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# Syntheses of 2,4-Dicyanophenoxyacetic Acid and Its Analogues

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With the aim of developing new pesticide, we have synthesized 2,4-dicyanophenoxyacetic acid (II) which has the structure similar to those of 2,4-dichlorophenoxyacetic acid (2,4-D) and its analogues {(III)~(IX)}. The reason why we chose the nitrile group was that the nitrile group has a large electron negativity like the chloro group, and that nitrile groups would be hydrolyzed smoothly in the nature.

The results of the tests of 2,4-dicyanophenoxyacetic acid (II) and its derivatives (III~IX) for their herbicidal, insecticidal and fungicidal activities showed that they had less remarkable pesticidal properties contrary to our expectation.

Salicylaldehyde (X) was converted to 2,4-diformylphenol (XI)[1] with Reimer-Tiemann reaction. In this reaction, we obtained (XI) and 2,6-diformylphenol (XII) at about 3:1 ratio. The dialdehyde (XI) was refluxed in acetic acid with hydroxylamine hydrochloride and sodium acetate to give cyanide which was regarded as equilibrium mixture of (XIII) and (XIV) from IR and NMR data, and this cyanide was condensed with ethyl bromoacetate to give ethyl 2,4-dicyanophenoxyacetate (III). The ester (III) was hydrolyzed to (II).

Similarly, (IV) and (V) were synthesized from *p*-cresol, (VI) and (VII) from salicylaldehyde, and (VIII) and (IX) from *p*-hydroxybenzaldehyde, respectively.

## EXPERIMENTAL

*2,4-Diformylphenol (XI)*

25 g of salicylaldehyde (X) was mixed with 50 g of chloroform and 50 g of sodium hydroxide in 150 ml of water, and refluxed for 15 hr. Then the mixture was cooled and acidified with diluted sulfuric acid and extracted with ethyl acetate. The ethyl acetate layer was extracted with aqueous sodium bicarbonate, and concentration of the organic layer recovered 13 g of unreacted salicylaldehyde. The aqueous layer was acidified and extracted with chloroform. The chloroform solution was dried and concentrated to give a crude crystalline mixture of (X), 2,4-diformylphenol (XI) and 2,6-diformylphenol (XII), which were separated with silicagel column chromatography with chloroform-ether elution. Yielded 0.8 g (6% yield) of (XII): mp 124~124.5°C. IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3500~3100 (OH) 1670 (CHO). NMR $\tau_{Me_4Si}^{CDCl_3}$: −1.62 (1H, singlet, OH), −0.21 (2H, singlet, CHO), 2.05 (2H, doublet, Ar-H), 2.88 (1H, triplet, Ar-H). *Anal.* Found: C, 63.78;

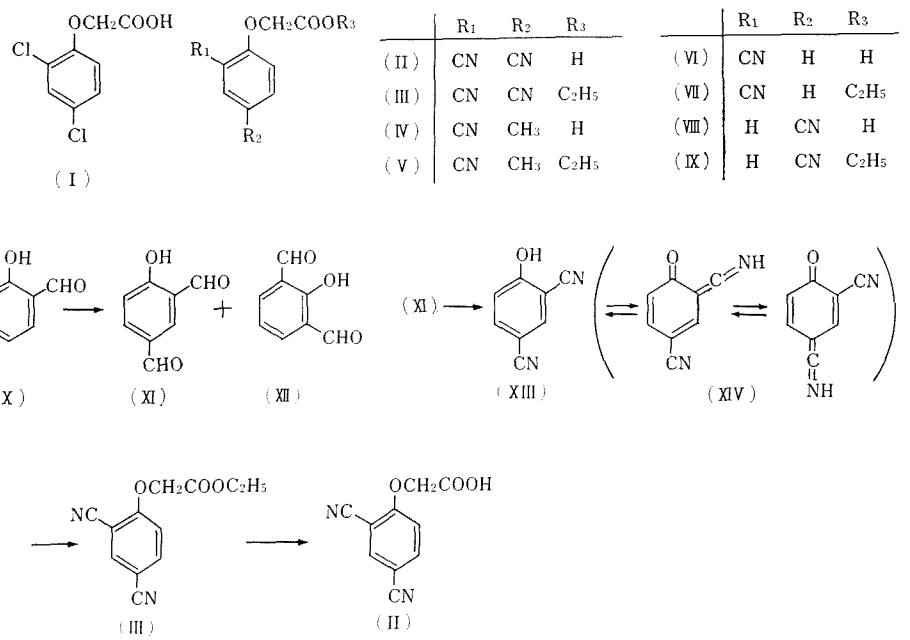


FIG. 1.

H, 4.06. Calcd. for $C_8H_6O_3$: C, 64.00; H, 4.03%.

And 2.6 g (19.3% yield) of (XI): mp 111~112°C. IR $\nu_{max}^{Nujol}cm^{-1}$: 3160 (Ar-OH), 1660 (CHO), 1695 (CHO). NMR $\tau_{Me_4Si}^{CDCl_3}$: −1.42 (1H, singlet, OH), 0.04 (1H, singlet, CHO) 0.08 (1H, singlet, CHO), 1.91 (1H, doublet, Ar-H), 2.0 (1H, double doublet, Ar-H), 2.94 (1H, doublet, Ar-H). *Anal.* Found: C, 64.27; H, 4.13. Calcd. for $C_8H_6O_3$: C, 64.00; H, 4.03%.

*2,4-Dicyanophenol (XIII)*

2.5 g of (XI) and 3.2 g of dried hydroxylamine hydrochloride and 4.2 g of freshly fused sodium acetate were suspended in 25 ml acetic acid and refluxed at 135°C for 24 hr. Then salts were filtered and the filtrate was poured into water and the precipitated crystals were filtered and recrystallized from benzene to give 1.8 g of cyanide and extraction with ethyl acetate from the mother liquor gave 0.2 g of the same product. The IR spectrum of this cyanide, in the state of solution ($CHCl_3$), showed the absence of the absorption peak at 3610 $cm^{-1}$ which sharply appeared in the case of 2-cyanophenol and 4-cyanophenol under the same condition. On the contrary, the former showed a peak at 1680 $cm^{-1}$, indicating the presence of enone (O=C-C=C), which was absent in the latter. All of them showed a broad peak at 3160~3440 $cm^{-1}$ (OH or NH). In the state of crystal (nujol mull), the spectra of 2 and 4-cyanophenol showed one peak at 3280 $cm^{-1}$ and 3240 $cm^{-1}$, respectively (OH), and also at 2228 $cm^{-1}$ and 2215 $cm^{-1}$, respectively (C≡N). This cyanide showed two peaks at 3190 $cm^{-1}$ and 3390 $cm^{-1}$, and also at 2230 $cm^{-1}$, and 2242 $cm^{-1}$; one of the latter disappeared in the state of solution. The NMR spectrum of this cyanide (in $CDCl_3$) showed peaks at $\tau$ 1.93 and $\tau$ 6.6 (broad), each integral indicated a half amount of one proton and they disappeared under the treatment with deuterium oxide. Then they were regarded as OH and NH proton, respectively. With those spectral data, this cyanide was considered to be a tautomeric mixture of (XIII) and (XIV). Yield was 2.0 g (83%): mp 185~240°C (sublime). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3390 (NH), 3190 (OH), 2242 (C≡N) 2230 (C≡N), 1680 (C=O), 1630 (C=N), NMR $\tau_{Me_4Si}^{DMSO}$: 1.93 (0.5H, singlet, OH), 2.0 (1H, doublet, Ar-H), 2.24 (1H, double doublet, Ar-H), 2.88 (1H, doublet, Ar-H) 6.6 (0.5 H, broad, NH). *Anal.* Found: C, 66.38; H, 2.69; N, 19.20. Calcd. for $C_8H_4ON_2$: C, 66.66; H, 2.80; N, 19.44%.

*Ethyl 2,4-dicyanophenoxyacetate (III)*

To a tautomeric mixture of cyanides XIII and XIV (2.7 g) in 20 ml dry acetone was added 4.2 g of potassium carbonate and stirred at room temperature for 30 min, then 4.7 g of ethyl bromoacetate in 5 ml of dry acetone was added and stirred and refluxed for 4 hr. After cooling, salts were filtered and the filtrate was poured into water and extracted with ether. The ether-solution was dried and concentrated to give crude crystals; recrystallization from benzene afforded 3.6 g (86%) of ethyl-(2.4-dicyanophenoxy) acetate (III): mp 141~142°C. IR $\nu_{max}^{Nujol}cm^{-1}$: 2230 (C≡N), 1760 (COO). NMR $\tau_{Me_4Si}^{CDCl_3}$: 2.12 (1H, doublet, Ar-H), 2.22 (1H, double doublet, Ar-H), 3.08 (1H, doublet, Ar-H), 5.16 (2H, singlet, $CH_2$), 5.73 (2H, quartet, $CH_2$) 8.70 (3H, triplet, $CH_3$). *Anal.* Found: C, 62.13; H, 4.40; N, 11.91. Calcd. for $C_{12}H_{10}O_3N_2$; C, 62.60; H, 4.38; N, 12.17%.

*2,4-Dicyanophenoxyacetic acid (II)*

1.5 g of the ester in 15 ml acetone and 6 g of potassium carbonate in 20 ml of water were mixed and stirred at room temperature for 2 days. 50 ml of water was added and extracted with ether. The ether solution was dried and concentrated to give unreacted ester (II) 0.2 g. The mother liquor was acidified and extracted with ether. The ether solution was dried and evaporated *in vacuo*, and the residual crystal was recrystallized from water to give 1.0 g (88%) of 2,4-dicyanophenoxyacetic acid (II): mp 192~194°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200~2400 (COOH), 2230 (C≡N) 1735 (COO). NMR $\tau_{Me_4Si}^{(CD_3)_2CO}$: 0.35 (1H, broad, COOH), 1.83 (1H, doublet, Ar-H), 2.01 (1H, double doublet, Ar-H), 2.62 (1H, doublet, Ar-H), 4.90 (2H, singlet, $CH_2$). *Anal.* Found: C, 58.88; H, 3.15; N, 13.66. Calcd. for $C_{10}H_6O_3N_2$: C, 59.41; H, 2.99; N, 13.86%.

*2-Cyano-4-methylphenol*

This compound was prepared from 2-formyl-4-methylphenol[2] which was the product of the Reimer-Tiemann reaction of *p*-cresol, with the same procedure as used for preparing XIII: mp 98~99.5°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3280 (OH), 2240 (C≡N). NMR $\tau_{Me_4Si}^{CCl_4}$: 2.76 (1H, doublet, Ar-H), 2.81 (1H, double doublet, Ar-H), 3.12 (1H, doublet, Ar-H), 3.7 (1H, broad, OH), 7.74 (3H, singlet, $CH_3$). *Anal.* Found: C, 72.30; H, 5.42; N, 10.49. Calcd. for $C_8H_7ON$: C, 72.16; H, 5.30; N, 10.52%.

*Ethyl 2-cyano-4-methylphenoxyacetate (V)*

Compound V was prepared from above 2-cyano-4-methylphenol and ethyl bromoacetate with the same procedure as used for preparing III: mp 32.5~34°C. IR $\nu_{max}^{film}cm^{-1}$: 2220 (C≡N), 1760 (COO). NMR $\tau_{Me_4Si}^{CCl_4}$: 2.75 (1.5 H, pseude singlet, Ar-H), 2.85 (0.5 H, doublet, Ar-H), 3.32 (1H, doublet, Ar-H), 5.38 (2H, singlet, $CH_2$), 5.84 (2H, quartet $CH_2$), 7.72 (3H, singlet, $CH_3$), 8.74 (3-H, triplet, $CH_3$). *Anal.* Found: C, 65.13; H, 5.85; N, 6.20. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39%.

*2-Cyano-4-methylphenoxyacetic acid (IV)*

Compound IV was prepared from V with the same

procedure as used for preparing II from III: mp 151~153°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400~2400 (COOH), 2220 (C≡N), 1720 (COO). NMR $\tau_{Me_4Si}^{(CD_3)_2CO}$: 2.4~2.9 (3H, broad and multiplet, Ar-H, COOH) 3.0 (1H, doublet, Ar-H), 5.14 (2H, singlet, $CH_2$). *Anal.* Found; C, 63.13; H, 4.74; N, 7.20. Calcd. for $C_{10}H_9O_3N$; C, 62.82; H, 4.75; N, 7.33%.

*Ethyl 2-cyanophenoxyacetate (VII)*

Compound VII was prepared from ethyl bromoacetate and 2-cyanophenol,[3] which was prepared from salicylaldehyde, with the same procedure as used for preparing III: mp 50~52°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2220 (C≡N). 1760 (COO). NMR $\tau_{Me_4Si}^{CCl_4}$: 2.4~2.7 (2H, multiplet, Ar-H), 2.9~3.3 (2H, multiplet, Ar-H), 5.32 (2H, singlet, $CH_2$), 5.80 (2H, quartet, $CH_2$) 8.72 (3H, triplet, $CH_3$). *Anal.* Found: C, 64.16; H, 5.52; N, 6.50. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83%.

*2-Cyanophenoxyacetic acid (VI)*[4]

Compound VI was prepared from VII with the same procedure as used for preparing II from III: mp 180~182°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200~2400 (COOH), 2220 (C≡N). 1720 (COO). NMR $\tau_{Me_4Si}^{(CD_3)_2CO}$: 2.25~2.5 (2H, multiplet, Ar-H), 2.7~3.7 (1H, broad, COOH), 5.07 (2H, singlet, $CH_2$). *Anal.* Found: C, 60.86; H, 4.22; N, 7.74. Calcd. for $C_9H_7O_3N$: C, 61.01; H, 3.98; N, 7.91%.

*Ethyl 4-cyanophenoxyacetate (IX)*

Compound IX was prepared from ethyl bromoacetate and 4-cyanophenol,[3] which was prepared from *p*-hydroxy benzaldehyde, with the same procedure as used for preparing III: mp 53~54°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2210 (C≡N) 1760 (COO). NMR $\tau_{Me_4Si}^{CCl_4}$: 2.49 (2H, multiplet, Ar-H), 3.14 (2H, multiplet, Ar-H), 5.43 (2H, singlet, $CH_2$), 5.80 (2H, quartet, $CH_2$), 8.72 (3H, triplet, $CH_3$). *Anal.* Found; C, 64.39; H, 5 43; N, 6.72. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83%.

*4-Cyanophenoxyacetic acid (VIII)*[4]

The compound VIII was prepared from IX with the same procedure of preparing II from III: mp 172~174°C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200~2400 (COOH), 2210 (C≡N), 1740, 1710 (COO). NMR $\tau_{Me_4Si}^{(CD_3)_2CO}$: 2.32 (2H, multiplet, Ar-H), 2.7~3.5 (1H, broad, COOH), 2.90 (2H, multiplet, Ar-H), 5.14 (2H, singlet, $CH_2$). *Anal.* Found: C, 60.86; H, 3.98; N, 7.64. Calcd. for $C_9H_7O_3N$: C, 61.01; H, 3.98; N, 7.91%.

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