475. *Addition Reactions of Heterocyclic Compounds. Part XXIII.** *The Formation of Kashimoto's Compound from* 1,2,3,4-*tetramethoxycarbonylquinolizinium Perchlorate and Related Reactions*

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1,2,3,4-Tetramethoxycarbonylquinolizinium perchlorate was converted by aqueous sodium hydrogen carbonate into Kashimoto's compound and by formic acid-sodium formate into 4-oxoquinolizine-2-carboxylic acid. The paths of these transformations are considered.

DIELS, ALDER, KASHIMOTO *et al.*[1] first obtained "Kashimoto's compound" as a by-product in the formation of tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (I) [2] from pyridine and dimethyl acetylenedicarboxylate but assigned incorrect structures to it and its degradation products.[3] Woodward and Kornfeld [4,5] showed that the correct formulation was (VIII) because methyl 2-pyridylacetate with dimethyl chlorofumarate and potassium methoxide gave mainly dimethyl 4-oxoquinolizine-1,2-dicarboxylate, which was converted by warm sulphuric acid into the same 4-oxoquinolizine-2-carboxylic acid (XIII) which had previously been obtained from Kashimoto's compound with hot concentrated

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* Part XXII, preceding Paper.

[1] O. Diels, K. Alder, T. Kashimoto, Friedrichsen, W. Eckart, and H. Klare, *Annalen*, 1932, **498**, 16.

[2] R. M. Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125.

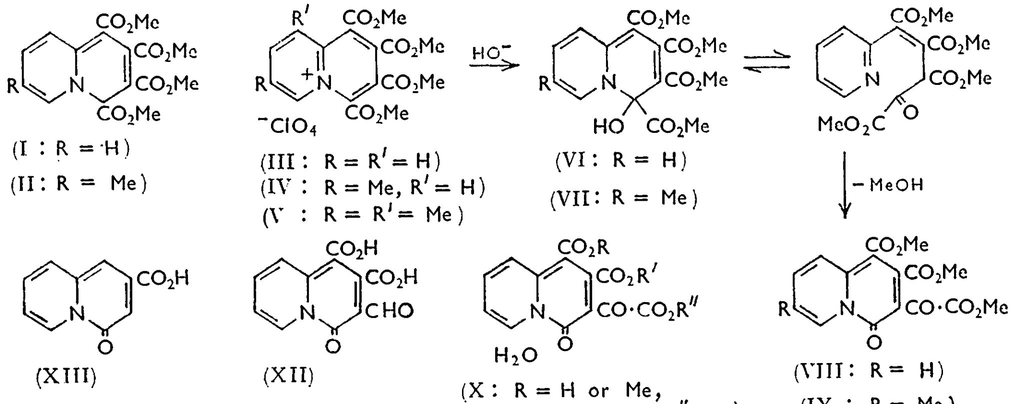
[3] O. Diels, K. Alder, Friedrichsen, H. Klare, Winkler, and Schrum, *Annalen*, 1933, **505**, 103.

[4] R. B. Woodward, private communication.

[5] E. C. Kornfeld, Ph.D. Thesis, Harvard, 1945.

hydrochloric or sulphuric acid;[3] they also re-interpreted the earlier data. The infrared,[6] ultraviolet,[6] and nuclear magnetic resonance spectra for Kashimoto's compound support its new formulation.

Two schemes which can account for the formation of Kashimoto's compound have been



(I : R = H)
(II: R = Me)
(III: R = R′ = H)
(IV : R = Me, R′ = H)
(V : R = R′ = Me)
(VI: R = H)
(VII: R = Me)
(XIII)
(XII)
(X : R = H or Me, R′ = Me or H, R″ = Na)
(XI: R = R′ = Me, R″ = H)
(VIII: R = H)
(IX : R = Me)

discussed[2] and the route (below) involving the known oxidation of the 4*H*-quinolizine (I) to the quinolizinium salt (III) and subsequent conversion in solution by base into the quinolizine (VI),[6] is consistent with our new results. The quinolizinium perchlorates (III and IV) with aqueous sodium hydrogen carbonate gave good yields of the quinolizones (VIII and IX); no reaction could be detected with the more sterically hindered salt (V). The nuclear magnetic resonance spectra of both quinolizones have been analysed and the most interesting features are the very low τ value for the 6-hydrogen atoms, and the fact that $J_{6,7}$ is less than $J_{8,9}$ as with the 4*H*-quinolizines.[7] The identity of our 7-methyl derivative (VII) with the Kashimoto compound homologue prepared by Jackman, Johnson, and Tebby[8] from β-picoline is strongly suggested by a comparison of their properties.

Treatment of the quinolizinium perchlorate (III) with aqueous sodium carbonate and subsequent acidification of the reaction mixture gave the sodium salt (X). Before it was realised that the compound contained sodium, it was converted in poor yield by diazomethane in a water–ether–methanol mixture into Kashimoto's compound (VIII), identified by mixed m. p. and infrared absorption spectrum. Potentiometric titration of the salt (X) in the cold showed 1·16 free acid groups per mol. and a pK_a of about 2·9; back titrations indicated that the ester group of the salt (X) was only partly hydrolysed after a few hours with excess of aqueous sodium hydroxide at 40°. Only on one occasion did acidification of the hydrolysis mixture give the diester (XI). The related monoester (X; replace Na by H) was probably obtained earlier from the quinolizone (VIII) by treatment with dilute hydrochloric acid.[1]

Attempts to hydrolyse the salt (X) further with 10% formic acid gave an intractable solid, while in the presence of sodium formate only a very small quantity of a compound possessing the properties expected of the quinolizone (XII) was isolated. The quinolizinium perchlorate (III) with hot aqueous sodium formate–formic acid evolved carbon dioxide and gave 4-oxoquinolizine-2-carboxylic acid, identified by its spectra and by comparison with Kornfeld's data. The ultraviolet absorption spectra of solutions of the quinolizones (IX and X) were only affected slightly by the addition of perchloric acid, but with a large excess of the acid the quinolizone (XIII) gave a new species, the spectrum of which

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[6] R. M. Acheson and G. A. Taylor, *J.*, 1960, 1691.
[7] R. M. Acheson, R. S. Feinberg, and J. M. F. Gagan, *J.*, 1965, 948.
[8] L. M. Jackman, A. W. Johnson, and J. C. Tebby, *J.*, 1960, 1579.

Ultraviolet absorption spectra

		$\lambda_{max.}$ (mμ) ($10^{-4}\varepsilon$)				
Compd.	Solv.*					
(IV)	MA	215 † (1·57)	238 † (2·13)	253 (2·27)	334 (0·89)	347·5 (1·05)
	MB	270 (1·13)	298·5 (1·21)	354·5 (0·71)	465 (1·23) ‡	
(IX)	M	227 (1·67)	273 (1·24)	343 (0·57)	438 (2·06)	
	MB	271 (1·23)	377 (0·53)			
	P	224 (1·90)	280 (1·09)	339 (0·58)	433 (1·96)	
(X)	MB	217 (1·35)	235 (1·21)	262 (1·23)	355 (0·55)	408 (1·15)
	M	225 † (1·33)	252 (1·05)	360 (0·51)	404 † (1·22)	419 (1·32)
	P	220 † (1·26)	261·5 (0·80)	342 (0·52)	424 (1·52)	
(XI)	M	252 † (2·10)	410 (1·81)			
(XII)	M	213 (2·25)	266 (1·25)	322 † (0·55)	341 (0·76)	389 (1·53)
	P	214 (1·74)	225 † (1·42)	262 † (0·93)	277·5 (1·24)	321 † (0·74)
		336 (0·90)	386 † (1·61)	398 (1·77)		
(XIII)	M	225 (2·46)	251 (1·22)	407 (1·17)		
	P	250·5 (1·71)	310 (0·21)	376 (1·10)		

* Solvents: A = acidified with a drop of 72% perchloric acid; B = basified with a trace of sodium methoxide; M = methanol; P = methanol: 72% perchloric acid, 2 : 1 by vol. † Inflexions. ‡ Absorption resembles that of the 4*H*-quinolizine (II) [6] as responsible species is probably compound (VII).

resembled that of quinoliz-4-one [9] much more closely than that of 2-carboxyquinolizinium bromide.[10]

EXPERIMENTAL

The nuclear magnetic resonance spectra were measured at 60 Mc./sec. with tetramethylsilane as the internal standard. Infrared spectra are for Nujol mulls; all the maxima within the ranges given for each compound are recorded; inflexions are marked with an asterisk.

Reactions of 1,2,3,4-*Tetramethoxycarbonylquinolizinium Perchlorate* (III).—(*a*) The perchlorate (2·00 g.) was shaken with water (20 ml.) and sodium hydrogen carbonate (5·0 g.) for 47 hr.; carbon dioxide was initially evolved. The precipitate (1·25 g., 83%) had m. p. 181—183° raised to 184—185·5° by recrystallisation from methanol, and was identical (mixed m. p., infrared and ultraviolet spectra) with an authentic sample of Kashimoto's compound (VIII). The nuclear magnetic resonance spectrum in deuterochloroform, in which it was very sparingly soluble, showed single proton resonances centred on τ 0·54 (6H), 2·48 (7H), 1·95 (8H), and 1·17 (9H) with $J_{6,7}$ = $J_{7,8}$ = 7·5, $J_{8,9}$ = 9, $J_{6,8} \simeq J_{7,9} \simeq$ 2 c./sec., and OMe groups at 6·03, 6·03, and 6·10 τ. In nitromethane the single protons appeared at τ 0·53, 2·27, 1·74, and 1·28, respectively.

(*b*) Water (25 ml.), the perchlorate (III) (2·68 g.), and anhydrous sodium carbonate (3·61 g.) were shaken for 47 hr. and then some unchanged perchlorate was filtered off. The filtrate (pH 8) was acidified with hydrochloric acid to pH 3 (carbon dioxide was evolved) and the yellow precipitate (1·85 g.) was collected; further acidification of the filtrate gave no additional solid product. The precipitate was dissolved in hot water, and ethanol was added until crystallisation commenced. The mixture was cooled to give the *sodium salt* (X) as square yellow plates which decomposed without melting at 161° (Found: C, 47·0; H, 2·9; N, 4·1; OMe, 9·3; residue 12·4. $C_{14}H_8NNaO_8,H_2O$ requires C, 46·9; H, 2·8; N, 3·9; OMe, 8·6; residue calc. as Na_2O_2, 10·9%); $\nu_{max.}$ 2·77 (free OH), 2·98 (OH), 3·6—4·5br (max. at 3·85 and 4·05, bonded OH), 5·64, 5·84, 5·95, 6·09, 6·14, 6·24*, 6·66, 6·90, 7·11w, 7·28vs (CO_2^-), 7·58, 7·74, 7·92, 8·13, 8·32, 8·53, 8·77, 9·25, 9·42, 9·62, and 9·72 μ (OH deformation). In the quinoliz-4-ones (VIII and IX) maxima are also found close to 7·28 and 9·72 μ, but are much less intense.

(*c*) A mixture of the perchlorate (1·0 g.), anhydrous sodium carbonate (1·0 g.), and water (7 ml.) was kept for 24 hr. by which time all the solid had dissolved and the ultraviolet absorption spectrum of the solution was that of a 4-quinolizone. The mixture was extracted with chloroform and acidified to give 1,2-*dimethoxycarbonyl*-4-*oxoquinolizine*-3-*glyoxylic acid* (XI) (0·68 g.), m. p. 175—176° (decomp.) (from methanol) (Found: C, 51·1; H, 3·8; N, 4·3; OMe, 16·4. $C_{15}H_{11}NO_8,H_2O$ requires C, 51·1; H, 3·7; N, 4·0; 2 OMe, 17·7%); $\nu_{max.}$ 2·95, 3·4, 4·1, 5·2, 5·60, 5·70, 5·95, 6·13, 6·53, 6·68, 6·88, and 6·98 μ. No further products were obtained by evaporation of the chloroform extract.

1,2,3,4-*Tetramethoxycarbonyl*-7-*methylquinolizinium Perchlorate* (IV).—Bromine (0·3 g.) was

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[9] V. C. Boekelheide and J. P. Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681.

[10] R. M. Acheson, J. M. F. Gagan, and G. A. Taylor, *J.*, 1963, 1903.

added to tetramethyl 7-methyl-4*H*-quinolizine-1,2,3,4-tetracarboxylate[6] (0·45 g.) in acetic acid (3 ml.) containing 72% perchloric acid (0·5 ml.). The mixture was warmed for 20 min. and then water (35 ml.) containing perchloric acid (2 ml.) was added. The mixture was cooled to about $-50°$, warmed slightly, and then filtered to give the quinolizinium perchlorate (0·26 g.) which crystallised as needles, m. p. 161—162·5 (decomp.) (lit.,[8] m. p. 165—166°), from methanol containing a trace of perchloric acid (Found: C, 45·4; H, 4·0. Calc. for $C_{18}H_{18}ClNO_{12}$: C, 45·4; H, 3·8%); $\nu_{max.}$ 5·77, 6·16, 6·32, 6·58, 6·90, 7·18, 7·31, 7·52, and 7·64 μ.

Methyl 1,2-*Dimethoxycarbonyl*-7-*methyl*-4-*oxoquinolizine*-3-*glyoxylate* (IX).—The perchlorate (IV) (0·19 g.) was shaken with sodium hydrogen carbonate (0·5 g.) in water (3 ml.) for 23 hr. at room temperature, and then the mixture was filtered to give the *quinolizone* (83 mg.) which crystallised from methanol as yellow prisms, m. p. 172—172·5° (Found: C, 56·2; H, 4·2. $C_{17}H_{15}NO_8$ requires C, 56·5; H, 4·15%); $\nu_{max.}$ 5·74, 5·83, 5·92, 6·07, 6·13, 6·42, 6·57, 6·73, and 6·94* μ. The nuclear magnetic resonance spectrum in nitromethane showed resonances centred on τ 0·69 (6H), 7·41 (7-Me), 1·84 (8H), and 1·35 (9H), the OMe resonances being obscured by the solvent, with $J_{8,9} = 9$ and $J_{6,8} = 2$ c./sec.

Hydrolysis of the Sodium Salt (X).—The salt (1·0 g.) was refluxed with sodium formate (1·50 g.), formic acid (2 ml.), and water (23 ml.) for 4 hr. and then the mixture was kept for 6 days at room temperature. The precipitate (11·5 mg.) was collected and crystallised from methanol to give the *quinolizone* (XII) (7·7 mg.) as hexagonal yellow plates, m. p. 230—231° (Found: C, 54·5; H, 2·9. $C_{12}H_7NO_6$ requires C, 55·1; H, 2·7%); $\nu_{max.}$ 3·00 (OH), 3·24 (aromatic H), 3·6—5·0 (broad, max. at 3·70 and 4·30, bonded OH), 5·66, 5·85, 5·90, 6·07, 6·26, 6·44, 6·64, and 6·87 μ. A solution of the compound in methanol showed a strong pale blue fluorescence under ultraviolet light.

4-*Oxoquinolizine*-2-*carboxylic Acid* (XIII).—The perchlorate (III) (1·0 g.), sodium formate (1·50 g.), formic acid (2 ml.), and water (25 ml.) were refluxed for 3 hr.; much carbon dioxide was evolved. The mixture was cooled and filtered, and the solid was crystallised from ethanol to give the acid as yellow needles (60 mg.), m. p. 278—288° (decomp.) (Found: C, 63·6; H, 3·7; N, 7·6. Calc. for $C_{10}H_7NO_3$: C, 63·5; H, 3·7; N, 7·4%); $\nu_{max.}$ 5·78, 5·82, 6·06, 6·16, 6·37, 6·59, 6·89, 7·30, 7·60, and 7·90 μ, which with methanolic hydrogen chloride yielded the corresponding methyl ester, m. p. 146—147°, lit.,[3,5] m. p.s 148—149°, and 148, respectively.

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