Synthesis of 3-Alkyl-*N*-hydroxyindole-2-carboxylic Acid

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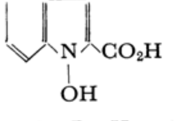
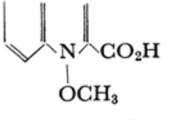
Only three *N*-hydroxyindole-2-carboxylic acids, Va, Vd and Ve have been known in the literature. Reissert[1,2] first prepared *N*-hydroxyindole-2-carboxylic acid (Va) from *o*-nitrobenzylmalonic acid or from *o*-nitrophenylpyruvic acid (I). Loudon and Wellings[3] reported the synthesis of 3-cyano-*N*-hydroxyindole-2-carboxylic acid (Vd) and 3-carbamoyl-*N*-hydroxyindole-2-carboxylic acid (Ve) from diethyl α-cyano-α-*o*-nitrobenzylmalonate and its amide respectively. However, 3-alkyl-*N*-hydroxyindole-2-carboxylic acid has never been synthesized.

During the course of an investigation of the synthesis of *N*-hydroxyindoles we succeeded to synthesize 3-methyl and 3-ethyl-*N*-hydroxyindole-2-carboxylic acids (Vb and Vc) from the corresponding pyruvic acid derivatives (IIb and IIc) through the sodium bisulfite addition compounds (IVb and IVc).[4] IVb and IVc afforded Vb and Vc respectively by reductive cyclization with sodium amalgam. We found three routes for the synthesis of Va from ethyl *o*-nitrophenylpyruvate (IIa), its potassium salt (III) or sodium bisulfite addition compound (IVa). The *N*-methoxy derivatives (VIb and VIc) were obtained by methylation of the corresponding *N*-hydroxy compounds (Vb and Vc).

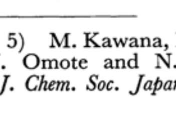
The structures of Vb, Vc, VIb and VIc are supported by the elemental analyses, color reactions, IR and UV spectra. The UV spectra of Va, Vb and Vc show the characteristic bathochromic shift[5] in alkaline medium (Table 1). The formation of a green color with ferric chloride[5] indicates the presence of *N*-hydroxyl group in Va, Vb and Vc. VIa, VIb and VIc give a negative ferric chloride test, and do not show a bathochromic shift of UV absorption maximum.



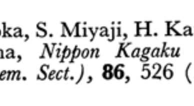
IIa, R=H
IIb, $R=CH_3$
IIc, $R=C_2H_5$



IVa, R=H
IVb, $R=CH_3$
IVc, $R=C_2H_5$



Va, R=H
Vb, $R=CH_3$
Vc, $R=C_2H_5$
Vd, R=CN
Ve, $R=CONH_2$



VIa, R=H
VIb, $R=CH_3$
VIc, $R=C_2H_5$

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[1] A. Reissert, *Ber.*, **29**, 639 (1896).

[2] A. Reissert, *ibid.*, **30**, 1030 (1897).

[3] J. D. Loudon and I. Wellings, *J. Chem. Soc.*, **1960**, 3462.

[4] W. Wislicenus and E. Thoma, *Ann.*, **436**, 42 (1924).

[5] M. Kawana, M. Yoshioka, S. Miyaji, H. Kataoka, Y. Omote and N. Sugiyama, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **86**, 526 (1965).

TABLE 1. ULTRAVIOLET ABSORPTION MAXIMA (mμ, MeOH)

Compound	Acid or Neutral	Basic[a]
I	262	327
IIa	271, 287	255, 336
III	270, 285	255, 331
IVa	257	256, 330
IVb	255	263, 290
IVc	255	262, 290
Va	230, 290, 296	244, 295, 304
Vb	238, 293, 301	247, 290, 298, 307
Vc	239, 293, 302	247, 293, 299, 308
VIa	222, 237, 289	237, 244, 289
VIb	228, 240, 292	240, 291
VIc	229, 240, 294	240, 292

a) 0.2 N NaOH-MeOH solution.

Experimental

All melting points are uncorrected.

***N*-Hydroxyindole-2-carboxylic Acid (Va).** *(A) From Ethyl o-Nitrophenylpyruvate.* To a mixture of 2 g of ethyl *o*-nitrophenylpyruvate (IIa)[4] and 24 m*l* of water, 8% sodium amalgam was added until the solution changed to purple-red and then decolorized. The solution was decanted from mercury, cooled in ice and acidified with hydrochloric acid. Greenish white solid, 0.6 g, was obtained and recrystallized from benzene to give colorless prisms, mp 159—160°C (decomp.) (lit. 159.5°C[1]). ν^{KBr} 3450, 1680, 940 and 745 cm^{-1}. *N*-Methoxyindole-2-carboxylic acid (VIa), mp 184—185°C(decomp.) (lit. 185°C[1]). ν^{KBr} 2900, 1685, 960 and 740 cm^{-1}.

(B) From Potassium Salt of Ethyl o-Nitrophenylpyruvate. One gram of potassium salt (III),[4] 12 m*l* of water and 8% sodium amalgam gave 0.35 g of Va, mp 159°C(decomp.) (from benzene).

(C) From Sodium Bisulfite Addition Compound. Sodium bisulfite addition compound (IVa)[4] (1 g) (ν^{KBr} 3500, 2980, 2900, 2860, 1720, 1528 and 1358 cm^{-1}), 20 m*l* of water and 8% sodium amalgam gave 0.25 g of Va.

3-Methyl-*N*-hydroxyindole-2-carboxylic Acid (Vb). Sodium bisulfite addition compound IVb[4] was prepared from 5 g of potassium salt of ethyl *o*-nitrophenylpyruvate (III) and 4 g of methyl iodide in 5 g of acetone by refluxing for 2 hr. After removing acetone, the residue was extracted with ether. The ether solution was shaken with 20 m*l* of aqueous saturated sodium bisulfite solution and ketp overnight to give a white solid, IVb, 3.5 g. ν^{KBr} 3500, 2960, 2930, 2860, 1745, 1520, and 1358 cm^{-1}. Vb was synthesized by the method A described above. The mixture of 1 g of IVb, 20 m*l* of water and 8% sodium amalgam gave 0.2 g of crude Vb, which gave faint red needles of Vb by recrystallization from benzene. Vb began to change to red at 125—128°C and decomposed completely at 163—164°C. ν^{KBr} 3350, 2900, 2840, 1665, 930 and 740 cm^{-1}. $\lambda_{max}^{\mathrm{MeOH}}$ (log ε) 238 (4.47), 293 (4.07) and 301 (4.12) mμ. $\lambda_{max}^{\mathrm{0.2N\ NaOH\text{-}MeOH}}$ (log ε) 247 (4.54), 290 (4.07), 298 (4.11) and 307 (4.06) mμ.

Found: C, 63.50; H, 4.81; N, 7.36%. Calcd for $C_{10}H_9O_3N$: C, 62.82; H, 4.75; N, 7.33%.

3-Methyl-*N*-methoxyindole-2-carboxylic Acid (VIb). To a solution of 0.024 g of sodium in 2 m*l* of methanol, 0.1 g of Vb and 0.15 g of methyl iodide were added. The mixture was refluxed for 30 min. After removing the solvent, the residue was dissolved in water, decolorized with active charcoal and acidified with hydrochloric acid to afford 0.07 g of precipitate, which was recrystallized from acetone-water to give faint red needles, mp 155°C (decomp.). ν^{KBr} 2950, 2900, 2860, 1685, 950 and 730 cm^{-1}. $\lambda_{max}^{\mathrm{MeOH}}$ (log ε) 228 (4.43), 240 (4.35) and 292 (4.20) mμ. $\lambda_{max}^{\mathrm{0.2N\ NaOH\text{-}MeOH}}$ (log ε) 240 (4.52) and 291 (4.32) mμ.

Found: C, 64.21; H, 5.47; N, 6.99%. Calcd for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83%.

3-Ethyl-*N*-hydroxyindole-2-carboxylic Acid (Vc). Sodium bisulfite addition compound IVc[4] was prepared from III and ethyl iodide in acetone by refluxing 3 hr. ν^{KBr} 3500, 2980, 2900, 1730, 1525 and 1350 cm^{-1}. The mixture of 1 g of IVc, 20 m*l* of water and 8% sodium amalgam gave 0.12 g of crude Vc, which was recrystallized from carbon tetrachloride to give faint green needles. Vc began to change to red at 110°C and decomposed at 155—156°C. ν^{KBr} 3400, 2980, 2950, 2880, 1680, 930 and 740 cm^{-1}. $\lambda_{max}^{\mathrm{MeOH}}$ (log ε) 239 (4.59), 293 (4.09) and 302 (4.15) mμ. $\lambda_{max}^{\mathrm{0.2N\ NaOH\text{-}MeOH}}$ (log ε) 247 (4.79), 293 (4.35), 299 (4.37) and 308 (4.32) mμ.

Found: C, 64.27; H, 5.57; N, 6.81%. Calcd for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83%.

3-Ethyl-*N*-methoxyindole-2-carboxylic Acid (VIc). The mixture of 0.023 g of sodium in 2 m*l* of methanol, 0.1 g of Vc and 0.14 g of methyl iodide gave 0.04 g of VIc, recrystallized from acetone-water, mp 131—132°C(decomp.). ν^{KBr} 2970, 2940, 2880, 1675, 940 and 740 cm^{-1}. $\lambda_{max}^{\mathrm{MeOH}}$ (log ε) 229 (4.55), 240 (4.45) and 294 (4.25) mμ. $\lambda_{max}^{\mathrm{0.2N\ NaOH\text{-}MeOH}}$ (log ε) 240 (4.55) and 292 (4.37) mμ.

Found: C, 66.15; H, 5.74; N, 6.56%. Calcd for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39%.

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