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Nitrenes. VIII.[1] A Novel Synthesis of 3-Cyano-2-ethoxy-6,7-disubstituted-quinolines with Triethyl Phosphite (Studies on the Syntheses of Heterocyclic Compounds. CDXVI[2])

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Treatment of ethyl 3,4-disubstituted-benzylidenecyanoacetate (V, VI and VII), whose ethoxycarbonyl group was oriented in the *trans* configuration to the benzene ring, with triethyl phosphite afforded the 3-cyano-2-ethoxy-6,7-disubstituted-quinolines (XI, XII, and XIII) in good yield.

Recently, the reaction of aromatic nitro compounds with triethyl phosphite has been investigated by many workers,[1,4–17] among whom Sundberg and his co-workers[7,11,12] have reported syntheses of indole derivatives by the treatment of *o*-nitrostyrene derivative with triethyl phosphite. We have also found that the reaction of the oxazolone derivative (I)[9,17] and styrene derivative (III),[1] having the *cis* configuration between the benzene ring and the carbonyl group, with triethyl phosphite afforded our expected quinoline derivatives (II and IV) in good yield.

I II

Chart 1

An extensive survey of condensation products from aromatic aldehyde and cyanoacetate or cyanoacetamide showed them to have the configuration in which the smaller cyano group was *cis* to the benzene ring.[18,19] Therefore, cyano derivatives (V, VI, and VII) were chosen

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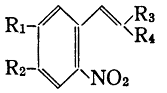
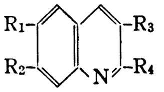
as the starting materials having the same relation to the above as has Zabicky's cyano ester.[18] Quinoline derivatives (XI, XII, and XIII) were obtained in comparatively good yield, though nitro and carbonyl groups were located in *trans*-configuration to each other. Herein we wish to report these results.



III: $R_1=R_2=OMe$, $R_3=R_4=COOEt$
V: $R_1=R_2=OMe$, $R_3=COOEt$, $R_4=CN$
VI: $R_1+R_2=OCH_2O$, $R_3=COOEt$, $R_4=CN$
VII: $R_1=OMe$, $R_2=OCH_2C_6H_5$, $R_3=COOEt$, $R_4=CN$
VIII: $R_1=R_2=OMe$, $R_3=COC_6H_5$, $R_4=CN$
IX: $R_1=OMe$, $R_2=OCH_2C_6H_5$, $R_3=COC_6H_5$, $R_4=CN$
X: $R_1+R_2=OCH_2O$, $R_3=COC_6H_5$, $R_4=CN$



IV: $R_1=R_2=OMe$, $R_3=COOEt$, $R_4=OEt$
XI: $R_1=R_2=OMe$, $R_3=CN$, $R_4=OEt$
XII: $R_1+R_2=OCH_2O$, $R_3=CN$, $R_4=OEt$
XIII: $R_1=OMe$, $R_2=OCH_2C_6H_5$, $R_3=CN$, $R_4=OEt$
XIV: $R_1=R_2=OMe$, $R_3=CN$, $R_4=C_6H_5$
XV: $R_1=OMe$, $R_2=OCH_2C_6H_5$, $R_3=CN$, $R_4=C_6H_5$
XVI: $R_1+R_2=OCH_2O$, $R_3=CN$, $R_4=C_6H_5$

Chart 2

Heating of V, VI, and VII with a 5 molar equivalent of triethyl phosphite at 160—170° for 20 hr afforded the corresponding 3-cyano-4-ethoxy-6,7-disubstituted-quinolines (XI, XII, and XIII) in fairly good yields. In the infrared (IR) spectra, the absorption bands due to the carbonyl and to the nitro group disappeared and the band attributable to C=N double bond appeared at 1620—1630 cm^{-1}. Furthrmore, the nuclear magnetic resonance (NMR) spectra also showed signals reasonably due to the quinoline derivatives, as shown in the experimental section. Accordingly, formation of the quinoline derivative was found in the case of *trans*-configuration in the present reaction as well as in *cis*-configuration in diethyl benzylidenemalonate. On the other hand, the treatment 3,4-disubstituted-6-nitrobenzylidenebenzoylacetonitriles (VIII, IX, and X), having a benzoyl group instead of an ethoxycarbonyl one, with triethyl phosphite gave the corresponding quinolines (XIV, XV, and XVI respectively) in poor yields. Accordingly, a probable explanation of the formation of IX would involve the initial formation of phosphate (Vb) *via* Va due to the conjugated addition to the olefinic group. Because of the presence of the nitrile group, by the nucleophilic solvent $P(OEt)_3$, the olefinic group has an increased susceptibility, so leading to free rotation

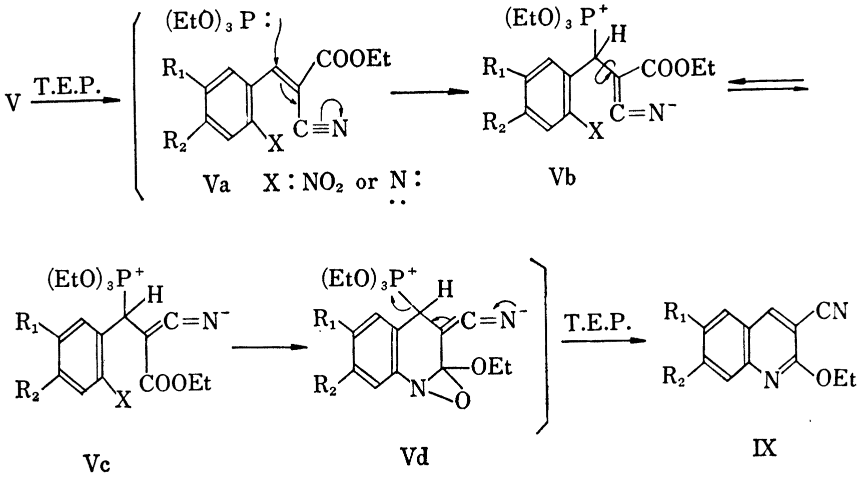


Chart 3

about the "double bond". The intramolecular cyclization of Vc through nitrene[16] led to the formation of IX. The poor yield in the syntheses of XIV, XV, and XVI seems to result from a hindrance of free rotation because of the presence of the bulky benzoyl group.

Experimental

All melting points were uncorrected. IR spectra were taken with a Hitachi EPI-S_2 spectrometer and ultraviolet (UV) spectra were taken on a Hitachi Model 124 spectrometer. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer and NMR spectra were taken on a Hitachi R-20 spectrometer with tetramethylsilane as an internal standard.

Ethyl 3,4-Dimethoxy-6-nitrobenzylidenecyanoacetate (V)——A mixture of 4.2 g of 6-nitroveratraldehyde, 2.5 g of ethyl cyanoacetate, 7.2 ml of Ac_2O and 3.0 g of $KHCO_3$ was heated on a water-bath for 2 hr. After cooling, the crystals separated were collected by filtration and washed with 50% AcOH and H_2O on filter. Recrystallization from EtOH gave 3.3 g (61.1%) of cyanoacetate (V) as yellow leaflets, mp 112—114°. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1730 (C=O). NMR (in $CDCl_3$) δ: 1.40 (3H, triplet, $J=7.5$ cps, $-CH_2C\underline{H}_3$), 4.01 (6H, singlet, $2\times OCH_3$), 4.40 (2H, quartet, $J=7.5$ cps, $-C\underline{H}_2CH_3$), 7.35 (1H, singlet, aromatic H), 7.72 (1H, singlet, aromatic H), 8.70 ppm (1H, singlet, olefinic H). *Anal.* Calcd. for $C_{14}H_{14}O_6N_2$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.12; H, 4.62; N, 9.13.

Ethyl 3,4-Methylenedioxy-6-nitrobenzylidenecyanoacetate (VI)——A mixture of 4.0 g of 6-nitropiperonal, 2.5 g of ethyl cyanoacetate, 5 drops of piperidine, and 50 ml of EtOH was heated under reflux on a water-bath for 8 hr. Collection of crystals separated, followed by recrystallization from EtOH, gave 3.7 g (63.8%) of cyanoacetate (VI) as yellow needles, mp 137—139°. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1730 (C=O). NMR (in $CDCl_3$) δ: 1.40 (3H, triplet, $J=7.5$ cps, $CH_2C\underline{H}_3$), 4.38 (2H, quartet, $J=7.5$ cps, $C\underline{H}_2CH_3$), 6.20 (2H, singlet, OCH_2O), 7.10 (1H, singlet, aromatic H), 7.66 (1H, singlet, aromatic H), 8.58 ppm (1H, singlet, olefinic H). *Anal.* Calcd. for $C_{13}H_{10}O_6N_2$: C, 53.80; H, 3.47; N, 9.65. Found: C, 54.24; H, 3.65; N, 9.95.

Ethyl 4-Benzyloxy-3-methoxy-6-nitrobenzylidenecyanoacetate (VII)——A mixture of 5.8 g of O-benzyl-6-nitrovanillin, 2.5 g of ethyl cyanoacetate, 7.2 ml of Ac_2O, and 3.0 g of $KHCO_3$ was heated on a water-bath for 8 hr. After cooling, the crystals separated were collected and washed with H_2O. Recrystallization from EtOH gave 5.8 g (88.0%) of VII as yellow needles, mp 128—130°. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1730 (C=O). NMR (in $CDCl_3$) δ: 1.40 (3H, triplet, $J=7.5$ cps, $CH_2C\underline{H}_3$), 4.00 (3H, singlet, OCH_3), 4.38 (2H, quartet, $J=7.5$ cps, $C\underline{H}_2CH_3$), 5.23 (2H, singlet, $OC\underline{H}_2C_6H_5$), 7.38 (6H, broad singlet, $CH_2C_6\underline{H}_5$ and aromatic H), 7.78 (1H, singlet, aromatic H), 8.70 ppm (1H, singlet, olefinic H). *Anal.* Calcd. for $C_{20}H_{18}O_6N_2$: C, 62.82; H, 4.75; N, 7.33. Found: C, 63.31; H, 4.64; N, 7.62.

3,4-Dimethoxy-6-nitrobenzylidenebenzoylacetonitrile (VIII)——A mixture of 10.6 g of 6-nitroveratraldehyde, 6.8 g of benzoylacetonitrile, 5 drops of piperidine, and 50 ml of EtOH was heated under reflux on a water-bath for 2 hr. After cooling, the crystals separated were collected, washed with a small amount of EtOH and recrystallized from EtOH–dimethylformamide to give 5.5 g (34.0%) of VIII as yellow prisms, mp 160—162°. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1670 (C=O). NMR (in $CDCl_3$) δ: 4.03 (6H, singlet, $2\times OCH_3$), 7.40—8.39 (7H, multiplet, aromatic H), 8.39 ppm (1H, singlet, olefinic H). *Anal.* Calcd. for $C_{18}H_{14}O_5N_2$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.64; H, 4.14; N, 8.09.

4-Benzyloxy-3-methoxy-6-nitrobenzylidenebenzoylacetonitrile (IX)——A mixture of 4.3 g of O-benzyl-6-nitrovanillin, 7.3 g of benzoylacetonitrile, 5 drops of piperidine, and 50 ml of EtOH was heated under reflux on a water-bath for 2 hr. After cooling, the crystals separated were collected, washed with a small amount of EtOH and recrystallized from $CHCl_3$–EtOH to give 10.6 g (44.2%) of IX as yellow needles, mp 171—173°. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1670 (C=O). NMR (in $CDCl_3$) δ: 4.06 (3H, singlet, OCH_3), 5.27 (2H, singlet, benzylic H), 7.36—8.07 (7H, multiplet, aromatic H), 8.42 ppm (1H, singlet, olefinic H). *Anal.* Calcd. for $C_{24}H_{18}O_5N_2$: C, 69.56; H, 4.38; N, 6.76. Found: C, 69.98; H, 4.19; N, 6.81.

3,4-Methylenedioxy-6-nitrobenzylidenebenzoylacetonitrile (X)——A mixture of 9.8 g of 6-nitropiperonal, 7.3 g of benzoylacetonitrile, 5 drops of piperidine, and 50 ml of EtOH was heated under reflux on a water-bath for 2 hr. After cooling, the crystals separated were collected, washed with a small amount of EtOH and recrystallized from $CHCl_3$–EtOH to give 9.8 g (60.9%) of X as yellow prisms, mp 198—200° (decomnp.). IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1670 (C=O). NMR (in $CDCl_3$) δ: 6.20 (2H, singlet, $-OCH_2O-$), 7.38—8.08 (7H, multiplet, aromatic H), 8.26 ppm (1H, singlet, olefinic H). *Anal.* Calcd. for $C_{17}H_{10}O_5N_2$: C, 63.35; H, 3.13; N, 8.69. Found: C, 62.90; H, 3.49; N, 8.63.

3-Cyano-2-ethoxy-6,7-dimethoxyquinoline (XI)——A solution of 2.7 g of V in 8.3 g of triethyl phosphite was refluxed at 160—170° in an oil-bath for 20 hr under a current of N_2. After cooling, the crystals separated were collected, and recrystallized from EtOH to give 1.2 g (50%) of XI as pale yellow leaflets, mp 178—181°. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1625 ($\rangle$C=N–). NMR (in $CDCl_3$) δ: 1.48 (3H, triplet, $J=7.5$ cps, $CH_2C\underline{H}_3$), 3.95, 4.01 (each 3H, two singlet, $2\times OCH_3$), 4.55 (2H, quartet, $J=7.3$ cps, $C\underline{H}_2CH_3$), 6.93, 7.13 (each 1H, two singlets, aromatic H), 8.13 ppm (1H, singlet, C_4-H). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.19; H, 5.67; N, 10.94.

3-Cyano-2-ethoxy-6,7-methylenedioxyquinoline (XII)——A mixture of 2.9 g of VI and 8.3 g of triethyl phosphite was heated at 160—170° in an oil-bath for 20 hr under a current of N_2. After cooling, the crystals separated were collected and recrystallized from EtOH to give 1.3 g (54.2%) of XII as pale brown needles, mp 192—193°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1615 (>C=N–). NMR (in $CDCl_3$) δ: 1.46 (3H, triplet, $J=7.5$ cps, $CH_2C\underline{H}_3$), 4.56 (2H, quartet, $J=7.5$ cps, $C\underline{H}_2CH_3$), 6.08 (2H, singlet, OCH_2O), 6.93, 7.10 (2H, each singlet, aromatic H), 8.80 ppm (1H, singlet, C_4-H). *Anal.* Calcd. for $C_{13}H_{10}O_3N_2$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.76; H, 4.28; N, 11.45.

7-Benzyloxy-3-cyano-2-ethoxy-6-methoxyquinoline (XIII)——A mixture of 1.7 g of VII and 4.2 g of triethyl phosphite was refluxed and then treated in the same manner as in case of VI. Recrystallization from EtOH afforded 0.8 g (53.3%) of XIII as yellow needles, mp 186—187°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1620 (>C=N–). NMR (in $CDCl_3$) δ: 1.47 (3H, triplet, $J=7.5$ cps, $CH_2C\underline{H}_3$), 3.95 (3H, singlet, OCH_3), 4.53 (2H, quartet, $J=7.5$ cps, $C\underline{H}_2CH_3$), 5.26 (2H, singlet, benzylic H), 6.90, 7.20 (2H, each singlet, aromatic H), 7.40 (5H, broad singlet, aromatic H), 8.12 ppm (1H, singlet, C_4-H). *Anal.* Calcd. for $C_{20}H_{18}O_3N_2$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.42; H, 5.33; N, 8.47.

3-Cyano-6,7-dimethoxy-2-phenylquinoline (XIV)——A mixture of 1.7 g of VIII and 8.3 g of triethyl phosphite was refluxed at 160—170° in an oil-bath for 20 hr under a current of N_2. After removal of a lower boiling substance by distillation under reduced pressure, the resulting viscous syrup was chromatographed on silica gel. Evaporation of the benzene eluate, followed by recrystallization from benzene–hexane, afforded 300 mg of XIV as colorless prisms, mp 172—174°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1625 (>C=N–). NMR (in $CDCl_3$) δ: 4.06 (6H, singlet, $2\times OCH_3$), 7.07—8.05 (7H, multiplet, aromatic H), 8.43 ppm (1H, singlet, (C_4-H). Mass Spectrum *m/e*: 290 (M^+). *Anal.* Calcd. for $C_{18}H_{14}O_2N_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.66; H, 5.04; N, 9.51.

7-Benzyloxy-3-cyano-6-methoxy-2-phenylquinoline (XV)——A mixture of 4.14 g of IX and 10 g of triethyl phosphite was refluxed at 160—170° in an oil-bath for 20 hr under a current of N_2, and then treated in the same manner as in the case of XIV. Recrystallization from benzene–hexane afforded 150 mg of XV as colorless prisms, mp 181—183°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200 (C≡N), 1628 (>C=N–). NMR (in $CDCl_3$) δ: 4.03 (3H, singlet, OCH_3), 5.28 (2H, singlet, benzylic H), 7.25—7.60 (7H, multiplet, aromatic H), 7.70—8.05 (5H, multiplet, aromatic H), 8.35 ppm (1H, singlet, C_4-H). *Anal.* Calcd. for $C_{24}H_{18}O_2N_2$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.25; H, 5.35; N, 7.68.

3-Cyano-6,7-methylenedioxy-2-phenylquinoline (XVI)——A mixture of 3.2 g of X and 10 g of triethyl phosphite was refluxed and then treated in the same manner as in the case of XIV. Recrystallization from benzene–hexane afforded 200 mg of XVI as colorless needles, mp 220—221°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡N), 1625 (>C=N–). NMR (in $CDCl_3$) δ: 6.13 (2H, singlet, OCH_2O), 7.02, 7.20 (2H, each singlet, aromatic H), 7.30—8.04 (5H, multiplet, aromatic H), 8.30 ppm (1H, singlet, C_4-H). *Anal.* Calcd. for $C_{17}H_{10}O_2N_2$: C, 74.44; H, 3.68; N, 10.21. Found: C, 74.24; H, 3.76; N, 10.21.

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