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Synthesis and Cycloaddition Reaction of 2-Cyano-3-indoleacetonitriles

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The reactions of 3-acylindoles [3-indolecarbaldehyde (**1**), 3-acetylindole (**12**), 3-benzoylindole (**13**), and *N*-substituted 3-indolecarbaldehydes (**20a—d**)] with diethyl phosphorocyanidate (DEPC) in the presence of lithium cyanide (LiCN) are described. Treatment of **1** with DEPC and LiCN gave a mixture of (*E*)- and (*Z*)-3-cyanomethylene-1-diethylphosphono-2-hydroxyindolines (**2** and **3**). On the other hand, reaction of **12**, **13** and **20a—d** with DEPC and LiCN afforded 2-cyano-3-indoleacetonitrile derivatives (**16**, **19** and **21a—d**). Strong base-induced cycloaddition reactions of 2-cyano-1-methyl-3-indoleacetonitrile (**21a**) with carbon–carbon triple bonds were carried out and gave the corresponding condensation products, 1-amino-4-cyanocarbazoles (**22a—e**), 6-amino-11-cyanobenzo[*b*]carbazole (**23**), pyrido[4,3-*b*]carbazole (**25**), and pyrido[3,4-*b*]carbazole (**26**), in moderate yields.

Keywords——diethyl phosphorocyanidate; cyanophosphorylation; 3-cyanomethyleneindoline; 2-cyano-3-indoleacetonitrile; orthoquinodimethane; acetylenic dienophile; 1-amino-4-cyano-carbazole; benzo[*b*]carbazole; pyrido[4,3-*b*]carbazole; pyrido[3,4-*b*]carbazole

In the previous papers, we reported that diethyl phosphorocyanidate [DEPC, $(EtO)_2P(O)CN$] reacts with a variety of aromatic ketones and α,β-unsaturated ketones in the presence of lithium cyanide (LiCN) to give the corresponding cyanophosphates, which were readily converted into α,β-unsaturated nitriles[1] and β-cyano-α,β-unsaturated ketones,[2] respectively. In particular, we were interested in the transformation of α,β-unsaturated ketone cyanophosphates (enone cyanophosphates) into conjugated allylic phosphates *via* a boron trifluoride etherate ($BF_3 \cdot Et_2O$)-catalyzed allylic rearrangement.[3] In connection with our studies on the enone cyanophosphates, we describe here the reaction of 1-substituted and unsubstituted 3-acyl(formyl, acetyl and benzoyl)indoles with DEPC and LiCN, involving a full account of the previous brief communication.[4]

Reaction of 3-Acylindoles with DEPC

Treatment of 3-indolecarbaldehyde (**1**) with DEPC (3 eq) and LiCN (3 eq) in tetrahydrofuran (THF) at $-5\,^{\circ}C$ afforded a mixture of (*E*)- and (*Z*)-3-cyanomethyleneindolines (**2** and **3**) in 85% yield, of which the former was predominant. The reaction of **1** with equimolar DEPC and LiCN was rather slow, and the products (**2** and **3**) were obtained in low yields, together with recovery of **1**. The (*E*)- and (*Z*)-stereochemistries were supported by the proton nuclear magnetic resonance (^{1}H-NMR) spectra, which showed the signal due to H-4 in **2** at δ 8.21, deshielded by the anisotropic effect of the CN group from that (δ 7.47) of **3**.[5] Confirmation of the structures of **2** and **3** was performed by the following chemical means : namely the (*Z*)-isomer (**3**) was isomerized to the (*E*)-isomer (**2**) by treatment with silica gel (SiO_2) in benzene. Catalytic hydrogenation of **2** over 5% palladium on charcoal (Pd–C) gave a mixture of **4** and **5** in the ratio of 7 : 3 in 40% yield. The *cis*- and *trans*-stereochemistries of the ring-junction of **4** and **5** were assigned on the basis of the coupling constants[6] in the ^{1}H-NMR

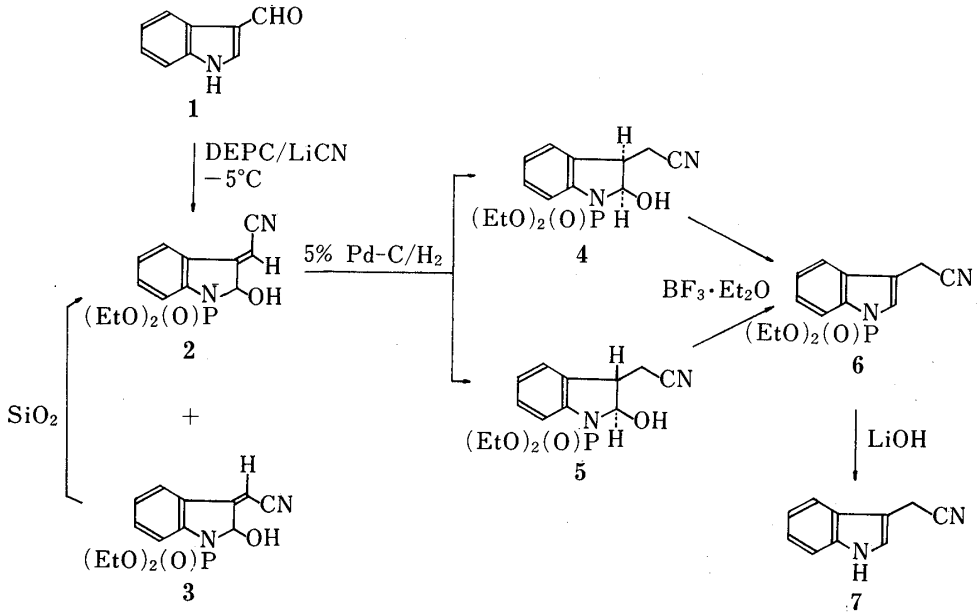


Chart 1

spectrum ($J=7$ Hz in **4** and $J=2$ Hz in **5**) of the H-2 signal, which appeared as a doublet at δ 5.94 in **4** and at δ 4.65 in **5** in the ^{1}H-NMR spectrum. These compounds were converted to the indole derivative (**6**) by treatment with $BF_3 \cdot Et_2O$ in benzene. Hydrolysis of **6** with lithium hydroxide (LiOH) in 95% ethanol (EtOH) gave indole-3-acetonitrile (**7**).[7] The mechanism of the formation of **2** (and **3**) from **1**, involving [3,3]sigmatropic rearrangement of the cyanophosphate, is proposed to be as shown in Chart 2. This mechanistic proposal is further supported by the following experiments. Treatment of **9a**, prepared according to the literature[8] from the enamine (**8**), with DEPC and LiCN in THF at 0 °C afforded a mixture of **2** and **3** in 92% yield. Similarly, the *N*-benzoyl and *N*-tosyl derivatives (**9b** and **9c**)[8] were converted to the corresponding 3-cyanomethyleneindolines (**10b** and **10c**) in 36% and 73% yields, respectively. Oxidation of **2** (and **3**), **10b** and **10c** with active manganese dioxide

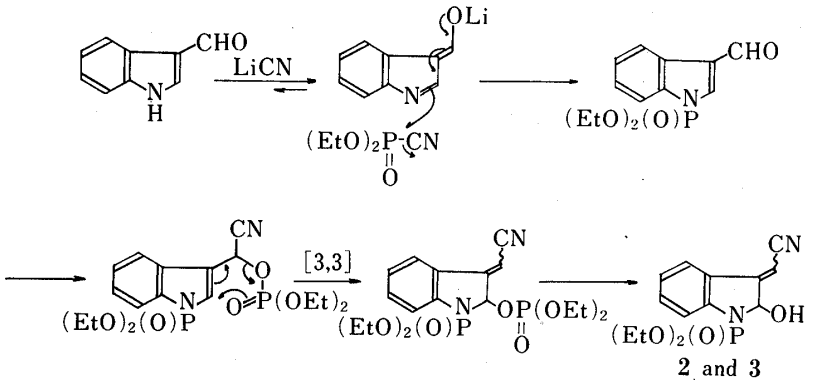
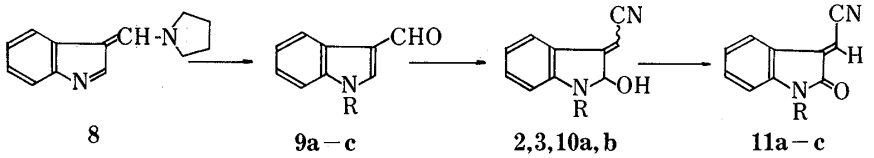


Chart 2



a : R=P(O)(OEt)$_2$ **b** : COPh **c** : $SO_2C_6H_4CH_3$

Chart 3

(MnO_2) gave the oxindoles (**11a—c**) in good yields; these products may be useful in the synthesis of alkaloids having an oxindole nucleus.[5] The (*E*)-stereochemistries of **11a—c** were established from their ^{1}H-NMR spectral data given in Experimental, particularly the signals ascribable to the C_4-protons at δ 8.14—8.24, deshielded by the anisotropic effect of the CN group.

On the other hand, treatment of 3-acetylindole (**12**) with DEPC and LiCN at room temperature gave 2-cyano-3-(α-methyl)indoleacetonitrile (**16**) in 87% yield, along with the *N*-diethylphosphono ketone (**14**) and *N*-diethylphosphono dinitrile (**15**) in low yields. Hydrolysis of **15** with LiOH in 95% EtOH at room temperature provided **16** in good yield. Furthermore, reaction of **14** with DEPC and LiCN was carried out under the conditions described for **12**, giving **15** and **16**. However, 1-methyl-3-acetylindole was recovered unchanged under the conditions described above. Thus, **14** was proved to be an intermediate of this reaction. The structure of **16** was supported by the following spectroscopic data [^{1}H-NMR: δ 1.83 (3H, d, J=7.3 Hz, $CHCH_3$), 4.35 (1H, q, J=7.3 Hz, $CHCH_3$). Infrared (IR) spectrum (KBr): 3330 (NH), 2230 and 2210 cm^{-1} (CN). Mass spectrum (MS) *m/e*: 195 (M^+)]. Therefore, we suggest that **16** is formed from the cyanophosphate *via* **14** by the mechanism depicted in Chart 5.

Analogously, 3-benzoylindole (**13**) reacted with DEPC and LiCN to give a mixture of **17** (20%), **18** (27%) and **19** (23%). Hydrolysis of **18** with LiOH gave **19** in a quantitative yield.

As mentioned above, **1** reacted with DEPC and LiCN to give a mixture of **2** and **3**, while 1-substituted 3-indolecarbaldehydes (**20a—d**), whose carbonyl groups are more reactive than that of 1-methyl-3-acetylindole, gave 1-substituted 2-cyano-3-indoleacetonitriles (**21a—d**), *via*

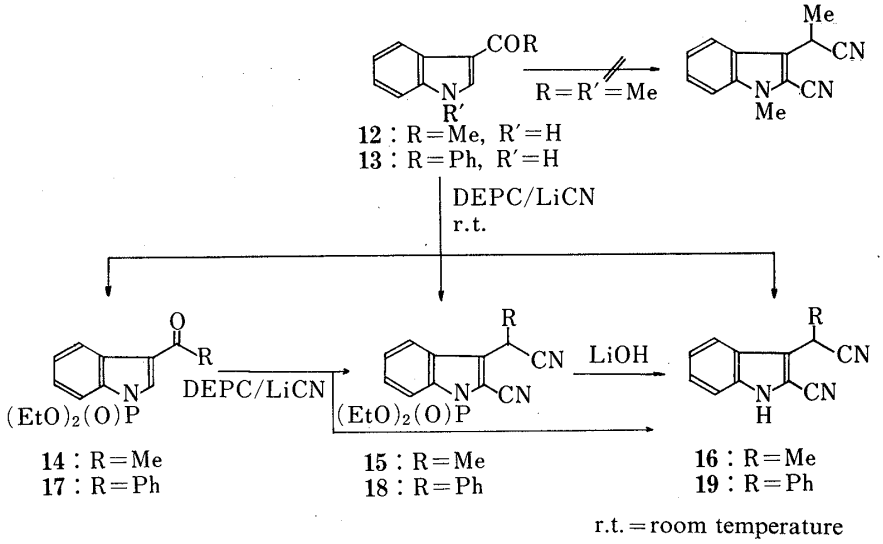


Chart 4

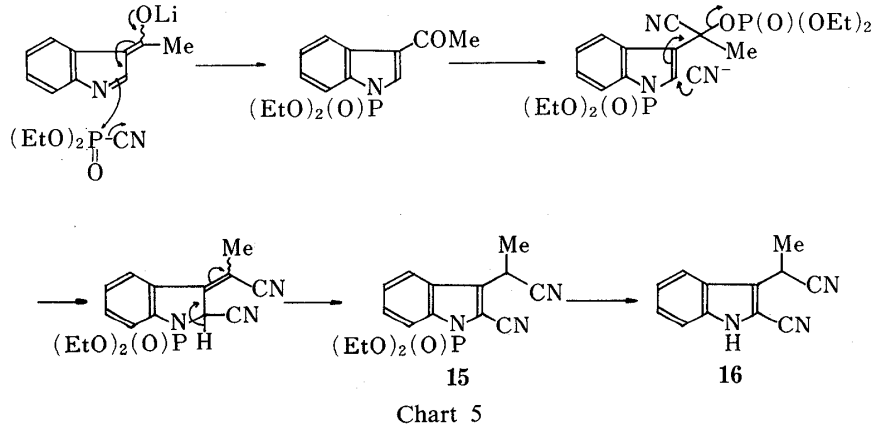
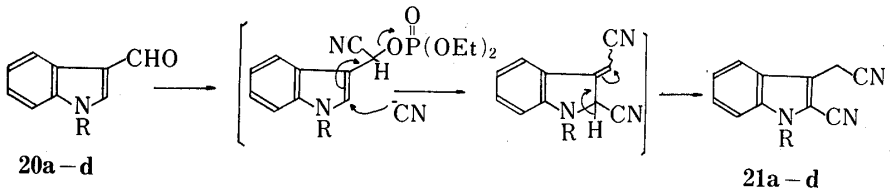


Chart 5

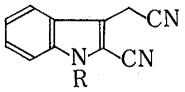


20a–d **21a–d**

a : R=Me **b** : R=Et **c** : R=CH_2Ph **d** : R=Ph

Chart 6

TABLE I. 2-Cyano-3-indoleacetonitrile Derivatives



Compd. No.	R	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
21a	Me	164—165	92	Benzene	$C_{12}H_9N_3$	73.83	4.65	21.53
						(74.09	4.44	21.32)
21b	Et	95—96	86	Ligroin	$C_{13}H_{11}N_3$	74.62	5.30	20.08
						(74.51	5.29	20.31)
21c	CH_2Ph	135—137	100	iso-PrOH	$C_{18}H_{13}N_3$	79.68	4.83	15.49
						(79.41	4.64	15.52)
21d	Ph	109—110	96	iso-PrOH	$C_{17}H_{11}N_3$	79.36	4.31	16.33
						(79.31	4.29	16.48)

the cyanophosphates, in excellent yields as shown in Chart 6. The results are summarized in Table I.

From the results described above, it became clear that 3-indolecarbaldehyde (**1**) reacts with DEPC and LiCN to give 3-cyanomethylene-2-hydroxyindolines (**2** and **3**), while 1-substituted 3-indolecarbaldehydes (**20a—d**) afforded 2-cyano-3-indoleacetonitriles (**21a—d**).

Cycloaddition Reaction

Extensive studies have been done on strong base-induced cycloaddition reactions of homophthalic[9] and heterohomophthalic anhydrides[10] with carbon–carbon triple bonds leading to *peri*-hydroxy polycyclic aromatic and heteroaromatic compounds. In this connection, reactions of **21a** with dienophiles in the presence of a strong base were carried out. Deprotonation of **21a** by treatment with sodium hydride (NaH) in THF at −5 °C yielded a dark-red solution, presumably due to formation of the so-called orthoquinodimethane intermediate.[11] After addition of 1.5 eq of acetylenic dienophile (dimethyl or diethyl acetylenedicarboxylate, methyl or ethyl propiolate, or ethyl tetrolate) to the mixture, the whole was stirred at room temperature to give the corresponding 1-amino-4-cyanocarbazole (**22a—d**). The results are summarized in Table II. The ^{1}H-NMR spectra of the diesters (**22a** and **22b**) showed the signal due to H-5 at δ 8.27, while the signals of the mono-esters (**22c**, **22d** and **22e**) appeared at δ 8.56, 8.57 and 8.63, respectively. Thus, it seems reasonable to assume that the ester groups in **22c** and **22d** and **22e** are attached to the C_2-position. Treatment of **21a** with 1.2 eq of benzyne [generated *in situ* from bromobenzene in the presence of lithium diisopropylamide (LDA)], in THF gave 6-amino-11-cyano-5-methylbenzo[*b*]carbazole (**23**) in 64% yield, together with a trace of 6,11-*o*-benzenobenzo[*b*]carbazole (**24**), the MS showed molecular ion peaks at *m/e*: 271 (**23**) and *m/e*: 347 (**24**). Finally, the cycloaddition of **21a** with 3,4-didehydropyridine[12] (generated *in situ* from 3-chloropyridine with LDA at −78 °C) in

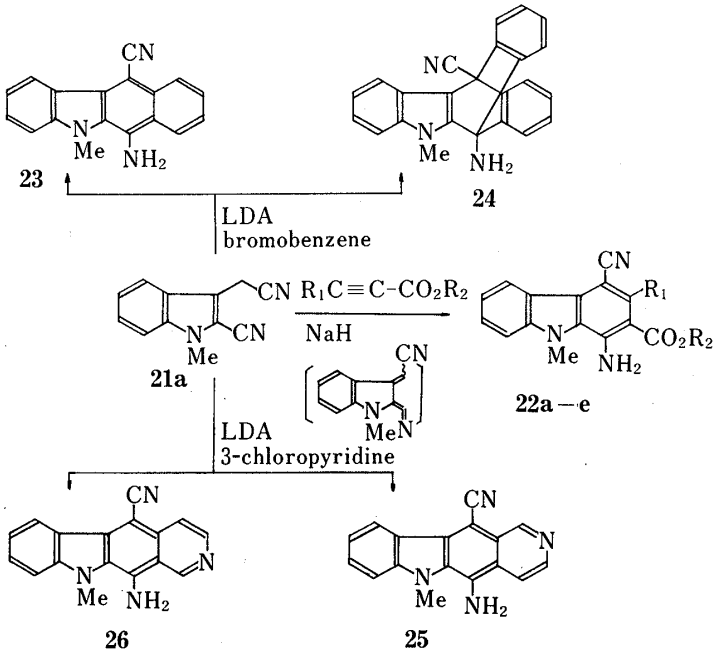
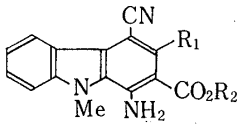


Chart 7

TABLE II. 1-Amino-4-cyanocarbazole Derivatives



Compd. No.	R_1	R_2	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
							C	H	N
22a	CO_2Me	Me	179—180	62	Benzene	$C_{18}H_{15}N_3O_4$	64.09	4.48	12.46
							(64.38	4.62	12.65)
22b	CO_2Et	Et	167—168	62	Benzene	$C_{20}H_{19}N_3O_4$ 1/4 H_2O	64.94	5.31	11.36
							(65.10	5.21	11.52)
22c	H	Me	259—260	45	CH_3CN	$C_{16}H_{13}N_3O_2$	68.80	4.69	15.05
							(69.04	4.72	15.31)
22d	H	Et	194—195	55	Benzene	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
							(69.36	5.01	14.58)
22e	Me	Et	170—171	50	Benzene	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67
							(70.44	5.62	13.87)

TABLE III. ^{1}H-NMR Data for Azabenzo[*b*]carbazole Derivatives (**25** and **26**) in DMSO-d_6 (300 MHz)

Compound	H-1	H-2, H-3 and H-4	H-7	H-8	H-9 and H-10
25	8.57 dd J=7.9, 2.5 Hz	7.37—7.78 m	7.86 bd J=5.5 Hz	8.51 b	9.86 b
26	8.60 dd J=7.9, 2.5 Hz	7.37—7.78 m	9.45 s		8.37 and/or 8.47 d J=6.3 Hz

THF was carried out and gave pyrido[4,3-*b*]carbazole (**25**) (45%), together with an isomeric pyrido[3,4-*b*]carbazole (**26**) (27%), which was separated by column chromatography. The ^{1}H-NMR spectrum of **23** showed the H-1 and H-9 proton signals at deshielded position (δ 8.51 and/or 8.58) owing to the anisotropic effect of the CN group. It is well known that the signals of α-protons of the pyridine nucleus generally appear at lower field than the others. The identities of the products (**25** and **26**) were evident from their ^{1}H-NMR spectra, as summarized in Table III: three signals (attributable to H-1, H-8 and H-10) of **25** and four signals (attributable to H-1, H-7, H-9 and H-10) of **26** appeared at lower field than the others.

Experimental

All melting points are uncorrected. The IR spectra were recorded on a JASCO IRA-1, and ^{1}H-NMR spectra on a Varian XL-300 (300 MHz) spectrometer with tetramethylsilane as an internal standard. MS were recorded with a Hitachi M-80 spectrometer. The solvent for extraction was a mixture of benzene–ethyl acetate (EtOAc) (1 : 1). For column chromatography, SiO_2 (Merck 7734) was used.

General Procedure for Reaction of 3-Acylindoles (1, 12, 13 and 20a—d) with DEPC and LiCN——A mixture of a 3-acylindole (1 mmol), DEPC (3 mmol) and LiCN (3 mmol) in THF (10 ml) was stirred at room temperature for 1 h (in the case of **1**, the reaction was carried out at -5—0 °C). After removal of the THF by evaporation, the residue was dissolved in water (10 ml) and benzene–EtOAc (1 : 1) (50 ml). The organic layer was separated, and washed with water (10 ml × 2) and saturated NaCl solution (10 ml). Drying over anhyd. Na_2SO_4 followed by evaporation gave the corresponding crude product. The *N*-phosphonates usually exhibited strong absorption bands at 1240—1290 and 970—1100 cm^{-1} in the IR spectra. The ^{1}H-NMR spectra of the *N*-phosphorates showed multiplets at δ 1.30—1.42 (6H, 2 × $OCH_2C\underline{H}_3$) and δ 4.05—4.20 (4H, 2 × $OC\underline{H}_2CH_3$).

(*E*)- and (*Z*)-3-Cyanomethylene-1-diethylphosphono-2-hydroxyindolines (2 and 3)——The crude products, obtained by the general procedure from **1** (145 mg, 1 mmol), DEPC (489 mg, 3 mmol) and LiCN (99 mg, 3 mmol), were purified by column chromatography. The first fraction of the benzene–EtOAc (5 : 1) eluate gave **3** (59 mg) as crystals, which were recrystallized from benzene–*n*-hexane, mp 159—160 °C. IR (KBr): 3200 (OH), 2200 (CN), 1620 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.53 (1H, d, J=5.3 Hz, OH), 5.81 (1H, d, J=2.0 Hz, CHCN), 6.36 (1H, br s, H-2), 7.0—7.40 (3H, m, Ar-H), 7.47 (1H, dd, J=7.9, 2.5 Hz, H-4). MS *m/e*: 308 (M^+). *Anal.* Calcd for $C_{14}H_{17}N_2O_4P$: C, 54.54; H, 5.56; N, 9.09. Found: C, 54.45; H, 5.55; N, 9.13. The second fraction eluted with the same solvent gave a mixture of **2** and **3** (132 mg) as an oil. The third fraction eluted with the same solvent gave **2** (72 mg) as an oil. IR (film): 3300—3160 (OH), 2200 (CN), 1620 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.35 (1H, m, OH), 5.60 (1H, d, J=2 Hz, CHCN), 6.10 (1H, d, J=2 Hz, H-2), 7.07—7.42 (3H, m, Ar-H), 8.21 (1H, dd, J=7.9, 2.5 Hz, H-4). MS *m/e*: 308 (M^+). High-resolution MS Calcd for $C_{14}H_{17}N_2O_4P$: 308.0922. Found: 308.0924. Total yield of a mixture of **2** and **3** was 85%.

(*E*)-1-Benzoyl-3-cyanomethylene-2-hydroxyindoline (10b)——The crude product, obtained by the general procedure from **9b** (2.49 g, 10 mmol), DEPC (4.89 g, 30 mmol) and LiCN (990 mg, 30 mmol), was purified by column chromatography. The benzene–EtOAc (10 : 1) eluate gave **10b** (858 mg, 31%) as crystals, which were recrystallized from ether, mp 141—143 °C. IR (Nujol): 3350 (OH), 2200 (CN), 1650 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.55 (1H, br s, OH), 5.66 (1H, d, J=2 Hz, CHCN), 6.35 (1H, br s, H-2), 7.35—7.90 (8H, m, Ar-H), 8.28 (1H, dd, J=7.9, 2.5 Hz, H-4). MS *m/e*: 276 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_2O_2 \cdot 1/5H_2O$: C, 72.95; H, 4.46; N, 10.01. Found: C, 72.94; H, 4.63; N, 10.19.

(*E*)-3-Cyanomethylene-2-hydroxy-1-*p*-tolunesulfonylindoline (10c)——The crude product, obtained by the general procedure from **9c** (897 mg, 3 mmol), DEPC (1.47 g, 9 mmol) and LiCN (297 mg, 9 mmol), was purified by column chromatography. The benzene–EtOAc (10 : 1) eluate gave **10c** (713 mg, 73%) as crystals, which were recrystallized from EtOH, mp 181—182 °C. IR (Nujol): 3340 (OH), 2200 (CN), 1350 and 1165 (SO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s, CH_3), 4.18 (1H, d, J=4.6 Hz, OH), 5.59 (1H, d, J=2 Hz, CHCN), 6.05 (1H, m, H-2), 7.40—7.95 (7H, m, Ar-H), 8.17 (1H, dd, J=7.9, 2.5 Hz, H-4). *Anal.* Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58. Found: C, 62.51; H, 4.31; N, 8.72.

3-Acetyl-1-diethylphosphonoindole (14), 2-Cyano-1-diethylphosphono-3-(α-methyl)indoleacetonitrile (15) and 2-Cyano-3-(α-methyl)indoleacetonitrile (16)——The crude product, obtained by the general procedure from **12** (1.59 g, 10 mmol), DEPC (4.89 g, 30 mmol) and LiCN (990 mg, 30 mmol), was purified by column chromatography. The first fraction of the benzene–EtOAc (20 : 1) eluate gave **16** (1.68 g, 87%) as crystals, which were recrystallized from benzene–*n*-hexane, mp 96—97 °C. IR (KBr): 3300 (NH), 2230 and 2210 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, d, J=7.3 Hz, $CHC\underline{H}_3$), 4.35 (1H, q, J=7.3 Hz, $C\underline{H}CH_3$), 7.30—7.44 (3H, m, Ar-H), 7.88 (1H, dd, J=7.9, 2.5 Hz, H-4), 8.99 (1H, br s, NH). MS *m/e*: 195 (M^+). *Anal.* Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.71; H, 4.67; N, 21.70. The second fraction eluted with the same solvent gave **15** (240 mg, 7.3%) as an oil. IR (film): 2215 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, d, J=7.0 Hz, $CHCH_3$), 4.12—4.42 (5H, m, $C\underline{H}CH_3$ and 2 × $OC\underline{H}_2CH_3$), 7.20—7.40 (2H, m, Ar-H), 7.93 and 8.14 (each 1H, each dd, J=7.9, 2.5 Hz, H-4 and/or H-7). MS

m/e: 331 (M^+). The benzene–EtOAc (10 : 1) eluate gave **14** (85 mg, 2.9%) as an oil. IR (film): 1660 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, CH_3), 7.35—7.41 (2H, m, Ar-H), 7.66 (1H, br d, J=7.5 Hz, H-4), 8.16 (1H, s, H-2), 8.42 (1H, br d, J=7.5 Hz, H-7). MS: *m/e* 295 (M^+).

3-Benzoyl-1-diethylphosphonoindole (17), 2-Cyano-1-diethylphosphono-3-(α-phenyl)indoleacetonitrile (18) and 2-Cyano-3-(α-phenyl)indoleacetonitrile (19)——The crude product, obtained by the general procedure from **13** (633 mg, 3 mmol), DEPC (1.47 g, 9 mmol) and LiCN (297 mg, 9 mmol), was purified by column chromatography. The first fraction of the benzene–EtOAc (20 : 1) eluate gave **19** (165 mg, 20%) as crystals, which were recrystallized from benzene–ligroin, mp 160—161 °C. IR (KBr): 3300 (NH), 2230 and 2210 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.31 (1H, s, CH), 7.20—7.80 (9H, m, Ar-H), 12.70 (1H, s, NH). MS *m/e*: 257 (M^+). *Anal.* Calcd for $C_{17}H_{11}N_3$: C, 79.36; H, 4.31; N, 16.33. Found: C, 79.62; H, 4.41; N, 16.45. The second fraction eluted with the same solvent gave **18** (318 mg, 27%) as crystal, which were recrystallized from ether, mp 95—96 °C. IR (KBr): 2220 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.40 (1H, s, CH), 7.48—8.04 (9H, m, Ar-H). MS *m/e*: 393 (M^+). *Anal.* Calcd for $C_{21}H_{20}N_3O_3P$: C, 64.12; H, 5.12; N, 10.68. Found: C, 64.37; H, 5.19; N, 10.43. The third fractions eluted with the same solvent gave **17** (236 mg, 22%) as an oil. IR (KBr): 1660 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.28—8.0 (9H, m, Ar-H), 7.45 (1H, s, H-2). MS *m/e*: 375 (M^+).

2-Cyano-1-methyl-3-indoleacetonitrile (21a)——This was prepared from **20a** (159 mg, 1 mmol). IR (KBr): 2240 and 2210 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s, CH_3), 4.35 (2H, s, CH_2CN), 7.25—7.83 (4H, m, Ar-H). MS *m/e*: 195 (M^+).

2-Cyano-1-ethyl-3-indoleacetonitrile (21b)——This was prepared from **20b** (865 mg, 5 mmol). IR (Nujol): 2240 and 2220 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7.3 Hz, $NCH_2C\underline{H}_3$), 3.99 (2H, s, CH_2CN), 4.35 (2H, q, J=7.3 Hz, $NC\underline{H}_2CH_3$), 7.26—7.77 (4H, m, Ar-H).

1-Benzoyl-2-cyano-3-indoleacetonitrile (21c)——This was prepared from **20c** (1.18 g, 5 mmol). IR (Nujol): 2235 and 2220 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.01 (2H, s, CH_2CN), 5.46 (2H, s, NCH_2), 7.15—7.81 (9H, m, Ar-H).

2-Cyano-1-phenyl-3-indoleacetonitrile (21d)——This was prepared from **20d**[13] (1.07 g, 4.84 mmol). IR (KBr): 2250 and 2230 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.08 (2H, s, CH_2CN), 7.26—7.86 (9H, m, Ar-H).

Isomerization of 3 to 2——A solution of **3** (31 mg, 0.1 mmol) in benzene (10 ml) containing SiO_2 (200 mg) was vigorously stirred at room temperature for 30 h. The reaction was monitored by thin layer chromatography (TLC) (SiO_2, benzene : EtOAc = 5 : 1). After removal of the SiO_2 by filtration, the filtrate was concentrated *in vacuo* to give **2** (30 mg), which was identical with an authentic sample (IR and ^{1}H-NMR spectral comparisons).

Catalytic Hydrogenation of 2——A solution of **2** (1.407 g, 4.57 mmol) in EtOH (20 ml) was hydrogenated for 5 h over 5% Pd–C (1.5 g) using a Skita apparatus. The catalyst was removed by filtration, and evaporation of the solvent left a solid, which was recrystallized from EtOH–*n*-hexane to give a mixture of *cis*- and *trans*-1-diethylphosphono-2-hydroxy-3-indolineacetonitriles (**4** and **5**) in the ratio of *ca.* 7 : 3. IR (film): 3260 (OH), 2230 (CN), 1240—1260 (P=O), 970—1100 (P–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) for the *cis*-isomer (**4**) δ: 1.33 (6H, m, 2 × $OCH_2C\underline{H}_3$), 2.87 (2H, m, CH_2CN), 3.73 (1H, m, H-3), 4.20 (4H, m, 2 × $OC\underline{H}_2CH_3$), 4.79 (1H, d, J=3.3 Hz, OH), 5.94 [1H, m, changed to doublet (J=7 Hz) on D_2O treatment, H-2], 7.0—7.35 (4H, m, Ar-H). ^{1}H-NMR ($CDCl_3$) for the *trans*-isomer (**5**) δ: 1.33 (6H, m, 2 × $OCH_2C\underline{H}_3$), 2.68 (2H, m, CH_2CN), 3.50 (1H, m, H-3), 4.10 (4H, m, 2 × $OC\underline{H}_2CH_3$), 4.57 (1H, d, J=3.3 Hz, OH), 5.65 [1H, m, changed to doublet (J=2 Hz) on D_2O treatment]. MS *m/e*: 310 (M^+).

1-Diethylphosphono-3-indoleacetonitrile (6)——$BF_3 \cdot Et_2O$ (142 mg, 1 mmol) was added to a solution of a mixture of **4** and **5** (155 mg, 0.5 mmol) in acetonitrile (5 ml), and the whole was stirred at room temperature for 20 min, then poured into water and extracted. The extract was washed with water, and dried over anhyd. Na_2SO_4. Removal of the solvent gave an oil which was purified by column chromatography. The benzene–MeOH (10 : 1) eluate gave **6** (292 mg, 100%) as an oil. IR (film): 2230 (CN), 1320—1280 (P=O), 1050—960 (P–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.43 (6H, t, J=7.5 Hz, 2 × $OCH_2C\underline{H}_3$), 3.80 (2H, s, CH_2CN), 3.95—4.40 (4H, m, 2 × $OC\underline{H}_2CH_3$), 7.20—7.85 (5H, m, Ar-H). MS *m/e*: 292 (M^+). High-resolution MS Calcd for $C_{14}H_{17}N_2O_3P$: 292.0975. Found: 292.0977.

3-Indoleacetonitrile (7)——A solution of **6** (106 mg, 0.36 mmol) and $LiOH \cdot H_2O$ (46 mg, 1.09 mmol) in 95% EtOH (3 ml) was allowed to stand for 4 h. After removal of the solvent by evaporation, the residue was extracted with EtOAc (20 ml). The extract was washed with saturated aqueous NaCl solution, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was purified by short column chromatography [benzene–EtOAc (20 : 1)] to give **7** (50 mg, 88%), which was identical with an authentic sample (^{1}H-NMR spectral comparison).

1-Diethylphosphono-3-indolecarbaldehyde (9a)——This was prepared according to the literature[8] from **8** (3.96 g, 20 mmol) and diethyl phosphorochloridate (3.78 g, 22 mmol) in EtOH (25 ml) to give **9a** (2.42 g, 43%) as crystals, which were not sufficiently stable for recrystallization. IR (Nujol): 1685 (CO), 1280—1270 (P=O), 1030—960 (P–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (6H, t, J=7.3 Hz, 2 × $OCH_2C\underline{H}_3$), 4.10—4.30 (4H, m, 2 × $OC\underline{H}_2CH_3$), 7.40 (2H, m, Ar-H), 7.33 (1H, m, H-7), 8.13 (1H, s, H-2), 8.35 (1H, m, H-4). MS *m/e*: 281 (M^+).

General Procedure for Preparation of Oxindoles (11a—c)——A solution of 2-hydroxyindoline (1 mmol) in $CHCl_3$ (10 ml) was stirred with active MnO_2 (30 mmol) at room temperature. Removal of the MnO_2 by filtration and concentration of the filtrate left oxindole.

3-Cyanomethylene-1-diethylphosphonooxindole (11a)——This was prepared by the general procedure (reaction time 2.5 h) from **2** (138 mg, 0.448 mmol) as a yellow oil, which was purified by column chromatography [benzene–

EtOAc (5 : 1)], in quantitative yield. IR (film): 2200 (CN), 1740 (CO), 1280—1260 (P=O), 1040—980 (P–O–C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (6H, t, J=7.5 Hz, 2×$OCH_2C\underline{H}_3$), 4.28 (4H, m, 2×$OC\underline{H}_2CH_3$), 6.32 (1H, s, =CHCN), 7.20—7.50 (2H, m, Ar-H), 7.90 (1H, d, J=8 Hz, H-7), 8.17 (1H, dd, J=8, 2.5 Hz, H-4). MS m/e: 306 (M^+). High-resolution MS Calcd for $C_{14}H_{15}N_2O_4P$: 306.0769. Found: 306.0771.

1-Benzoyl-2-cyanomethyleneoxindole (11b)——This was prepared by the general procedure (reaction time 1 h) from **10b** (100 mg, 0.362 mmol) as yellow crystals (90 mg, 92%), which were recrystallized from EtOH, mp 194—195 °C. IR (Nujol): 2200 (CN), 1740 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.30 (1H, s, =CHCN), 7.35—7.73 (7H, m, Ar-H), 7.92 (1H, d, J=7.8 Hz, H-7), 8.24 (1H, dd, J=7.9, 2.5 Hz, H-4). *Anal.* Calcd for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.68; N, 10.21. Found: C, 74.33; H, 3.68; N, 9.95.

2-Cyanomethylene-1-*p*-toluenesulfonyloxindole (11c)——This was prepared by the general procedure (reaction time 40 min) from **10c** (100 mg, 0.307 mmol) as yellow crystals (86 mg, 89%), which were recrystallized from MeOH, mp 188—190 °C. IR (Nujol): 2200 (CN), 1740 (CO), 1380—1170 (SO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s, CH_3), 6.26 (1H, s, =CHCN), 7.27—8.0 (7H, m, Ar-H), 8.14 (1H, dd, J=8, 2.5 Hz, H-4). *Anal.* Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.76; H, 3.89; N, 8.56.

General Procedure for the Hydrolysis of *N*-Diethylphosphonates (15 and 18)——A solution of an *N*-diethylphosphonate (1 mmol) and $LiOH \cdot H_2O$ (3 mmol) in 95% EtOH (15 ml) was stirred at room temperature for 2 h. After removal of the solvent by evaporation, the residue was extracted with EtOAc (20 ml). The extract was washed with saturated aqueous NaCl solution, dried over anhyd. Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography [benzene–EtOAc (20 : 1)] to give pure **16** (100%) or **19** (95%), respectively.

General Procedure for the Cycloaddition of 21a to Dienophiles——A mixture of **21a** (1 mmol) and NaH (80% in mineral oil, 1.5 mmol) in anhyd. THF (30 ml) was stirred at −5 °C for several minutes, then a solution of dienophile (1.5—3 mmol) in anhyd. THF (5 ml) was added dropwise. The reaction mixture was stirred at 40 °C for 5 h. The whole was quenched by the addition of saturated aqueous NH_4Cl (5 ml) and partitioned between 5% acetic acid (5 ml) and $CHCl_3$ (50 ml). The organic layer was washed with saturated aqueous NaCl (10 ml), dried over anhyd. Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using benzene–EtOAc (10 : 1) as the eluting solvent to give the corresponding adduct.

Dimethyl 1-Amino-4-cyano-9-methylcarbazole-2,3-dicarboxylate (22a)——This was prepared from **21a** (195 mg, 1 mmol) and dimethyl acetylenedicarboxylate (213 mg, 1.5 mmol). IR (KBr): 3320 (NH_2), 2200 (CN), 1725 and 1690 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.87 and 3.99 (each 3H, each s, 2×CO_2CH_3), 4.17 (3H, d, NCH_3), 6.45 (2H, s, NH_2), 7.13—7.55 (3H, m, Ar-H), 8.27 (1H, dd, J=8, 2.5 Hz, H-5). MS m/e: 337 (M^+).

Diethyl 1-Amino-4-cyano-9-methylcarbazole-2,3-dicarboxylate (22b)——This was prepared from **21a** (195 mg, 1 mmol) and diethyl acetylenedicarboxylate (255 mg, 1.5 mmol). IR (KBr): 3500 and 3340 (NH_2), 2220 (CN), 1720 and 1680 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 and 1.47 (each 3H, each t, J=7.3 Hz, 2×$CO_2CH_2C\underline{H}_3$), 4.17 (3H, s, NCH_3), 4.36 and 4.44 (each 2H, each q, J=7.3 Hz, 2×$CO_2C\underline{H}_2CH_3$), 6.49 (2H, s, NH_2), 7.15—7.53 (3H, m, Ar-H), 8.27 (1H, dd, J=8, 2.5 Hz, H-5). MS m/e: 365 (M^+).

Methyl 1-Amino-4-cyano-9-methylcarbazole-2-carboxylate (22c)——This was prepared from **21a** (195 mg, 1 mmol) and methyl propiolate (125 mg, 1.5 mmol). IR (KBr): 3480 and 3330 (NH_2), 2200 (CN), 1670 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s, CO_2CH_3), 4.23 (3H, s, NCH_3), 6.84 (2H, s, NH_2), 7.28—7.60 (3H, m, Ar-H), 8.16 (1H, s, H-3), 8.59 (1H, d, J=8 Hz, H-5). MS m/e: 279 (M^+).

Ethyl 1-Amino-4-cyano-9-methylcarbazole-2-carboxylate (22d)——This was prepared from **21a** (195 mg, 1.5 mmol) and ethyl propiolate (147 mg, 1.5 mmol). IR (KBr): 3480 and 3340 (NH_2), 2220 (CN), 1675 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7.3 Hz, $CO_2CH_2C\underline{H}_3$), 4.20 (3H, s, NCH_3), 4.40 (2H, q, J=7.3 Hz, $CO_2C\underline{H}_2CH_3$), 4.86 (2H, s, NH_2), 8.16 (1H, s, H-3), 8.57 (1H, dd, J=7.9, 2.5 Hz, H-5). MS m/e: 293 (M^+).

Ethyl 1-Amino-4-cyano-3,9-dimethylcarbazole-2-carboxylate (22e)——This was prepared from **21a** (195 mg, 1 mmol) and ethyl tetrolate (336 mg, 3 mmol). IR (KBr): 3450 and 3330 (NH_2), 2220 (CN), 1670 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.3 Hz, $CO_2CH_2C\underline{H}_3$), 2.73 (3H, s, CH_3), 4.13 (3H, s, NCH_3), 4.45 (2H, q, J=7.3 Hz, $CO_2C\underline{H}_2CH_3$), 5.85 (2H, s, NH_2), 7.26—7.57 (3H, m, Ar-H), 8.63 (1H, dd, J=8, 2.5 Hz, H-5). MS m/e: 307 (M^+).

Reaction of 21a with Benzyne——A 10% *n*-BuLi hexane solution (6.5 ml, 10 mmol) was added dropwise to a solution of diisopropylamine (1.01 g, 10 mmol) in anhyd. THF (10 ml) with stirring over a period of 10 min. After completion of the addition, stirring was continued for a further 10 min. A solution of **21a** (585 mg, 3 mmol) and bromobenzene (942 mg, 6 mmol) in THF (10 ml) was added with stirring. Stirring was continued for a further 20 min and the whole was acidified with 5% acetic acid. During these procedures, the temperature was kept at −60 °C. The reaction mixture was concentrated *in vacuo* and extracted. The extract was washed with saturated aqueous $NaHCO_3$, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The remaining crude solid was recrystallized from acetonitrile to give 6-amino-11-cyano-5-methylbenzo[*b*]carbazole (**23**) (520 mg, 65%) as yellow crystals, mp 282—285 °C. IR (KBr): 3400 (NH_2), 2210 (CN) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.19 (3H, s, NCH_3), 6.72 (2H, s, NH_2), 7.29—8.14 (4H, m, Ar-H), 8.51 and 8.58 (each 1H, each dd, J=7.9, 2.5 Hz, C_1- and/or C_{10}-H). MS m/e: 271 (M^+). *Anal.* Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.58; H, 4.66; N, 15.70. The filtrate from the recrystallization was concentrated *in vacuo* and the residue was purified by column chromatography. The fraction eluted with

benzene–EtOAc (5 : 1) gave 6-amino-11-cyano-6,11-dihydro-5-methyl-6,11-*o*-benzenobenzo[*b*]carbazole (**24**) (28 mg, 2.6%) as crystals. Recrystallization from benzene caused partial decomposition and therefore the melting point was not determined. IR (KBr): 3400 (NH_2), 2250 (CN) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.23 (3H, s, NCH_3), 5.76 (2H, s, NH_2), 6.40—8.44 (12H, m, Ar-H). MS *m/e*: 347 (M^+). High-resolution MS Calcd for $C_{24}H_{17}N_3$: 347.1424. Found: 347.1422.

Reaction of 21a with 3,4-Didehydropyridine——After the preparation of LDA from diisopropylamine (404 mg, 4 mmol), a solution of **21a** (390 mg, 2 mmol) in anhyd. THF (10 ml) was added with stirring. A solution of 3-chloropyridine (452 mg, 4 mmol) in THF (10 ml) was added over a period of 20 min. During these procedures, the temperature was kept at −78 °C. The reaction flask was then removed from the cooling bath and stirred at room temperature for 30 min. THe whole was acidified with 50% acetic acid, neutralized with aqueous saturated $NaHCO_3$, then concentrated *in vacuo*. The remaining crude solid was extracted with hot EtOAc in a Sohxlet apparatus for 24 h. Concentration of the EtOAc extract gave a yellow solid, which was purified by Al_2O_3 column chromatography (Merck Art 1097). The first fraction of the $CHCl_3$–MeOH (50 : 1) eluate gave 11-amino-5-cyano-10-methylpyrido[3,4-*b*]carbazole (**26**) (147 mg, 27%), which was recrystallized from dimethylformamide (DMF)–H_2O as yellow crystals, mp >290 °C. IR (KBr): 3340 (NH_2), 2190 (CN) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.22 (3H, s, NCH_3), 6.88 (2H, br s, NH_2); other signals are summarized in Table II. MS *m/e*: 272 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.87; H, 4.44; N, 20.31. The second fraction of the $CHCl_3$–MeOH (50 : 1) eluate gave 5-amino-11-cyano-6-methylpyrido[4,3-*b*]carbazole (**25**) (245 mg, 45%), which was recrystallized from DMF–H_2O as yellow crystals, mp >290 °C. IR (KBr): 3340 (NH_2), 2190 (CN) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.22 (3H, s, NCH_3), 7.28 (2H, s, NH_2); other signals are summarized in Table III. MS *m/e*: 272 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.95; H, 4.40; N, 20.56.

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