

Synthesis and Absorption Spectra of 4,5-Disubstituted Pyridine-2,6-(1*H*,5*H*)-diones

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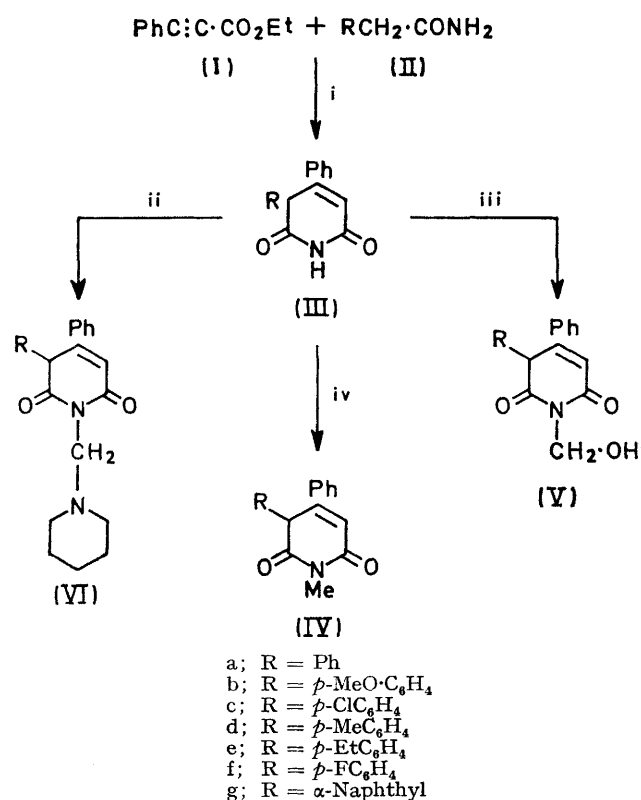
The synthesis of a variety of disubstituted pyridine-2,6(1*H*,5*H*)-diones is described. The i.r. spectra of 21 such compounds have been recorded and are analysed in the region 1640—1770 cm⁻¹; they all showed a three-band system. The u.v. and n.m.r. spectral data are discussed.

RECENTLY,¹ we reported that 5-*p*-methoxyphenyl-4-phenylpyridine-2,6(1*H*,5*H*)-dione (IIIb) was obtained by the condensation of ethyl phenylpropiolate (I) and *p*-methoxyphenylacetamide (IIb). Here a more general

procedure is described which gives a better yield. In addition this method was extended to cover other 4,5-disubstituted compounds (IIIa—g) as well as their *N*-methyl (IVa—g), *N*-hydroxymethyl (Va—e), and *N*-piperidinomethyl (VIa, b) derivatives (see Scheme).

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¹ H. N. Al-Jallo, I. E. El-Kholy, M. Y. Shandala and F. H. Al-Hajjar, *J. Chem. Soc. (C)*, 1969, 915.

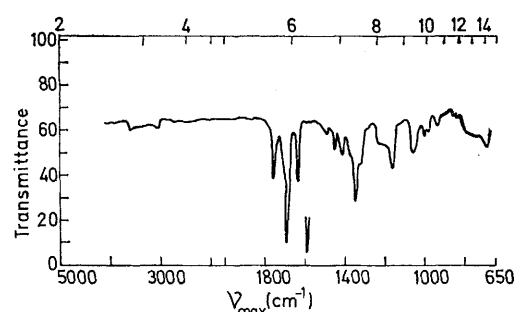


SCHEME

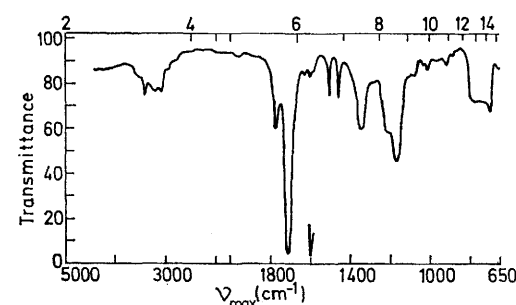
i, Na-Et₂O; ii, MeOH-HCHO-C₅H₁₁N; iii, MeOH-HCHO;
iv, Me₂SO₄.

The i.r. spectra (Table I) of compounds (IIIa–g) showed the absorption bands between 3200–3400 cm⁻¹

(ν_{NH}) as well as a three-band system at 1760–1770, 1700–1720, and 1640–1650 cm⁻¹ [Figure 1: for (IIIa)].

FIGURE 1 I.r. spectrum of compound (IIIa) in CHCl₃

The band in the range 1640–1650 cm⁻¹ is assigned to $\nu(\text{C}=\text{C})$ since the spectrum of the corresponding saturated imide (VII) (Figure 2) contains no such absorption. The

FIGURE 2 I.r. spectrum of compound (VII) in CHCl₃

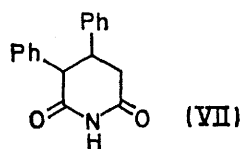
absorption in the range 1700–1720 cm⁻¹ (usually strong) and 1760–1770 cm⁻¹ (weak-medium) may be attributed

TABLE I
Physical data and analyses for compounds (III) and (VII)

Compd.	M.p.	Yield (%)	Formula	C (%)		H (%)		N (%)		N.m.r. (CDCl ₃) ^d			EtOH		CHCl ₃		0.1N-NaOH	
				Found	Calc.	Found	Calc.	Found	Calc.	$\lambda_{\text{max.}}$, cm ⁻¹ ^e	τ	Protons	$\lambda_{\text{max.}}$, nm	log $\epsilon_{\text{max.}}$	$\lambda_{\text{max.}}$, nm	log $\epsilon_{\text{max.}}$	$\lambda_{\text{max.}}$, nm	log $\epsilon_{\text{max.}}$
(IIIa)	220°	96.1	C ₁₇ H ₁₃ NO ₂	77.5	77.55	5.1	5.0	5.35	5.3	3590 (NH) 1767 (CO) 1710 (CO) 1646 (C=C) 3400 (NH) 1770 (CO) 1720 (CO) 1643 (C=C)	1.6 2.8 2.2 (d) 5.22 (d) 1.62 2.83 3.12 (d) 5.25 (d)	NH ArH C:CH :CH NH ArH C:CH :CH	220 290 290 296	4.15 4.28 4.28 4.28	223 240 292	3.28 3.18 4.05 4.51	223 292	4.17 4.34
(IIIb)	206	60.3	C ₁₈ H ₁₅ NO ₂ ^a	74.1	73.7	5.4	5.15	4.6	4.75	3400 (NH) 1770 (CO) 1720 (CO) 1643 (C=C)	1.62 2.83 3.12 (d) 5.25 (d)	NH ArH C:CH :CH	215(sh) 225 286	4.15 4.24 4.29	223 245 292	3.46 4.05 4.51	228 290	4.21 4.27
(IIIc)	181	57.8	C ₁₇ H ₁₂ ClNO ₂ ^b	68.1	68.5	4.0	4.1	4.7	4.7	3425 (NH) 1770 (CO) 1720 (CO) 1646 (C=C)	0.97 2.97 2.25 (d) 5.25 (d)	NH ArH C:CH :CH	212(sh) 225 290	4.50 4.21 4.24	223 242 296	3.30 3.40 4.35	223(sh) 228 292	4.21 4.25 4.30
(IIId)	196	44.7	C ₁₈ H ₁₅ NO ₂	77.4	77.8	5.4	5.4	5.2	5.1	3430 (NH) 1770 (CO) 1720 (CO) 1643 (C=C)	1.18 3.0 2.23 (d) 5.23 (d)	NH ArH C:CH :CH	211(sh) 223 291	4.04 4.24 4.32	223 244 295	2.23 3.68 4.36	226 292	4.28 4.30
(IIIe)	202	60	C ₁₉ H ₁₇ NO ₂	78.4	78.7	6.0	5.9	4.7	4.8	3375 (NH) 1766 (CO) 1720 (CO) 1648 (C=C)	1.07 2.83 2.27 (d) 5.24 (d)	NH ArH C:CH :CH	210(sh) 222 226(sh) 290	4.16 4.29 4.27 4.34	223 249 295	3.20 3.61 4.28	223 228 292	4.28 4.51 4.42
(IIIf)	218–219	50	C ₁₇ H ₁₃ FNO ₂	72.25	72.6	4.4	4.3	4.65	4.95	3200 (NH) 1760 (CO) 1710 (CO) 1643 (C=C) 3200 (NH) 1760 (CO) 1703 (CO) 1643 (C=C)	0.4 2.9 2.17 (d) 5.22 (d) 2.77 2.18 5.72	NH ArH C:CH :CH NH ArH C:CH :CH	221 227(sh) 288 290	4.09 4.05 4.29 4.34	223 294 292	3.42 4.35 4.28	222 227(sh) 290	4.14 4.12 4.35
(IIIg)	222	11.1	C ₂₁ H ₁₅ NO ₂	80.6	80.3	5.1	4.8	4.55	4.45	3200 (NH) 1760 (CO) 1703 (CO) 1643 (C=C)	2.77 2.18 5.72	NH ArH C:CH :CH	226 287	4.54 4.21	223 242	3.51 3.78	225 285	4.63 4.21
(VII)										3400 (NH) 1780 (CO) 1720 (CO)	1.0 2.9 6.3–2.9	NH ArH 2CH ₂ ,CH ₂	218 257	3.76 2.7				

^a OMe%, Found; 10.2; Calc: 10.5. ^b Cl%, Found; 12.3; Calc: 11.9. ^c I.r. in Nujol. ^d NH, exchangeable; ArH appeared as multiplet.

to the carbonyl stretching vibrations by analogy with those of compound (VII).³



The high frequency band (1760–1770 cm^{-1}) seems to be unusual for the six-membered conjugated imides.³ This band could not be due to vibrational coupling of Fermi-resonance type,⁴ as there were no strong absorption bands between 850–900 cm^{-1} . Thus, such a band is considered as a fundamental band and may be the result of some type of vibrational coupling which exists in the system ($-\text{CO}-\text{X}-\text{CO}$) where the central atoms have a lone pair of electron available for resonance interaction. The separation of the two coupled bands is of the order of 50 cm^{-1} similar to that in cyclic anhydrides.⁵

The u.v. absorption spectra of these compounds (IIIa–g, Table 1) showed two main absorption bands near 225 nm (with a shoulder near 220 nm) and 290 nm. Since the last-mentioned absorption is absent in the

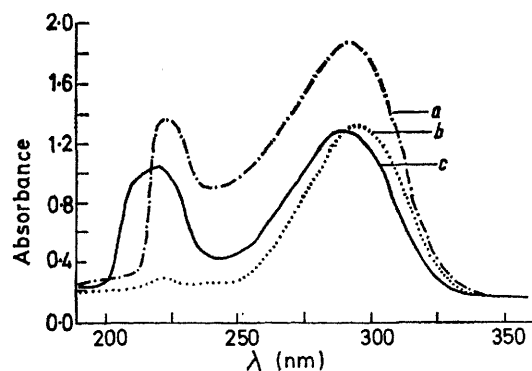
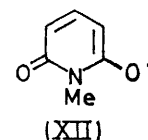
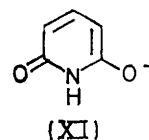
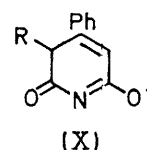
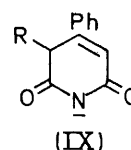
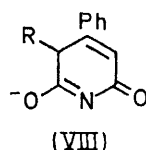


FIGURE 3 U.V. spectra of compound (IIIa) in A, 0.1N-NaOH; B, CHCl_3 ; C, EtOH

spectrum of the corresponding saturated imide (VII), it may be attributed to the conjugated system formed by the unsaturated imide nucleus with the benzene ring. The lower absorption bands may be assigned to the partial chromophoric saturated imide group which is also observed in the saturated imide compound (VII). Spectra recorded for the compounds in the presence of sodium hydroxide showed shifts to higher wavelength with intensification of the bands (Figure 3). This may be explained in terms of contribution of the tautomeric anions (VIII)–(X). Similar contributions are sug-

gested⁶ for the anions of glutaconimide (XI) and *N*-methyl derivatives (XII).

In chloroform the absorption bands are generally shifted toward higher wavelengths (Figure 3). In addition, the absorption involved intensification of the



bands near 290 nm as well as a marked decrease in the intensity of the bands in the range 220–250 nm.

The n.m.r. spectral data (Table 1) gave further evidence for the structures (IIIa–g). Generally, the spectra showed signals at τ (CDCl_3) 0.4–1.62 τ (CONHCO assigned to imido-proton exchangeable by deuterium⁷) 5.22–5.72 (d, J 2 Hz, H) attributed to methine proton, split by the ethylenic⁸ proton at 2.12–2.27 (d, J 2 Hz, H). The aromatic protons absorbed at τ 2.77–3.0 (10H). These values were similar to those of the corresponding saturated compound (VII).

The alkali-soluble imido-compounds (IIIa–g) were readily converted into *N*-methyl derivatives (IVa–g) with dimethyl sulphate and sodium hydroxide. The presence of the *N*-Me group was confirmed by n.m.r. spectroscopy (Table 2) which gave resonance at τ 6.87–6.93 (s, 3H). The i.r. spectra (Table 2) also indicate the three-band system in the range 1770–1648 cm^{-1} . Generally the middle band showed a red shift with an average value of 10 cm^{-1} in chloroform solution, which might be due to the inductive effect of the methyl group. A similar shift has been mentioned for the unsaturated six-membered lactones.⁹ The u.v. spectra for these *N*-methyl derivatives (IVa–g) are closely similar to those of the original imides (IIIa–g, Table 1).

The *N*-hydroxymethyl derivatives (Va–e) were obtained in excellent yields *via* the reaction of (IIIa–g) with formaldehyde. The u.v. spectral data (Table 3) indicated that the absorption bands are more intense than those of the corresponding imides (IIIa–g). It seems likely that this intensification and that of the *N*-methyl compounds arises simply from *N*-substitution by hydroxymethyl and methyl groups respectively.

⁷ G. Gasini and M. L. Salri, 'Nuclear Magnetic Resonance in Chemistry,' ed. Biagis Pesce, Academic Press, London, 1965, p. 325.

⁸ L. M. Jackman, 'Application of N.m.r. Spectroscopy in Organic Chemistry,' Pergamon, London, 1959, p. 87.

⁹ R. N. Jones and C. Sandorfy, 'Chemical Applications of Spectroscopy,' vol. IX of 'Technique of Organic Chemistry,' ed. Weissberger, Interscience, New York, 1956, p. 458.

² N. N. Al-Jallo and F. H. Al-Hajjar, unpublished work.

³ L. J. Bellamy, 'Advances in Infrared group Frequencies,' Methuen, London, 1968, pp. 156 and 165.

⁴ Ref. 3, p. 127.

⁵ L. J. Bellamy, B. R. Connelly, A. R. Philpotts, and R. L. Williams, *Z. Elektrochem.*, 1960, **64**, 563.

⁶ A. R. Katritzky, F. D. Popp, and J. D. Rowe, *J. Chem. Soc. (B)*, 1966, 562.

TABLE 2
Physical data and analyses for compounds (IV)

Compd. (IVa) ^c	M.p. 170—171° ^a	Yield (%) 93.8	Formula C ₁₉ H ₁₅ NO ₂	C (%)		H (%)		N (%)		$\lambda_{\max.}$ (EtOH) /nm	log $\epsilon_{\max.}$	$\nu_{\max.}/\text{cm}^{-1}$	τ (CDCl ₃)	Protons
				Found	Calc.	Found	Calc.	Found	Calc.					
				77.45	77.95	5.45	5.45	5.35	5.05	211 222 235	4.14 4.24 4.43	1703 (CO) 1766 (CO) 1648 (C=C)	2.7 2.1(d) 5.24(d) 6.87(s)	ArH C:CH :CH NMe
(IVb) ^d	145—146 ^b	96.8	C ₁₉ H ₁₇ NO ₃	74.6	74.2	5.5	5.55	5.0	4.55	212 227 289	4.12 4.23 4.27	1708 (CO) 1768 (CO) 1648 (C=C)	2.83 2.1(d) 5.28(d) 6.22(s) 6.87(s)	ArH C:CH :CH ArOMe NMe
(IVc)	166—167 ^b	96.7	C ₁₈ H ₁₄ ClNO ₂	69.6	69.6	4.3	4.5	4.6	4.5			1700 (CO) 1768 (CO) 1648 (C=C)	2.7 2.27(d) 5.4(d)	ArH C:CH :CH
(IVf) ^e	139—141 ^b	76.9	C ₁₈ H ₁₄ FNO ₂	73.35	73.2	4.9	4.75	4.95	4.75	221 227 290	4.28 4.25 4.47	1700 (CO) 1765 (CO) 1648 (C=C)	2.88 2.12(d) 5.27(d) 6.87(s)	ArH C:CH :CH NMe
(IVd)	193 ^b	78.1	C ₁₉ H ₁₇ NO ₂	77.9	78.3	6.3	5.9	4.7	4.8	210 223 292	4.08 4.20 4.29	1710 (CO) 1772 (CO) 1653 (C=C)	3.03 2.18(d) 5.3(d) 6.88(s) 7.7(s)	ArH C:CH :CH NMe ArMe
(IVe)	138 ^b	96.7	C ₂₀ H ₁₉ NO ₂	78.1	78.6	6.7	6.3	4.4	4.6	215 223 292	4.24 4.33 4.40	1708 (CO) 1768 (CO) 1652 (C=C)	3.03 2.2 5.32(d) 6.92(s) 7.43(q) 8.85(f)	ArH C:CH :CH NMe ArCH ₂ -Me
(IVg)	137 ^b	95.2	C ₂₂ H ₁₇ NO ₂	80.2	80.6	5.35	5.35	3.75	4.25	226 288	4.64 4.36	1710 (CO) 1770 (CO) 1652 (C=C)	2.69 2.25 4.57 6.93(s)	ArH C:CH :CH NMe

^a Recrystallised from ethanol. ^b Recrystallised from methanol. ^c NMe₃%, Found: 10.55; Calc: 10.45. ^d OMe₃%, Found: 10.6; Calc: 10.0. ^e F%, Found: 6.15; Calc: 6.45. ^f ArH appeared as a multiplet.

TABLE 3
Physical data and analyses for compounds (V) and (VI)

Compd. (Va)	M.p. 181—182	Yield (%) 94	Formula C ₁₈ H ₁₅ NO ₃	C (%)		H (%)		N (%)		$\lambda_{\max.}$ (EtOH)/ nm	log $\epsilon_{\max.}$	$\lambda_{\max.}$ (Nujol) /cm ⁻¹	N.m.r. (CDCl ₃) ^a	
				Found	Calc.	Found	Calc.	Found	Calc.				τ	Protons
				74.2	73.7	5.25	5.15	5.15	4.75	211(sh) 220 290	4.19 4.27 4.41	3450 (OH) 1690 (CO) 1750 (CO) 1640 (C=C)	4.85 2.8 2.15(d) 5.26(d) 4.85	OH ArH C:CH :CH NCH ₂ O
(Vb)	171	95	C ₁₉ H ₁₇ NO ₄	70.95	70.55	5.65	5.3	4.3	4.35	211(sh) 225 288	4.18 4.36 4.41	3460 (OH) 1680 (CO) 1747 (CO) 1640 (C=C)	4.75 2.91 2.12 (d) 5.26 (d) 4.88 6.22	OH ArH C:CH :CH NCH ₂ O ArOMe
(Vc)	142—143	88	C ₁₈ H ₁₄ NO ₃ Cl	65.15	65.95	4.2	4.0			225 290	4.41 4.42	3488 (OH) 1690 (CO) 1750 (CO) 1640 (C=C)	4.75 2.73 2.1(d) 5.25(d) 4.88	OH ArH C:CH :CH NCH ₂ O
(Vd)	170—171	90	C ₁₉ H ₁₇ NO ₃	74.35	74.25	5.35	5.55	4.5	4.55	211(sh) 223 290	4.26 4.40 4.46	3490 (OH) 1686 (CO) 1747 (CO) 1635 (C=C)	4.78 2.8 2.15(d) 5.3(d) 4.92(s) 7.72(s)	OH ArH C:CH :CH NCH ₂ O -Me
(Ve)	166—167	91	C ₂₀ H ₁₉ NO ₃	74.55	75.05	6.1	5.95			210(sh) 223 291	4.13 4.35 4.48	3440 (OH) 1688 (CO) 1750 (CO) 1640 (C=C)	4.77 2.76 2.1(d) 5.25(d) 4.87 7.37(q) 8.78(t)	OH ArH C:CH :CH NCH ₂ O ArCH ₂ -Me
(VIa)	155—156	48.5	C ₂₃ H ₂₄ N ₂ O ₂	76.1	76.65	6.4	6.7	8.0	7.75	220 226 289	4.09 4.05 4.29	1695 (CO) 1762 (CO) 1642 (C=C)	2.7 2.15(d) 5.25(d) 5.42(s) 7.45 8.6	ArH C:CH :CH NCH ₂ N Piperidine
(VIb)	156—157	65	C ₂₄ H ₂₆ N ₂ O ₃ + 1/2 CH ₃ OH	72.3	72.4	6.55	5.95	6.55	6.9	223 227 286	4.25 4.27 4.36	1695 (CO) 1760 (CO) 1640 (C=C)	2.9 2.15(d) 5.3(d) 5.42(s) 6.22(s) 7.47 6.58	ArH C:CH :CH NCH ₂ N ArOMe Piperidine

^a OH, exchangeable; ArH appeared as a multiplet.

The i.r. spectra of these compounds showed a pronounced red-shift in the region of the three-band system as compared with the original imides (IIIa—g). The shift is of the order of 20, 30, and 6 cm^{-1} from higher to lower values of frequencies.

The n.m.r. spectral data (Table 3) also confirmed the above structures (Va—e). The hydroxylic proton between τ 4.75—4.85 is exchanged with deuterium.

The Mannich-bases (VIa, b) were obtained in good yield by condensation of the imides (IIIa—g) with formaldehyde and piperidine in the presence of methanol. The i.r. spectra (Table 3) again showed the three-band system with a similar shift to lower frequencies as in the spectra of (IVa—e). Similarly the u.v. spectra (Table 3) showed the same pattern as compounds (III) and (IV). The n.m.r. spectra (Table 3) gave confirmatory evidence of the structures.

EXPERIMENTAL

Unless otherwise stated, i.r. spectra were measured with a Unicam SP 200 instrument for solutions in chloroform, ^1H n.m.r. spectra with a Varian A-60D instrument for solutions in carbon tetrachloride with tetramethylsilane as internal standard, and u.v. spectra with Unicam SP 800 instrument in ethanol (ϵ_{max} values are in $\text{l mol}^{-1} \text{cm}^{-1}$ units). Compounds were analysed at the Max Plank Institute, Ruhr, West Germany. M.p.s were determined with a Kofler hot-stage apparatus.

Condensation of Ethyl Phenylpropionate and Arylacetamides.—A modified form of the previously published¹ procedure for the condensation of *p*-methoxyphenylacetamide was used in this work.

Arylacetamide (1 mol. equiv.) in dry benzene was heated under reflux with powder sodium (1 g-atom equiv.) for 20 h. Ethyl phenylpropionate (1 mol. equiv.) was then added and the heating was continued for further 2 h. The mixture

was then poured into water (200 ml) and the benzene layer was separated. The aqueous layer was acidified with dilute sulphuric acid and then extracted with ether. The ethereal extracts were shaken with sodium hydrogen carbonate solution, and the combined ether-benzene extracts were dried (MgSO_4) and evaporated to give the appropriate 4,5-disubstituted pyridine-2,6(1*H*,5*H*)-dione which was crystallised from methanol (Table 1). The sodium hydrogen carbonate washing after acidification, extraction with ether, and evaporation gave a solid which was mainly phenylpropionic acid, m.p. and mixed m.p. 138°.

*Action of Dimethyl Sulphate on 4,5-Disubstituted Pyridine-2,6(1*H*,5*H*)-diones (IIIa—g).*—A solution of the appropriate compound (IIIa—g, 0.3 g) in 1% sodium hydroxide solution (100 ml) was treated with dimethyl sulphate (1 ml). The reaction mixture was cooled to give the corresponding 4,5-disubstituted 1-methylpyridine-2,6(1*H*,5*H*)-dione (IVa—g) which crystallised from a suitable solvent as needles (see Table 2).

*Hydroxymethylation of 4,5-Disubstituted Pyridine-2,6(1*H*,5*H*)-diones (IIIa—e).*—A mixture of the appropriate imido-compound (IIIa—e) (1.0 g), formaldehyde (35%, 10 ml) and methanol (50 ml), was heated under reflux for 3 h, and cooled in ice for at least 12 h. The solid which separated was crystallised from benzene to give the corresponding 4,5-disubstituted 1-hydroxymethylpyridine-2,6(1*H*,5*H*)-dione (Va—e) as needles (Table 3).

*Mannich Reaction with 4,5-Disubstituted Pyridine-2,6(1*H*,5*H*)-diones (IIIa, b).*—Formaldehyde (35%; 6 ml) was added to a suspension of the appropriate imido-compound (IIIa, b) (0.01 mol. equiv.) and piperidine (0.02 mol. equiv.) in methanol (50 ml). The reaction mixture was heated on a water-bath and was then kept in ice overnight. The solid which separated was crystallised from carbon tetrachloride to give the corresponding 4,5-disubstituted 1-piperidinomethylpyridine-2,6(1*H*,5*H*)-dione (VIa, b) as crystals (Table 3).

[1/260 Received, March, 12th, 1971]