 1340, 1400, 1459, 1523, 1543, 1699, 1708, 1742, 2869, 2930, 2963, and 3010 cm.$^{-1}$.

8-*Methylindolizine-2-carboxylic Acid*.—(i) Trimethyl 8-methylindolizine-1,2,3-tricarboxylate (200 mg.) was heated with potassium hydroxide (1 g.) in water (2 c.c.) under reflux until a clear solution was obtained (30 min.). The product was diluted with water (10 c.c.) and acidified with 2N-sulphuric acid. After 4 hr., the *acid* was separated and crystallised from aqueous methanol (charcoal), forming colourless needles (40 mg.), m. p. 240—242° (Found: C, 68·8; H, 5·3; N, 7·7. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%), $\lambda_{max.}$ 233, 290, 301, 337, 353, and 371 mμ (log ε 4·34, 3·43, 3·47, 3·34, 3·35, and 3·14), inflection 320 mμ (log ε 3·26).

(ii) Ethyl bromopyruvate [7] (3 c.c.) and 2,3-lutidine (2·5 c.c.) were heated in dry ethanol (20 c.c.) for 3 hr. After the product had been kept for 4 days, the solvent was removed under reduced pressure, the residue was diluted with water (20 c.c.), and the solution extracted with chloroform (2 × 20 c.c.). The chloroform extracts were washed with water and the washings added to the main aqueous solution which was treated with saturated aqueous sodium hydrogen carbonate solution until effervescence ceased, and then extracted with ether (3 × 20 c.c.). The aqueous layer was next treated with solid sodium hydrogen carbonate (1·5 g.) and heated on the steam-bath for 4 hr. Charcoal (0·5 g.) was added, and after a further 15 min. on the steam-bath the hot solution was filtered, acidified with dilute sulphuric acid, and kept overnight. The acid which separated was removed and crystallised twice from methanol (charcoal), forming colourless needles (30 mg.), m. p. 238—240° with previous sintering, not depressed on admixture with the product from the previous experiment (Found: C, 68·3; H, 5·3; N, 7·7%). The ultraviolet absorption was identical with that of the previous product.

6-*Methylindolizine-2-carboxylic Acid* (IX).—(i) Trimethyl 6-methylindolizine-1,2,3-tricarboxylate (800 mg.) was hydrolysed with aqueous potassium hydroxide as described above for the 8-methyl analogue. The *monocarboxylic acid* (150 mg.) was crystallised twice from methanol (charcoal), forming colourless needles (20 mg.), m. p. 230—232° (decomp.) (Found: C, 68·7; H, 5·3; N, 7·95. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%), $\lambda_{max.}$ 238, 294, 305, 342, and 356 mμ (log ε 4·70, 3·34, 3·48, 3·38, and 3·38 respectively), inflection 375 mμ (log ε 3·13).

(ii) Ethyl bromopyruvate (11 c.c.) and 2,5-lutidine (10 c.c.) in dry ethanol (50 c.c.) were treated in the manner described above for 2,3-lutidine. 6-Methylindolizine-2-carboxylic acid crystallised from methanol (charcoal) as needles (50 mg.), m. p. 230—232° (decomp.) not depressed on admixture with the product from the foregoing experiment. The light absorption was also identical with that of the previous acid.

Unstable Adduct from β-Picoline and Dimethyl Acetylenedicarboxylate.—(i) Dimethyl acetylenedicarboxylate (12 c.c.) was added to dry ether (50 c.c.) and cooled to −50°. β-Picoline (5 c.c.) was added in a thin stream and the temperature of the mixture was allowed to rise slowly to 0° in the refrigerator for 2—3 hr. The cream-coloured solid was separated and washed with ether without the precipitate being allowed to dry. The ether was then quickly removed by filtration and finally in a vacuum, while the temperature was kept below 10°. The *adduct* (12 g.) was an amorphous cream solid (Found: C, 56·6; H, 4·85; N, 4·35. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·1; N, 3·7. $C_{14}H_{13}NO_4$ requires C, 62·6; H, 5·65; N, 6·1%).

(ii) In another experiment dry toluene was substituted for ether in the above preparation with a similar result.

(iii) By a similar method the adduct from β-picoline and diethyl acetylenedicarboxylate was prepared. It decomposed (see below) in a similar manner.

Decomposition of the β-Picoline Unstable Adduct.—(i) The dry adduct from the foregoing experiment (i) was allowed to warm to room temperature. After a few minutes an exothermic decomposition occurred whereby the adduct formed a dark brown gum with copious evolution of gas. The gas was shown to be carbon dioxide by chemical tests and this was confirmed by the infrared spectrum. Quantitative decompositions showed that one mole of carbon dioxide was evolved per mole of adduct.

(ii) The unstable adduct (20 g.) was decomposed in the same manner, and the oily residue dissolved in methanol (35 c.c.) and kept for 3 days. The yellow crystals (1·3 g.) were separated and then by fractional crystallisation there were obtained the labile β-picoline adduct (0·3 g.),

m. p. 121°, and the stable β-picoline adduct, m. p. 224° (0·3 g.), both identical with the products described earlier. The combined mother-liquors were distilled in steam until 125 c.c of distillate had been collected. The distillate was acidified and extracted with di-isopropyl ether (3 × 200 c.c.). After removal of solvent from the dried extract, the residue partly crystallised. The solid was separated and crystallised from methanol as colourless needles (7 mg.), m. p. 105°. The ultraviolet (log ε 4·22 at 209 mμ) and the infrared absorption were in accord with those of authentic dimethyl fumarate. The oil (270 mg.) had b. p. 210°, equiv. wt. (by saponification) 89, and absorbed at 237 mμ ($E^{1\%}_{1\,cm.}$ 355) [Found: C, 48·2; H, 6·15%; *M* (Rast), 172]. The infrared absorption also showed a strong band at 1725 cm.$^{-1}$ (αβ-unsaturated ester). Alkaline hydrolysis gave the corresponding acid as a colourless solid, m. p. 156—157° [Found: C, 42·4; H, 4·7%; equiv. (by titration), 73; *M* (Rast), 142, 150], $\lambda_{max.}$ 243 mμ ($E^{1\%}_{1\,cm.}$ 464).

The acidified steam-distillate, after extraction, was made alkaline and extracted with ether. After removal of the solvent from the dried extract, the oily residue was treated with picric acid, giving the picrate of β-picoline, m. p. 151—152° (0·3 g.).

Unstable Adduct from Pyridine and Dimethyl Acetylenedicarboxylate.—This was obtained by the method described above for β-picoline. It (10 g.) decomposed in a similar manner, giving carbon dioxide, the yellow stable pyridine adduct (0·9 g.), m. p. 187—188°, not depressed on admixture with an authentic specimen, and free pyridine, isolated as the picrate (2·5 g.), m. p. 166—167°.

Reaction of β-Picoline Labile Adduct with Bases.—(a) *β-Picoline.* The β-picoline labile adduct, m. p. 120—121° (1 g.), was dissolved in β-picoline (5 c.c.) and methanol (5 c.c.) and heated under reflux for 3 hr. After removal of the methanol, the residue was acidified with dilute sulphuric acid and extracted with benzene (3 × 30 c.c.). The benzene extract was washed with aqueous sodium hydrogen carbonate, dried and evaporated to small volume; the yellow stable adduct (0·55 g.), m. p. 222—223°, not depressed on admixture with an authentic specimen (above), was obtained.

(b) *α-Picoline.* By a similar method there was obtained the yellow β-picoline adduct, m. p. 207—208° (0·4 g.).

(c) *Pyridine.* The product was the yellow stable pyridine adduct (0·5 g.), m. p. 187° alone and mixed with an authentic specimen (see below).

(d) *γ-Picoline.* The product (0·3 g.) was the orange stable γ-picoline adduct, m. p. 190° alone and mixed with an authentic specimen (below).

Reaction of γ-Picoline and Dimethyl Acetylenedicarboxylate.—γ-Picoline (10 c.c.) was added to a solution of dimethyl acetylenedicarboxylate (25 c.c.) in dry ether (140 c.c.) at room temperature. After 24 hr. the ether was removed by distillation and the residue dissolved in warm methanol (25 c.c.) and then cooled. The orange crystals of *tetramethyl 8-methyl-*4H*-quinolizine-*1,2,3,4*-tetracarboxylate* were separated and crystallised twice from methanol; they had m. p. 190° (1·5 g.) (Found: C, 57·4; H, 5·25; N, 4·0. $C_{18}H_{19}NO_8$ requires C, 57·3; H, 5·1; N, 3·7%), $\lambda_{max.}$ 213, 258, 309, 347, and 438 mμ (log ε 4·19, 3·92, 4·19, 3·99, and 4·08), inflection 218 mμ (log ε 4·19).

Reaction of α-Picoline and Dimethyl Acetylenedicarboxylate.—Prepared by the foregoing method for γ-picoline, the yellow stable α-picoline adduct [20] (3·5 g.) had m. p. 238—239° (Found: C, 57·0; H, 5·3; N, 3·75%), $\lambda_{max.}$ 266, 307, 347, and 445 mμ (log ε 3·98, 4·06, 4·06, and 4·04 respectively), $\nu_{max.}$ 683, 706, 736, 773, 803, 823, 862, 968, 982, 1008, 1026, 1042, 1089, 1137, 1164, 1180, 1220, 1240, 1286, 1337, 1354, 1419, 1446, 1483, 1507, 1549, 1588, 1627, 1670, 1707, 1741, 2955, 3020, and 3470 cm.$^{-1}$.

Reaction of Pyridine and Dimethyl Acetylenedicarboxylate.—Prepared similarly from pyridine, the yellow stable adduct [19] (7·5 g.) had m. p. 187° (Found: C, 56·3; H, 5·1; N, 4·05. Calc. for $C_{17}H_{17}NO_8$: C, 56·2; H, 4·7; N, 3·85%), $\lambda_{max.}$ 215, 261, 307, 350, and 443 mμ (log ε 4·10, 3·95, 4·18, 4·00, and 4·02 respectively), $\nu_{max.}$ 750, 792, 831, 882, 994, 1036, 1072 1130, 1162, 1218, 1240, 1298, 1342, 1360, 1399, 1440, 1489, 1535, 1573, 1633, 1675, 1697, 1747, 2961, and 3470 cm.$^{-1}$.

Reaction of 3-Methylisoquinoline and Dimethyl Acetylenedicarboxylate.—Dimethyl acetylenedicarboxylate (5 c.c.) was added to a solution of 3-methylisoquinoline [21] in dry ether (30 c.c.), and the mixture kept for 3 days at room temperature. After removal of the solvent, warm methanol (10 c.c.) was added to dissolve the residual gum and, after cooling, the orange-brown

[20] Diels and Pistor, *Annalen*, 1937, **530**, 87.
[21] Mills and Smith, *J.*, 1922, **121**, 2732.

crystals (3 g.) were separated and washed with methanol. After recrystallisation from methanol, the labile adduct, *tetramethyl 6-methyl-11bH-benzo[a]quinolizine-1,2,3,4-tetracarboxylate* (XVIII) (2·5 g.) had m. p. 200—200·5° (Found: C, 61·8; H, 5·05; N, 3·3. $C_{22}H_{21}NO_8$ requires C, 61·8; H, 4·95; N, 3·3%), $\lambda_{max.}$ 204, 241, 291, and 422 mμ (log ε 4·45, 4·30, 4·13, and 3·69 respectively), $\nu_{max.}$ 655, 701, 723, 737, 759, 766, 771, 785, 820, 837, 857, 899, 952, 998, 1025, 1142, 1178, 1191, 1214, 1253, 1329, 1362, 1443, 1481, 1516, 1611, 1703, 1718, 1739, and 2955 $cm.^{-1}$. Titration of an acetic acid solution against perchloric acid showed that the adduct was non-basic. It was unchanged after being heated under reflux in benzene.

When heated with β-picoline in methanolic solution as described for the β-picoline labile adduct, the product from 3-methylisoquinoline formed the stable adduct, *tetramethyl 5-methyl-4H-benzo[a]quinolizine-1,2,3,4-tetracarboxylate* (XIX), which was obtained as red rods, m. p. 215°, from methanol (Found: C, 61·7; H, 5·05; N, 3·5. $C_{22}H_{21}NO_8$ requires C, 61·8; H, 4·95; N, 3·3%), $\lambda_{max.}$ 204, 231, 262, 324, and 468 mμ (log ε 4·34, 4·55, 3·91, 4·08, and 4·07 respectively), inflection 350 mμ (log ε 3·91).

Condensation of β-Picoline and Bromomalonic Ester.—Bromomalonic ester (12·15 g.) was added to β-picoline (4·65 g.) and kept at room temperature for 24 hr. The resulting red gum was dissolved in chloroform and washed with saturated aqueous sodium carbonate. The *product* was precipitated by addition of light petroleum (b. p. 60—80°), and the yellow solid (6 g.) crystallised from acetone; it was obtained as yellow needles, m. p. 186—188° (Found: C, 61·8; H, 7·0; N, 5·8. $C_{13}H_{17}NO_4$ requires C, 62·1; H, 6·8; N, 5·6%), $\lambda_{max.}$ 247 and 398 mμ (log ε 4·39 and 3·21). The zwitterion was very soluble in methanol and chloroform, moderately soluble in acetone, benzene, and water, and insoluble in light petroleum.

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