Enaminones in the Mannich Reaction. Part 2.[1] Further Investigations of Internal Mannich Reactions

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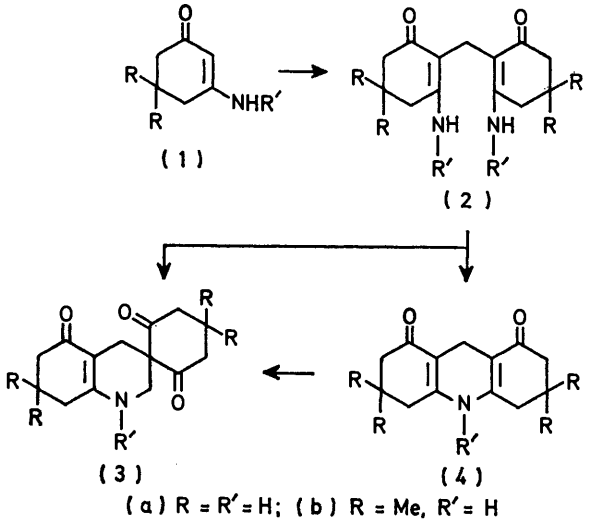
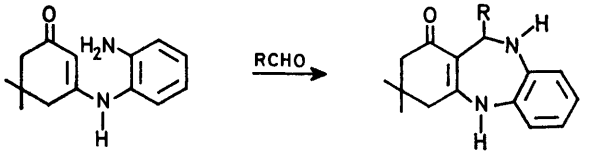
The reactions of two 3-aminocyclohex-2-enones with formaldehyde have been investigated in detail. The course of each reaction has been followed by u.v. spectroscopy and the conclusions confirmed by chromatography. The *gem*-dimethyl group of the dimedone derivative directs the reaction to give exclusively the spiran formed by an internal Mannich reaction, but the unsubstituted cyclohexanedione enaminone gives mixtures of spiran and acridinedione derivatives. The results are rationalised on the basis of the different rates of hydrolysis of the enaminones.

PREVIOUS work in this laboratory[1] showed that the simple enaminone (1b) was readily converted into an unexpected spiran (3b) by formaldehyde and dilute



(a) R = R′ = H; (b) R = Me, R′ = H

hydrochloric acid at room temperature. The suggested mechanism involved an internal Mannich reaction. A recent report[2] described a series of internal Mannich reactions on the dimedone derivative of *o*-phenylenediamine (Scheme 1).



SCHEME 1 R = H, Me, Et, Ph, or *p*-ClC_6H_4

The potential synthetic value of Mannich reactions in which enaminones replace the amine components persuaded us to continue our investigations. Since our previous report, however, it has become well known that mixtures of formaldehyde and hydrochloric acid give, as a by-product, the highly carcinogenic dichlorodimethyl ether.[3] We began, therefore, by repeating our previous reaction using a series of different acid catalysts. The results, included in Table 1, showed that several other acids are as suitable as hydrochloric acid.

When the experiments were repeated using 3-aminocyclohex-2-enone (1a) most catalysts gave the acridinedione (4a) as the only crystallisable product. Only trichloracetic acid gave the spiran (3a), see Table 1. However, t.l.c. showed both products present in each reaction mixture. One acetic acid experiment gave, by column chromatography, (3a) in 25% and (4a) in 58% yield while a trichloracetic acid run gave (3a) 67% and (4a) 19%.

TABLE 1

Yields isolated from formaldehyde reactions

Enaminone	Catalyst	Conditions	Product	Yield (%)
(1a)	H_2SO_4 aq.	*a*	(4a)	56
(1a)	TsOH	*b*	(4a)	58
(1a)	$HClO_4$	*a*	(4a)	62
(1a)	HOAc	*a*	(4a)	58
(1a)	HOAc	*b*	(4a)	56
(1a)	Cl_3CCO_2H	*a*	(3a)	58
(1a)	Cl_3CCO_2H	*b*	(3a)	54
(1b)	HCl aq.	*a*	(3b)	70
(1b)	H_2SO_4 aq.	*a*	(3b)	68
(1b)	BF_3	*b*	(3b)	60
(1b)	TsOH	*b*	(3b)	60
(1b)	$HClO_4$	*a*	(3b)	70
(1b)	HOAc	*a*	(3b)	53
(1b)	HOAc	*b*	(3b)	53
(1b)	Cl_3CCO_2H	*a*	(3b)	68

[a] Aqueous solution, room temperature. [b] Paraformaldehyde, refluxing ethanol.

To gain further insight, reactions of the two methylenebisenaminones (2a, b) were conducted in aqueous solution at room temperature and followed by u.v. spectroscopy. For enaminone (2a) the time required increased markedly with increasing pH (3 h at pH 0.2, 4 days at pH 3.4) but at both ends of the range only the spiran (3a) was formed. At intermediate acid concentrations a peak for the acridinedione (4a) was seen, the highest observed yields were at pH 2.5 and 3.0 (*ca.* 35%). After several more days the acridinedione peak disappeared. Similar work with the dimedone derivative (2b) gave only the spiran (3b) with no measurable amount of acridinedione (4b) at any of six pH values. Conversion of pure samples of both acridinediones (4a, b) into spirans (3a, b) by acid formaldehyde was confirmed by u.v. and on the preparative scale.

The methylenebisenaminones (2) are readily formed from the enaminones (1) and can be isolated in the

absence of acid. They are converted into the products (3), (4) with equal facility. It is reasonable to assume, therefore, that the acid formaldehyde reactions always proceed *via* methylenebisenaminones. We therefore discuss the conversions (2a, b) ⟶ (3a, b) + (4a, b) to explain our results.

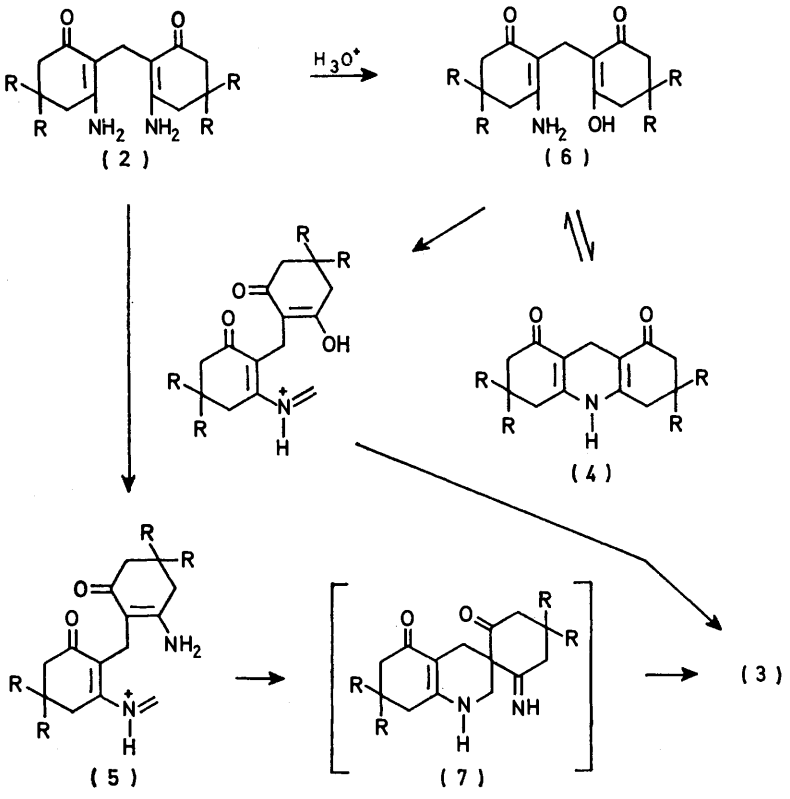
TABLE 2

First-order rate constants for enaminone hydrolysis (s^{-1})

	pH 2	pH 3	pH 4	pH 5	pH 6	pH 7
(1a)	2 240	5 050	1 590	225	56	12.5
(1b)	212	364	102	22	3.1	

It seemed that the explanation may be related to the rates of hydrolysis of the methylenebisenaminones (2a, b), but it was not possible to determine these because of acridinedione formation. The first-order rate constants for hydrolysis of the parent enaminones were to hand [4] and are shown in Table 2. Both compounds showed the expected maximum in the pH *vs.* first-order rate constant curve,[5] in both cases at pH 2.93. But it can be seen that (1a) is hydrolysed 10—15 times faster than (1b). Dipole moment studies have shown that the *gem*-dimethyl group of dimedone enaminones introduces strain into the molecule and causes twisting about the C(1)–C(2) bond. Cyclohexane-1,3-dione derivatives adopt the ideal planar configuration [6] and this accounts for the higher hydrolysis rates generally observed for the latter compounds.[5]

The mechanisms for the reactions under consideration are shown in Scheme 2. In formaldehyde and acid there is competition between formation of the Mannich intermediate (5a, b) and the hydrolysed derivative (6a, b). The Mannich intermediate (5a, b) would rapidly close to give the spiran (3a, b) *via* the imine (7a, b). On the other hand intermediate (6a, b) would rapidly ring close to give the acridinedione (4a, b). It is reasonable to suppose that the methylenebisenaminone (2a) would hydrolyse significantly faster than (2b) since (1a) is faster than (1b); this explanation accounts for the observed formation of acridinedione from (1a) and (2a) whereas none was seen when (1b) or (2b) was used. If the partially hydrolysed intermediate (6a, b) remained available for long enough, it would be converted into the spiran as shown. This explains the conversion of acridinediones into spirans since the acridinediones would be expected to hydrolyse in acid solution (they are vinylogous imides) and an equilibrium (6) ⇌ (4) would exist.

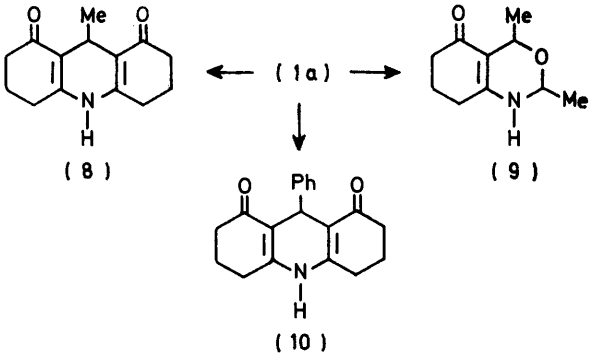


SCHEME 2 a, R = H; b, R = Me

The methylamine derivatives (1; R = H, R′ = Me) and (1; R = R′ = Me) were allowed to react in the presence of all the previously used acids and the products were analysed by t.l.c. In every case both the spiran and acridinedione derivatives were present as well as the parent dione from hydrolysis of the starting enaminone. By choice of catalyst it was possible to isolate pure samples of each compound.

In some other reactions investigated, the enaminone (1a) behaved in a similar way to that previously re-

ported [1] for (1b). With acetaldehyde and trichloracetic acid it gave the 9-methylacridinedione (8) but with dilute hydrochloric acid it was possible to isolate the tetrahydrobenzoxazinone (9). This structure was confirmed by comparison of its spectra with those of the previously reported dimedone derivative.[1] From benzaldehyde only the 5-phenylacridinedione (10) could be isolated.



The aniline derivative (1; R = Me, R′ = Ph) was converted into the methylenebidenaminone (2; R = Me, R′ = Ph) in the presence of perchloric acid at room temperature but more forcing contitions gave tars. One phenylethylamine enaminone (1; R = H, R′ = $PhCH_2$-CH_2H) also gave a methylenebisenaminone (2; R = H, R′ = $PhCH_2CH_2$) but another (1; R = Me, R′ = $PhCH_2CH_2$) could be converted into a spiran (3; R = Me, R′ = $PhCH_2CH_2$).

The dimedone enaminone (1b) is readily converted into the spiran (3b) with no significant by-products. For the cyclohexane-1,3-dione enaminone (1a) both the spiran (3a) and the acridinedione (4a) are likely to be formed whatever the conditions; the proportion, however, of each is clearly very sensitive to the reaction conditions. In dilute aqueous solution, pH is an important factor, but when high proportions of acid are used in aqueous or alcoholic solution analysis is much more difficult. A trial and error approach enabled us to optimise yields of required derivatives.

EXPERIMENTAL

For t.l.c. work silica plates were eluted with 10% methanol–chloroform. U.v. spectra were determined for aqueous *ca.* 3×10^{-5}M-solutions with a Unicam SP 800 spectrophotometer.

2,2′-*Methylenebis*-(3-*aminocyclohex*-2-*enone*) (2a).—A solution of 3-aminocyclohex-2-enone (1.1 g) and aqueous 37% formaldehyde (0.6 ml) was stirred ½ h and then set aside for 2 h. The precipitate was collected to give the *methylenebisenaminone* (0.9 g, 73%), m.p. 250 °C (from ethanol) (Found: C, 66.3; H, 7.3; N, 11.9. $C_{13}H_{18}N_2O_2$ requires C, 66.7; H, 7.7; N, 12.0%), i.r. $\nu_{max.}$ (KBr) 1 540 and 1 670 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 280 nm (ε 43 000); $\lambda_{max.}$ (0.1M-HCl) 275 nm (ε 36 300).

1,2,3,4,7,8-*Hexahydroquinoline*-3-*spirocyclohexane*-2′,5(6H),6′-*trione* (3a).—(*a*) A solution of 3-aminocyclohex-2-enone (1.1 g), and trichloroacetic acid (3.2 g) in aqueous 37% formaldehyde (10 ml) was stirred 24 h. The product was basified with sodium hydroxide solution and extracted with chloroform (4 × 100 ml) to give the *spiran* (0.7 g, 58%), m.p. 246 °C (from ethanol) (Found: C, 68.1; H, 7.2; N, 5.6. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%), i.r. $\nu_{max.}$ (KBr) 1 555, 1 700, and 1 725 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 299 nm (ε 23 500); $\lambda_{max.}$ (0.1M-HCl) 291 nm (ε 17 200); $\lambda_{max.}$ (0.1M-NaOH) 303 nm (ε 25 800).

(*b*) A solution of 3,4,5,6,9,10-hexahydroacridine-1(2*H*),8(7*H*)-dione (0.5 g), aqueous 37% formaldehyde (20 ml), and dilute sulphuric acid (5 ml) in ethanol (20 ml) was refluxed 12 h and then set aside overnight. After neutralisation with ammonium hydroxide the solution was extracted with chloroform (4 × 100 ml) to give the *spiran* (0.2 g, 34%), identical (m.p., mixed m.p., and i.r.) with the compound obtained above.

3,4,5,6,9-10-*Hexahydroacridine*-1(2H),8(7H)-*dione* (4a).—A solution of 3-aminocyclohex-2-enone (1.1 g) and glacial acetic acid (5 ml) in aqueous 37% formaldehyde (10 ml) was stirred 24 h. The product was basified with sodium hydroxide and extracted with chloroform (5 × 50 ml) to give the *hexahydroacridinedione* (0.62 g, 58%), m.p. 270 °C (from ethanol) (Found: C, 71.5; H, 7.2; N, 6.5. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.9; N, 6.5%), i.r. $\nu_{max.}$ (KBr) 1 600 and 1 630 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 249 (ε 21 000) and 395 nm (8 200).

Reactions of Enaminones with Formaldehyde.—(*a*) A solution of the appropriate enaminone (1 mmol) and appropriate acid (2 mmol) in aqueous 37% formaldehyde (1 ml) was stirred 24 h. After basification (NaOH) the products were extracted with chloroform (3 × 10 ml) and analysed by t.l.c.

(*b*) A solution of the enaminone (1 mmol), paraformaldehyde (3 mmol), and the acid (1 mmol) in ethanol (2 ml) was refluxed 2 h. After basification (NaOH) the products were extracted with chloroform and analysed by t.l.c.

(c) The methylenebisenaminone (*ca.* 0.5 mmol) was added to aqueous 37% formaldehyde (15 ml) and sufficient dilute sulphuric acid to bring the final concentration to 0.001, 0.005, 0.01, 0.1, 1, and 5M. The mixture was diluted to 100 ml with water and set aside at room temperature. Immediately after dilution and at suitable intervals 1 ml of this reaction mixture was diluted to 100 ml with water and the u.v. spectrum determined. A pH-meter equipped with glass and calomel electrodes was used to check the acidity of each solution at the beginning and end of the run.

1,2,3,4,7,8-*Hexahydro*-4′,4′,7,7-*tetramethylquinoline*-3-*spirocyclohexane*-2′,5(6H),6′-*trione* (3b).—A solution of 3,4,5,6,9,10-hexahydro-3,3,6,6-tetramethylacridine-1(2*H*),8(7*H*)-dione (0.35 g), aqueous 37% formaldehyde (20 ml), and ethanol (10 ml) in dilute sulphuric acid (40 ml) was heated on a boiling water-bath, 4 h. The mixture was evaporated at the water pump to low bulk, cooled, and the precipitate collected to give the spiran (0.35 g, 92%), identical (m.p., t.l.c. and i.r.) with an authentic sample.[1]

3,4,5,6,9,10-*Hexahydro*-10-*methylacridine*-1(2H),8(7H)-*dione* (4; R = H, R′ = Me).—A solution of 3-methylaminocyclohex-2-enone (0.5 g) and aqueous 37% formaldehyde (5 ml) in dilute sulphuric acid (5 ml) was kept at room temperature for 24 h. The product was basified with sodium hydroxide solution and extracted with chloroform (3 × 100 ml) to give the *hexahydroacridinedione* (0.3 g, 65%), m.p. 210—211 °C (from ethyl acetate) (Found: C, 72.4; H, 7.6; N, 5.8. $C_{14}H_{17}NO_2$ requires C, 72.7; H,

7.4; N, 6.1%), i.r. $\nu_{max.}$ (KBr) 1 565 and 1 610 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 254 (ε 20 200), 274 (11 600), and 406 nm (7 200).

1,2,3,4,7,8-*Hexahydro*-1-*methylquinoline*-3-*spirocyclohexane*-2',5(6H),6'-*trione* (3; R = H, R' = Me).—A solution of 3-methylaminocyclohex-2-enone (0.5 g), aqueous 37% formaldehyde, and trichloracetic acid (1.3 g) in ethanol (10 ml) was refluxed for 2 h. The solvent was evaporated and the residue basified with saturated sodium hydrogencarbonate solution and extracted with chloroform (3 × 100 ml) to give the *spiran* (0.3 g, 58%), m.p. 165—166 °C (from ethanol) (Found: C, 68.7; H, 7.6; N, 5.0. $C_{15}H_{19}NO_3$ requires C, 69.0; H, 7.3; N, 5.4%), i.r. $\nu_{max.}$ (KBr) 1 550, 1 605, 1 680, and 1 710 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 310 nm (ε 24 900); $\lambda_{max.}$ (0.1M-HCl) 296 nm (ε 19 300); $\lambda_{max.}$ 0.1M-NaOH) 314 nm (ε 30 500).

3,4,5,6,9,10-*Hexahydro*-9-*methylacridine*-1(2H),8(7H)-*dione* (8).—A solution of 3-aminocyclohex-2-enone (1.1 g), acetaldehyde (5 ml), and trichloroacetic acid (3.2 g) in ethanol (10 ml) was kept at room tempertaure 2 days. The product was basified with sodium hydroxide solution and extracted with chloroform (3 × 100 ml) to give the *hexahydroacridinedione* (0.54 g, 47%) (Found: C, 72.7; H, 7.3; N, 6.1. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%), i.r. $\nu_{max.}$ (KBr) 1 605 and 1 635 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 251 (ε 24 500) and 381 nm (9 800).

1,2,7,8-*Tetrahydro*-2,4-*dimethyl*-4H-3,1-*benzoxazin*-5(6H)-*one* (9).—A solution of 3-aminocyclohex-2-enone (0.5 g) and acetaldehyde (5 ml) in dilute hydrochloric acid (50 ml) was kept at room temperature for 2 days. The product was washed with diethyl ether (20 ml), basified with sodium hydroxide, and extracted with chloroform (2 × 100 ml) to give the *tetrahydrobenzoxazinone* (0.3 g, 37%), m.p. 160—161 °C (from ethyl acetate) (Found: C, 66.0; H, 8.4; N, 8.1. $C_{10}H_{15}NO_2$ requires C, 66.3; H, 8.3; N, 7.7%), i.r. $\nu_{max.}$ (KBr) 1 540 and 1 580 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 298 nm (ε 22 300); $\lambda_{max.}$ (0.1M-HCl) 291 nm (ε 20 100); n.m.r. ($CDCl_3$) τ 5.05 (2 H, m, 2 × CH–Me), 7.70 (4 H, m, 2 × CH_2), 8.00 (2 H, m, CH_2 position 7), and 8.58 (6 H, d, 2 × CH_3).

3,4,5,6,9,10-*Hexahydro*-9-*phenylacridine*-1(2H),8(7H)-*dione* (10).—A solution of 3-aminocyclohex-2-enone (1.1 g), benzaldehyde (1 ml), and dilute hydrochloric acid (10 ml) in ethanol (5 ml) was kept at room temperature 3 days. The precipitate was collected to give the *hexahydroacridinedione* (0.8 g, 57%), m.p. 275—276 °C (from ethanol) (Found: C, 77.5; H, 6.1; N, 4.8. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.5; N, 4.8%), i.r. $\nu_{max.}$ (KBr) 1 600 and I 630 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 251 (ε 17 900) and 380 nm (9 000).

2,2'-*Methylenebis*-(5,5-*dimethyl*-3-*phenylaminocyclohex*-2-*enone*) (2; R = Me, R' = Ph).—A solution of 5,5-dimethyl-3-phenylaminocyclohex-2-enone (1.1 g) and aqueous 37% formaldehyde (15 ml) in perchloric acid (20 ml) was kept at room temperature 24 h. The precipitate was collected to give the *methylenebisenaminone* (0.8 g, 72%), m.p. 191—192 °C (from methanol) (Found: C, 78.5; H, 7.7; N, 6.3. $C_{29}H_{34}N_2O_2$ requires C, 78.7; H, 7.7; N, 6.3%), i.r. $\nu_{max.}$ (KCl) 1 580 and 1 610 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 310 nm (ε 21 600).

2,2'-*Methylenebis*-(3-*phenylethylaminocyclohex*-2-*enone*).—A solution of 3-phenylethylaminocyclohex-2-enone [7] (2.15 g), toluene-*p*-sulphonic acid (3.8 g), and paraformaldehyde (0.9 g) in ethanol (40 ml) was refluxed for 2 h. The solvent was evaporated, the residue neutralised with sodium hydrogencarbonate solution and extracted with chloroform (4 × 100 ml) to give the *methylenebisenaminone* (1.2 g, 54%), m.p. 178—179 °C (from ethyl acetate) (Found: C, 78.7; H, 7.9; N, 6.2. $C_{29}H_{34}N_2O_2$ requires C, 78.7; H, 7.7; N, 6.3%). I.r. $\nu_{max.}$ (KCl) 1 570 and 1 620 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 292 nm (ε 58 600); $\lambda_{max.}$ (0.1M-HCl) 282 nm (ε 46 900).

1,2,3,4,7,8-*Hexahydro*-4',4',7,7-*tetramethyl*-1-(2-*phenylethyl*)*quinoline*-3-*spirocyclohexane*-2',5(6H),6'-*trione*.—A solution of 5,5-dimethyl-3-phenylethylaminocyclohex-2-enone [7] (2.4 g) and aqueous 37% formaldehyde (20 ml) in dilute sulphuric acid (35 ml) was kept at room temperature 24 h. The product was basified with sodium hydroxide and extracted with chloroform to give the *spiran* (1 g, 49%), m.p. 158—159 °C [from ethyl acetate–light petroleum (b.p. 40—60 °C)] (Found: C, 76.4; H, 8.1; N, 3.6. $C_{26}H_{33}NO_3$ requires C, 76.7; H, 8.1; N, 3.4%), i.r. $\nu_{max.}$ (KCl) 1 560, 1 615, 1 695, and 1 730 cm^{-1}; u.v. $\lambda_{max.}$ (H_2O) 316 nm (ε 28 600); $\lambda_{max.}$ (0.1M-HCl) 307 nm (ε 24 200); $\lambda_{max.}$ (0.1M-NaOH) 319 nm (ε 30 300).

[8/848 *Received*, 8*th May*, 1978]

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