307. *Heterocyclic Compounds with Bridgehead Nitrogen Atoms. Part II.*[1] *Condensation of Diethyl β-Oxoglutarate with Electrophilic Ethoxymethylene Compounds; Synthesis of a 6-Hydroxyquinolizin-4-one*

By D. Leaver and J. D. R. Vass

The structures of the products formed during the base-catalysed condensation of diethyl β-oxoglutarate with the esters and nitriles of ethoxymethylenemalonic acid have been elucidated. A derivative of 6-hydroxyquinolizin-4-one has been synthesised in two stages from diethyl β-aminoglutaconate and diethyl ethoxymethylenemalonate.

The peripherally conjugated tricyclic compound (I), which has been given [2] the trivial name cycl[3,3,3]azine, is of considerable theoretical interest since it is iso-π-electronic with the phenalenyl anion [3] and is expected, on the basis of molecular-orbital calculations,[2] to possess a high resonance energy. The most attractive synthetical approach to the compound, by way of 4,6-dimethylquinolizinium salts, unaccountably fails [4] but an alternative approach from 6-hydroxyquinolizin-4-ones, *e.g.*, (II), seemed possible. The latter compounds may be regarded, in many ways, as analogous to tropolones and might be expected to yield derivatives of cycl[3,3,3]azine by a sequence similar to that employed by Nozoe and his co-workers [5] in their synthesis of azulenes from 2-chloro- and 2-methoxytropones.

Adams and Reifschneider [6] obtained compound (II; R = H) by condensation of diethyl ethoxymethylenemalonate with 6-ethoxycarbonylmethyl-2-pyridone but the latter compound is only accessible by tedious elaboration from 6-methyl-2-pyridone. A rapid synthesis of a suitably substituted pyridone from aliphatic starting materials seemed desirable and our first object was the preparation of the pyridone (III) from diethyl β-oxoglutarate. At the same time we undertook a more general investigation into the base-catalysed reactions of this oxo-diester with the esters and nitriles of ethoxymethylenemalonic acid.

Simonsen [7] showed that ethyl acetoacetate reacts with diethyl ethoxymethylenemalonate, in presence of sodium ethoxide, to give the pyrone (IV; R = H, R′ = CO_2Et)

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[1] Part I, D. Leaver, W. K. Gibson, and J. D. R. Vass, *J.*, 1963, 6053.

[2] R. J. Windgassen, W. H. Saunders, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1959, **81**, 1459.

[3] V. Boekelheide and C. E. Larrabee, *J. Amer. Chem. Soc.*, 1950, **72**, 1245.

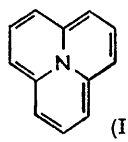
[4] H. V. Hansen and E. D. Amstutz, *J. Org. Chem.*, 1963, **28**, 393; V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Kaempfen, *Tetrahedron*, 1964, **20**, 33.

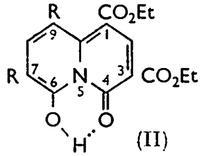
[5] T. Nozoe, S. Matsumura, Y. Murase, and S. Seto, *Chem. and Ind.*, 1955, 1257; T. Nozoe, *Croat. Chem. Acta*, 1957, **29**, 207.

[6] R. Adams and W. Reifschneider, *J. Amer. Chem. Soc.*, 1959, **81**, 2537.

[7] J. L. Simonsen, *J.*, 1908, 1022.

and Mitra[8] claimed that a compound (m. p. 106°), formulated as (IV; R = R′ = CO_2Et), which might have been a suitable precursor of the required pyridone, was formed in a similar way from diethyl β-oxoglutarate. Mitra's conclusions were drawn, apparently, in ignorance of the earlier work of Errera[9] who had shown, by convincing degradative studies, that the product (m. p. 104—105°) of the latter reaction was the resorcinol derivative (V; R′ = CO_2Et). In confirmation of Errera's conclusions, the product (our m. p. 106—107°) gave a deep reddish-brown colour with ferric chloride and showed infrared absorptions (Table 1) characteristic of a chelated ester.


(I)



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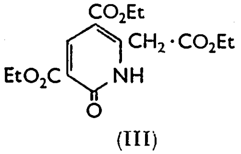

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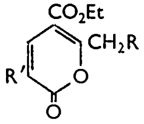

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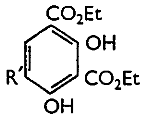

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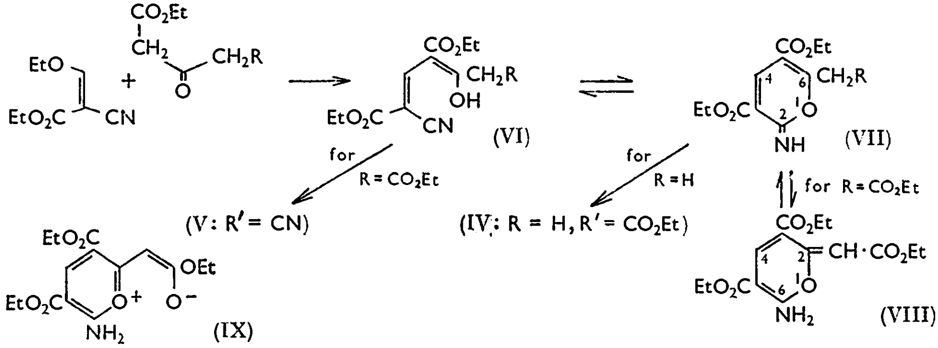

TABLE 1

Infrared spectra * between 3000 and 1580 cm.$^{-1}$

Compound	OH or NH stretch †	C⋮N stretch †	C:O stretch ‡	C:C stretch ‡	NH_2 deformn. †
(II; R = CO_2Et)			1722	1617	
(III)	3160vb, 2825vb		1748, (1722), 1719, 1668	1610	
(IV; R = H, R′ = CO_2Et)			1783, 1727	1625	
(IV; R = R′ = CO_2Et) ...			1785, 1748, 1726	1630	
(V; R′ = CO_2Et)............	2400—3500vb		1745, 1677	1625	
(V; R′ = CN)	2300—3400vb	2230	1678	1607	
(VIII)	3470, (3360)b, 3310s, 3255, 3120b		1720, (1688), 1682	1640	1580
(XI)	3455, 3355b, 3295, 3245, 3155b	2220	(1700—1725)b 1690	1640	1590
(XIII)	3150vb §		1780, 1733, 1675	1630, 1608	
(XIV)...........................	3485s, 3408s, 3345b, 2300—3200vb	2220	(1687), 1683, 1668	1620	1580
(XV)		2230	1745, 1732, 1705	1623	
(XIX)...........................	3355, 3255, 2600—3150vb		1754, 1716, 1690, 1670	1625, 1600	

Wavenumbers in parentheses refer to shoulders; b = broad; vb = very broad; s = sharp.

* Excluding CH stretching bands. † Solvent chloroform unless otherwise stated. ‡ Solvent carbon tetrachloride. § Solvent deuterochloroform.

The structure (IV; R = CO_2Et, R′ = CN) proposed by Mitra[8] for the product (m. p. 142°) of the reaction between the oxo-diester and ethyl ethoxymethylenecyanoacetate, in presence of an excess of sodium ethoxide, also seemed questionable since Simonsen[7] had previously shown that the cyano-group of the latter compound participates in its reaction

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[8] S. K. Mitra, *J. Indian Chem. Soc.*, 1938, **15**, 455.

[9] G. Errera, *Ber.*, 1899, **32**, 2792.

TABLE 2

Ultraviolet and visible spectra (wavelengths in mμ)*

Compound	$\lambda_{\text{max.}}$	log ε	$\lambda_{\text{max.}}$	log ε	$\lambda_{\text{max.}}$	log ε	$\lambda_{\text{max.}}$	log ε	$\lambda_{\text{max.}}$	log ε	$\lambda_{\text{max.}}$	log ε
(V; R′ = CO_2Et)	203	3·8	235	4·71	(256)	(4·1)	308	3·74				
(V; R′ = CN)	207	4·1	227	4·64	(261)	(4·1)	322	3·81				
			244	4·30								
(XIV)	210	4·1	234	4·52	260	4·28	335	3·85				
					285	4·20						
(VIII)	203	4·0			255	4·12	312	4·33	393	4·18		
	221	4·00					322	4·32				
(IV; R = R′ = CO_2Et †)	216	3·8			262	4·00	(311)	(4·0)	353	3·88		
							320	4·13	396	4·11		
(IV; R = R′ = CO_2Et ‡)	208	4·0	249	3·87			318	3·75				
(IV; R = H, R′ = CO_2Et ‡)	207	4·0	249	3·97			318	3·84				
(XI)	205	4·2			255	4·08	305	4·14	350	4·07	511	4·45
(XIII)	207	4·4	240	4·27			301	4·03	365	4·17		
(III)	208	4·3			262	4·19	332	3·98				
(XV)	213	4·4	225	4·41	266	4·15					427	4·35
(II; R = CO_2Et)	209	4·4	(235)	(4·2)	273	4·02			360	4·04	450	4·37
											(472)	(4·2)

Values in parentheses refer to shoulders or inflexions.

* In ethanol unless otherwise indicated. † Solvent ethanol containing sodium ethoxide. ‡ Solvent cyclohexane.

with ethyl acetoacetate to give, after loss of ammonia, the pyrone (IV; R = H, R′ = CO_2Et). The infrared spectrum (Table 1) of the compound (our m. p. 139—140°), the reddish-brown colour of its ferric complex, and the resemblance of its ultraviolet spectrum (Table 2) to that of compound (V; R′ = CO_2Et) show it to be the resorcinol derivative (V; R′ = CN), formed from the reactants by elimination of two molecules of ethanol.

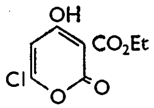
When the reaction between equimolar quantities of the oxo-diester and the cyano-ester was carried out in presence of only one mole of sodium ethoxide, however, the deep yellow main product was formed by elimination of only one mole of ethanol and its infrared spectrum (Table 1) showed the presence of an amino-group and the absence of a cyano-group. The formation of Simonsen's pyrone (IV; R = H, R′ = CO_2Et) from ethyl acetoacetate and ethyl ethoxymethylenecyanoacetate clearly involves an intramolecular addition of the enolic hydroxyl group in the intermediate condensation product (VI; R = H) to the cyano-group, followed by hydrolysis of the resulting unstable imino-pyran (VII; R = H). In the corresponding reaction with diethyl β-oxoglutarate, however, the imino-pyran (VII; R = CO_2Et) can tautomerise owing to the presence of a reactive methylene group at position 6, and it seemed probable that the yellow compound was the resulting, more stable, amino-pyran (VIII). An absorption at 1720 cm.$^{-1}$ in the infrared spectrum of the product was attributed to the ethoxycarbonyl group at position 3, and a much stronger, barely resolved doublet at 1682—1688 cm.$^{-1}$ to the ethoxycarbonyl groups at position 5 and at the exocyclic carbon atom. The frequencies of the two latter groups will be lowered, respectively, by conjugate chelation to the 2-amino-group and by the contribution of the pyrylium-betaine structure (IX) to the resonance hybrid. Confirmation of the amino-pyran structure (VIII) was obtained by treatment of the compound with ethanolic hydrogen chloride to give ammonium chloride and the α-pyrone (IV; R = R′ = CO_2Et), whose ultraviolet spectrum (Table 2) was practically identical with that of Simonsen's pyrone (IV; R = H, R′ = CO_2Et). The transformations (VI) ⟶ (VII) ⟶ (VIII) are evidently reversible since more vigorous treatment of the pyran (VIII) with ethanolic sodium ethoxide gave the resorcinol derivative (V; R′ = CN) which was clearly formed by Dieckmann cyclisation of the intermediate compound (VI; R = CO_2Et).

An attempt to convert the pyrone (IV; R = R′ = CO_2Et) into the pyridone (III), by treatment with ammonia, gave only a yellow ammonium salt which was evidently derived from the enolic form (VIII; OH for NH_2) of the pyrone. The tendency of the pyrone to enolise was further shown by the similarity of its ultraviolet spectrum (Table 2), in alkaline ethanol, to that of compound (VIII) in neutral ethanol, and by the development of a reddish-black colour on treatment with ferric chloride.

The high-frequency carbonyl absorption (1783, 1785 cm.$^{-1}$) in the infrared spectra (Table 1) of the pyrones (IV) appears to be characteristic of 3-alkoxycarbonyl-α-pyrones and, although α-pyrones normally absorb [10] in the region 1720—1740 cm.$^{-1}$, it is assigned to the lactone carbonyl group rather than to an ethoxycarbonyl group since the α-pyrone (X), in which the assignments [11] are unambiguous owing to lowering of the ester carbonyl frequency (1650 cm.$^{-1}$) by conjugate chelation, shows a similar high-frequency absorption (1789 cm.$^{-1}$).

Gradual addition of diethyl β-oxoglutarate to two moles of ethyl ethoxymethylenecyanoacetate in cold ethanolic sodium ethoxide gave a bright red compound [also obtained as a by-product during the formation of compound (VIII)] to which we assign the structure (XI or a geometrical isomer) on the basis of its spectral characteristics (Tables 1 and 2) and its reaction with ethanolic hydrogen chloride to give ammonium chloride and a pale yellow 3-ethoxycarbonyl-α-pyrone ($\nu_{\max.} = 1780$ cm.$^{-1}$). The only analytically detectable difference between the red compound and the pale yellow pyrone was in the replacement of one nitrogen by one oxygen atom, but the absence of a C≡N stretching band in the infrared spectrum of the pyrone (Table 1) and of a nuclear magnetic resonance absorption characteristic of a hydrogen atom (other than those of the OEt groups) bonded to saturated carbon, eliminated monocyclic structures such as (XII). The structure (XIII), however, is consistent with the presence of infrared absorptions at 3150 (very broad; N–H stretch) and 1675 cm.$^{-1}$ (chelated ester) and with the nuclear magnetic resonance spectrum which showed sharp one-proton singlets at 1·33 and 1·57 τ (pyran ring protons) and at —2·17 τ (NH proton).

Ethoxymethylenemalononitrile reacted with diethyl β-oxoglutarate, in ethanol containing a two-fold excess of potassium hydroxide, to give a *m*-aminophenol derivative (XIV) whose structure follows from its infrared spectrum (Table 1), from the reddish-brown colour of its ferric complex [cf. compounds (V)], and from the resemblance of its ultraviolet spectrum (Table 2) to those of the resorcinol derivatives (V). When only one mole of potassium hydroxide was used, the reaction was complex and the only product isolated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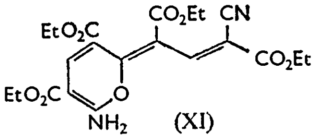
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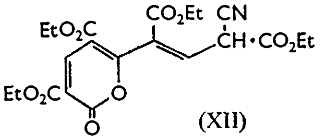
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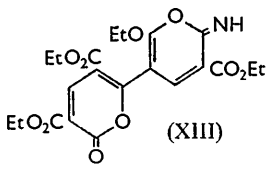
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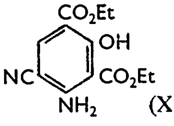
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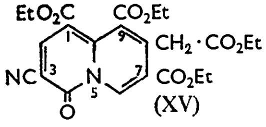
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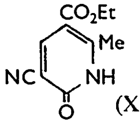
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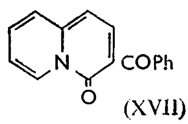
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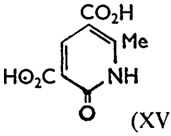
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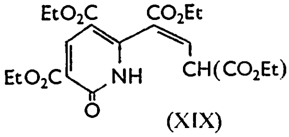
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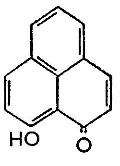
(XX)

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[10] J. D. Bu'Lock and H. G. Smith, *J.*, 1960, 502.
[11] J. A. Elvidge, *J.*, 1962, 2606.

(low yield) was a yellow compound which showed the characteristic ultraviolet spectrum (Table 2) of a quinolizin-4-one.[12] After taking into account possible mechanisms for its formation, we assigned the structure (XV) to this compound on the basis of the following evidence.

(i) The compound gave no colour with ferric chloride, was insoluble in alkali, and showed no infrared absorptions attributable to OH or NH groups. (ii) Its infrared spectrum (Table 1) showed absorptions attributable to cyano-, conjugated ester-, and unconjugated ester-groups. (iii) Its nuclear magnetic resonance spectrum showed that the ratio of methylene to methyl protons (5 : 6) was in excess of that required for the ethoxy-groups alone (2 : 3). The group of lines due to the methylene protons contained one sharp singlet (5·52 τ; approximately two protons) that did not fit into the pattern of overlapping quartets produced by the OCH_2 groups and was therefore attributed to the methylene group at position 8. (iv) The same spectrum also showed a sharp singlet at 1·52 τ, of intensity ten times less than that of the CH_2 multiplet, attributed to the proton at position 2 [cf. the 4-proton absorption of compound (XVI)[13] at 1·47 τ], and another sharp singlet of the same intensity at 0·05 τ which, in the absence of an aldehydic proton (no reaction with 2,4-dinitrophenylhydrazine), could only be due to the α-pyridine proton (normal value[14] *ca.* 1·5 τ) at position 6 where it is subject to the additional deshielding influences of the 4-carbonyl [cf. the 6-proton absorption of compound (XVII)[1] at 0·74 τ] and 7-ethoxycarbonyl groups (cf. the 2-proton absorption of ethyl nicotinate at 0·83 τ). A compound of structure (XV) could formally be derived from two molecules of diethyl β-oxoglutarate, one of ethoxymethylenemalononitrile, and one of ethyl formate * but the actual sequence of reactions involved is unknown and the structure cannot be regarded as proven.

The pyridone (III) was ultimately synthesised from diethyl β-aminoglutaconate[16] and diethyl ethoxymethylenemalonate, and its structure was proved by degradation in boiling aqueous acid to the known[17] 2-pyridone (XVIII). Treatment of the pyridone (III) with another mole of the ethoxymethylenemalonate, in boiling *NN*-dimethylformamide containing one mole of sodium ethoxide, and then dilution of the reaction mixture with water, afforded the 6-hydroxyquinolizin-4-one (II; $R = CO_2Et$) as its sodium salt which, surprisingly, was soluble in chloroform and dichloromethane. Similar water-insoluble salts were formed when lithium or potassium ethoxides were used as condensing agents. The sodium salt was unaffected by trituration with aqueous mineral acids but was converted into the parent hydroxy-compound by shaking its solution, in dichloromethane, with hydrochloric acid. The hydroxy-compound was more conveniently prepared, however, by using benzyltrimethylammonium methoxide as catalyst for the condensation so that it was obtained directly by acidification of the mixture. The sodium salt was rapidly decomposed by treatment with ethanolic hydrogen chloride but the product was then the colourless pyridone (XIX, or a tautomer) rather than the hydroxyquinolizinone. The same pyridone was obtained during the initial condensation when boiling was insufficiently prolonged; it was converted into the sodium salt of the quinolizinone by continued boiling with sodium ethoxide in *NN*-dimethylformamide.

The hydroxy-compound gave a green colour with ferric chloride and showed the characteristic ultraviolet spectrum (Table 2) and fluorescence of a quinolizin-4-one.[12] Its nuclear magnetic resonance spectrum substantiated the symmetrical, hydrogen-bonded

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* Ethyl formate is known[15] to be formed from ethoxymethylenemalononitrile in presence of potassium hydroxide and is the most probable source of C-6 in compound (XV).

[12] V. Boekelheide and J. P. Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681; F. Bohlmann, A. Englisch, J. Politt, H. Sander, and W. Weise, *Chem. Ber.*, 1955, **88**, 1831.

[13] G. Errera, *Ber.*, 1900, **33**, 2969.

[14] H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Canad. J. Chem.*, 1957, **35**, 1487.

[15] S. G. Cottis and H. Tieckelmann, *J. Org. Chem.*, 1961, **26**, 79.

[16] W. O. Emery, *Ber.*, 1890, **23**, 3761.

[17] E. Ochiai and Y. Ito, *Ber.*, 1941, **74**, 1111.

structure (II; R = CO_2Et) since the 2- and 8-protons gave rise to a single sharp peak at 1·27 τ and the OH proton gave a very broad hump between —6 and —7 τ (cf. the enolic forms of β-diketones[18]). The stability of the alkali-metal salts towards aqueous acid is no doubt due, in part, to their low solubility, but their relatively high solubility in non-hydroxylic solvents suggests that the metal ion is unusually strongly chelated. (When a 0·024M-solution of the hydroxy-compound, in dichloromethane, was shaken with saturated aqueous sodium chloride, 30% of the theoretical amount of hydrogen ion was liberated in the aqueous phase and an approximately equivalent yield of the sodium salt of the quinolizinone was recovered from the organic phase). Alkali-metal complexes are rare but a number of examples have been reported[6,19] and, in some of these, the ligands show structural features similar to those of compound (II; R = CO_2Et).

It was not possible to achieve the original object, of converting compound (II; R = CO_2Et) into a derivative of cyclo[3,3,3]azine, owing to the failure of all attempts to methylate or sulphonylate the hydroxyl group or to replace it by a chlorine atom. The similarly constituted phenalone (XX) is also resistant to methylation and acylation.[20]

EXPERIMENTAL

Extracts were dried over anhydrous sodium sulphate and all evaporations were carried out under reduced pressure. Ultraviolet, infrared, and nuclear magnetic resonance spectra (the last in deuterochloroform) were measured by using Perkin-Elmer 137UV, 237 grating, and R10 (60 Mc./s.) spectrometers, respectively. The values of chemical shifts reported are not corrected for the effect of concentration. Light petroleum refers to the fraction of b. p. 60—80°.

*Diethyl 6-Amino-2-ethoxycarbonylmethylene-2*H*-pyran-3,5-dicarboxylate* (VIII).—Ethyl ethoxymethylenecyanoacetate (3·4 g.) was added, during 10 min., to a stirred, ice-cold solution of sodium ethoxide (1 mole) or potassium hydroxide (1·5 g.) and diethyl β-oxoglutarate (4·0 g.) in ethanol (20 ml.). The solution was stirred at room temperature for 1 hr., and poured into water (150 ml.) containing acetic acid (10 ml.). The resulting red precipitate (1·85 g.) was recrystallised from light petroleum–ethyl acetate to give the *pyran*, yellow needles, m. p. 158—159° (Found: C, 55·5; H, 5·5; N, 4·3. $C_{15}H_{19}NO_7$ requires C, 55·4; H, 5·9; N, 4·3%). In one experiment (KOH as catalyst) slow evaporation of the mother-liquors yielded a mixture of red and colourless crystals which were separated manually and shown, by infrared comparison, to be the pyran (XI) and the pyridone (III), respectively.

*Diethyl 6-Ethoxycarbonylmethyl-2-oxo-2*H*-pyran-3,5-dicarboxylate* (IV; R = R′ = CO_2Et).—The foregoing pyran (1 g.) was boiled, in ethanol (25 ml) saturated with hydrogen chloride, for 30 min. The solution rapidly became colourless and deposited a solid which, after addition of ether (50 ml.), was filtered off and shown to be ammonium chloride (0·11 g.). Washing the filtrate with water to remove ethanol and then shaking the ethereal solution with aqueous sodium carbonate caused precipitation of a yellow sodium salt from which a colourless solid (0·8 g.) was obtained by treatment with dilute hydrochloric acid. Recrystallisation from light petroleum gave the *pyrone*, elongated plates, m. p. 61—62° (Found: C, 55·2; H, 5·4. $C_{15}H_{18}O_8$ requires C, 55·2; H, 5·5%). Treatment of the pyrone, in ether, with gaseous ammonia gave a yellow precipitate of the ammonium salt.

Diethyl 5-Cyano-2,4-dihydroxybenzene-1,3-dicarboxylate (V; R′ = CN).—The yellow aminopyran (1 g.) was boiled for 1 hr. in ethanol (30 ml.) containing sodium ethoxide (from 0·5 g. sodium) and the resulting sodium salt was filtered off and treated with 6% aqueous sulphuric acid. Recrystallisation from ethanol then yielded the cyano-compound, needles, m. p. 139—140° (lit.,[8] m. p. 142°) (Found: C, 55·8; H, 4·6; N, 5·5. Calc. for $C_{13}H_{13}NO_6$: C, 55·9; H, 4·7; N, 5·0%).

*Diethyl 6-Amino-2-(3-cyano-1,3-diethoxycarbonylallylidene)-2*H*-pyran-3,5-dicarboxylate* (XI).—Diethyl β-oxoglutarate (4·0 g.), in ethanol containing sodium ethoxide (from 1 g. sodium),

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[18] R. W. Hay and P. P. Williams, *J.*, 1964, 2270; J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, 1964, **86**, 2105.

[19] G. A. Guter and G. S. Hammond, *J. Amer. Chem. Soc.*, 1956, **78**, 5166; H. Irving and J. J. R. F. Da Silva, *J.*, 1963, 448.

[20] C. F. Koelsch and J. A. Anthes, *J. Org. Chem.*, 1941, **6**, 558.

was added slowly, with stirring, to ethyl ethoxymethylenecyanoacetate (6·8 g.) in ice-cold ethanol (100 ml.). The solution was stirred for 3 hr. at room temperature, poured into ice-water covered with a layer of light petroleum, and acidified with acetic acid. The resulting deep red solid (3·5 g.) was recrystallised from light petroleum–ethyl acetate to give the *pyran* (2·5 g.), scarlet needles, m. p. 157—159° (Found: C, 56·4; H, 5·2; N, 6·7. $C_{21}H_{24}N_2O_9$ requires C, 56·4; H, 5·4; N, 6·3%). Occasionally, the pyran crystallised as a *hydrate*, deep red prisms, m. p. 160—162° (Found: C, 54·0; H, 5·8; N, 6·0. $C_{21}H_{26}N_2O_{10}$ requires C, 54·1; H, 5·6; N, 6·0%) which could be made anhydrous by recrystallisation from light petroleum–ethyl acetate with azeotropic removal of water. The pyran and its hydrate showed identical infrared spectra in solution ($CHCl_3$ or CCl_4) but the spectra of the solids (Nujol mull) were different, that of the hydrate showing an additional band at 3600 cm.$^{-1}$ as well as other minor differences.

Diethyl 6-(6-*Ethoxy*-3-*ethoxycarbonyl*-2-*imino*-2H-*pyran*-5-*yl*)-2-*oxo*-2H-*pyran*-3,5-*dicarboxylate* (XIII).—The red hydrate (1 g.), in ethanol (6 ml.), was mixed with saturated ethanolic hydrogen chloride (3·5 ml.) and concentrated hydrochloric acid (1 ml.). After 3 hr. at room temperature, the yellow solid (0·6 g.) which had crystallised was filtered off and recrystallised from ethanol to yield the *imine*, pale yellow needles, m. p. 151—152° (Found: C, 56·1; H, 4·9; N, 3·2. $C_{21}H_{23}NO_{10}$ requires C, 56·1; H, 5·1; N, 3·1%). In a separate experiment, in which the concentrated hydrochloric acid was omitted, dilution of the ethanolic solution with ether, after boiling for 1 hr., gave an almost quantitative yield of ammonium chloride.

Diethyl 4-*Amino*-5-*cyano*-2-*hydroxybenzene*-1,3-*dicarboxylate* (XIV).—Ethoxymethylenemalononitrile (2·4 g.) was added, during 5 min., to a stirred, ice-cold solution of potassium hydroxide (3 g.) and diethyl β-oxoglutarate (4·0 g.) in ethanol (40 ml.). The solution was stirred at room temperature for 1 hr. and poured into water containing acetic acid. The resulting precipitate was recrystallised from ethanol to yield the *amino-compound* (1·3 g.), needles, m. p. 129—130° (Found: C, 56·4; H, 5·5; N, 9·7. $C_{13}H_{14}N_2O_5$ requires C, 56·1; H, 5·0; N, 10·1%).

Triethyl 3-*Cyano*-8-*ethoxycarbonylmethyl*-4-*oxo*-4H-*quinolizine*-1,7,9-*tricarboxylate* (XV).—Repetition of the foregoing experiment with half the quantity (1·5 g.) of potassium hydroxide afforded the *quinolizinone* (0·5 g.), yellow needles, m. p. 164—166° (from ethanol) (Found: C, 58·4; H, 4·8; N, 6·4. $C_{23}H_{24}N_2O_9$ requires C, 58·6; H, 5·3; N, 5·95%).

Diethyl 6-*Ethoxycarbonylmethyl*-1,2-*dihydro*-2-*oxopyridine*-3,5-*dicarboxylate* (III).—Diethyl ethoxymethylenemalonate (8·6 g.) was added, during 15 min., to a stirred, ice-cold solution of diethyl β-aminoglutaconate [16] (8·1 g.) and sodium ethoxide (from 1 g. sodium) in ethanol (25 ml.). The solution was stirred at room temperature for 30 min. and poured into water (300 ml.) containing sulphuric acid (2·5 ml.). The oil that separated crystallised on treatment with ether. Recrystallisation from ethanol afforded the *pyridone* (7 g.), needles, m. p. 121—122° (Found: C, 55·7; H, 5·6; N, 3·8. $C_{15}H_{19}NO_7$ requires C, 55·4; H, 5·9; N, 4·3%). The pyridone (1 g.) was boiled in ethanol (5 ml.) and 2N-hydrochloric acid (25 ml.) for 1 hr. Extraction with ether yielded 3,5-dicarboxy-6-methyl-2-pyridone (0·1 g.), m. p. 303—304° (lit.,[17] 305°).

Alkali-metal Salts of Tetraethyl 4-*Oxo*-4H-*quinolizine*-1,3,7,9-*tetracarboxylate*.—The foregoing pyridone (8·1 g.), diethyl ethoxymethylenemalonate (5·4 g.) and dry sodium ethoxide (1·6 g.) were boiled in *NN*-dimethylformamide (75 ml.) for 4 hr. Dilution with water, extraction with chloroform, and evaporation of the extract gave a yellow solid (4·2 g.) which was recrystallised from ethanol–chloroform to yield the *sodium salt*, yellow needles, m. p. 307—308° (Found: C, 53·6; H, 5·0; N, 3·2. $C_{21}H_{22}NNaO_{10}$ requires C, 53·5; H, 4·7; N, 3·0%). The lithium salt, m. p. 318—319°, obtained under the same conditions with lithium ethoxide, was more difficult to purify and yielded unsatisfactory analytical results. Formation of the very insoluble potassium salt, m. p. *ca.* 320° (analysis unsatisfactory), necessitated boiling with potassium ethoxide for 8 hr.; shorter reaction times yielded a product contaminated with varying quantities of the pyridone (XIX).

Tetraethyl 6-*Hydroxy*-4-*oxo*-4H-*quinolizine*-1,3,7,9-*tetracarboxylate* (II; R = CO_2Et).—The pyridone (III) (3·25 g.), diethyl ethoxymethylenemalonate (2·2 g.), and benzyltrimethylammonium methoxide (4·5 ml.; 40% solution in methanol) were boiled in *NN*-dimethylformamide (30 ml.) for 6 hr. Dilution with water containing a slight excess of sulphuric acid gave an oil which slowly solidified, and extraction of the remaining aqueous solution with ether gave a further small amount of the solid. Recrystallisation from ethanol gave the *quinolizinone* (2·5 g.), yellow needles, m. p. 120—121° (Found: C, 56·0; H, 5·0; N, 3·2. $C_{21}H_{23}NO_{10}$ requires

C, 56·1; H, 5·1; N, 3·1%). The same compound was also obtained by shaking a solution of its sodium salt in dichloromethane with 0·1N-hydrochloric acid and evaporation of the solvent.

Diethyl 1,2-*Dihydro*-2-*oxo*-6-(1,3,3-*triethoxycarbonylprop*-?-*enyl*)-*pyridine*-3,5-*dicarboxylate* (XIX or a tautomer).—The sodium salt (0·15 g.) of the hydroxyquinolizinone was boiled briefly in ethanol (100 ml.) saturated with hydrogen chloride. The yellow colour and fluorescence of the quinolizinone were rapidly discharged, and dilution with water and extraction with ether then afforded the *pyridone* (0·05 g.), prisms, m. p. 133—134° (Found: C, 56·1; H, 6·1; N, 3·3. $C_{23}H_{29}NO_{11}$ requires C, 55·8; H, 5·9; N, 2·8%). On being boiled with sodium ethoxide in *NN*-dimethylformamide the pyridone (1 g.) afforded the sodium salt (0·4 g.), m. p. and mixed m. p. 305—307°, of the hydroxyquinolizinone.

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