Chemistry of Diaminomaleonitrile. II. Preparation of the Open-Chain Adduct with Ketone in Phosphorus Pentoxide–Ethanol System[1]

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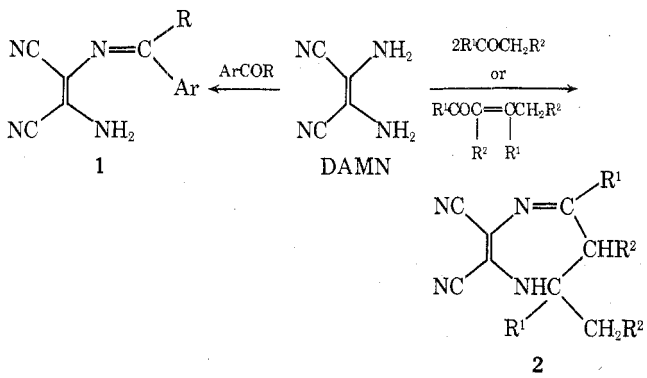
Condensations between diaminomaleonitrile (DAMN) and ketones in phosphorus pentoxide–ethanol gave the open-chain adducts. Aromatic α-ketones and acyl cyanides gave the Schiff bases (**1** and **5**), several of which were converted to alkyl DAMN (**3** and **7**), addition product with methyl vinyl ketone (**4**), and pyrazine derivatives (**6** and **8**). The condensation with β-keto esters and with β-diketones gave another type of adducts, enamines (**9** and **12**), which were converted to 2-substituted 4,5-dicyanoimidazoles (**10** and **11**) and the fragmentation products by α-C–C bond cleavage. Enamines **12** and phosphorus pentoxide in ethanol gave 1,4-diazepines **13**.

In recent years diaminomaleonitrile (DAMN) has received much interest as a source of nitrogen heterocycles.[1-4] The reactions most widely used in those syntheses are condensations with carbonyl compounds. The condensation of DAMN with aldehydes or amides gives Schiff bases, which can be cyclized to imidazoles.[2,5,6] Condensation of DAMN and ketones gives a greater variety of products. This reaction, however, is less clearly understood, since cyclic products are generally obtained in one step and the open-chain adducts have been isolated in few special instances.[2,7,8] Isolation of open-chain adducts and investigation of their chemical properties have now been carried out to extend the synthetic versatility of DAMN.

Schiff Bases of Diaminomaleonitrile and Ketones. From preliminary experiments, phosphorus pentoxide–ethanol was found to be an effective reagent for the condensation of DAMN and ketones under mild conditions. Using this system, condensations with a number of aromatic or heteroaromatic ketones were carried out and Schiff bases **1** were obtained. The results are summarized in Table I. The reaction with dialkyl ketones or α,β-unsaturated ketones under similar conditions gave dihydrodiazepines **2**.

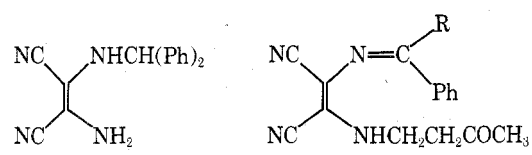


1 2

The condensation proceeded smoothly to give **1** as stable compounds. When a stronger acid ($POCl_3$) was used, it has been reported[2] that the condensation of ketones, including aromatic α-ketones, gave **2** exclusively, and that an isolated Schiff base (**1a**) hydrolyzed in moist air.

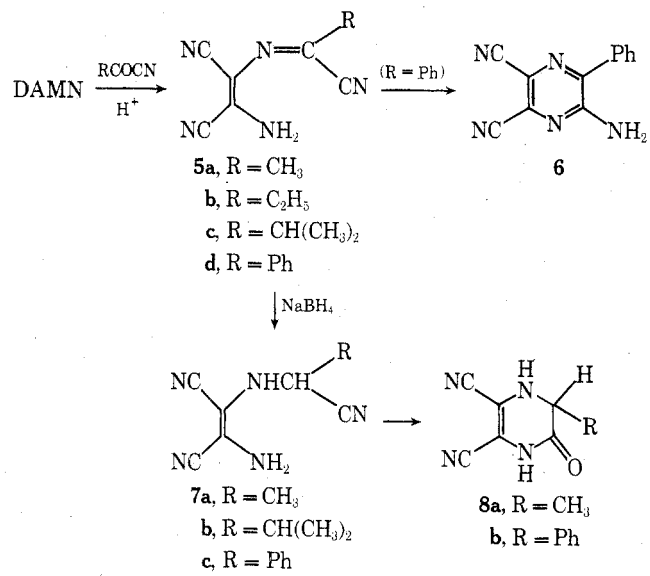
In the present reaction, the electron-deficient ketones condense readily with DAMN to give excellent yields of **1** (Table I). The reaction with *p*-methoxyacetophenone gave an 8% yield of **2** ($R^1 = CH_3$; R^2 = Ph-*p*-OCH_3) after 24 hr of refluxing in ethanol. The reaction failed with 2- and 4-acetylpyridine.

Reduction of the azomethine bond in **1d** (R = Ar = Ph) was carried out with sodium borohydride, giving **3** (Table II) under similar conditions to the reduction of the aldehyde Schiff bases.[2] Reaction of **1d** with methyl vinyl ketone afforded the N′-addition product **4a**. Similarly, treatment of benzylidene DAMN with methyl vinyl ketone gave **4b**.



3 **4a**, R = Ph; **b**, R = H

Condensation of acyl cyanides and DAMN gave the Schiff bases **5** (Table I). This reaction was catalyzed by acids, such as phosphorus pentoxide–alcohol, *p*-toluenesulfonic acid, or a trace of hydrogen bromide which was present in the crude acyl cyanide.



5a, R = CH_3; **b**, R = C_2H_5; **c**, R = $CH(CH_3)_2$; **d**, R = Ph

6

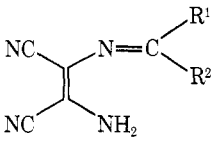
7a, R = CH_3; **b**, R = $CH(CH_3)_2$; **c**, R = Ph

8a, R = CH_3; **b**, R = Ph

When **5d** (R = Ph) was refluxed in ethanol, aminopyrazine **6** was obtained; the other alkyl homologues, **5a–c**, were not cyclized by this treatment. Sodium borohydride reduction of **5a**, **5c**, and **5d** gave the corresponding aminonitriles **7a**, **7b**, and **7c** (Table II). Cyclization of **7a** or **7b** in refluxing ethanol gave tetrahydropyrazines **8a** and **8b**, respectively.

Enamine Derivative of Diaminomaleonitrile. Reaction of DAMN and ethyl acetoacetate with acid catalyst, phosphorus pentoxide–ethanol, or a drop of sulfuric acid gave an enamine **9a**. The structure was evidenced by the vinyl proton singlet at δ 4.43 (1 H), the NH_2 protons broad

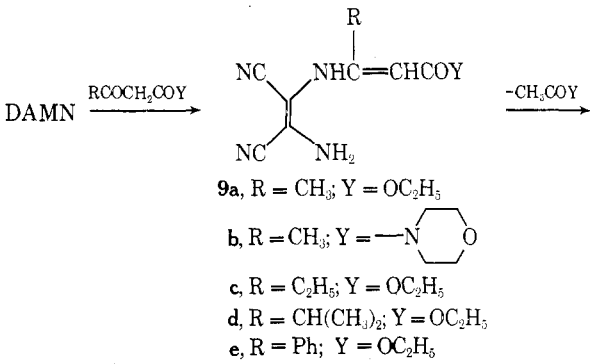
Table I[d]
Schiff Bases of Diaminomaleonitrile



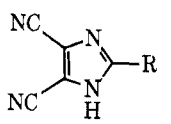
Compd[a] R¹	R²		Reaction conditions	Yield, %	Crystn solvent	Mp, °C	Appearance
CH_3	Ph	(1a)	1 hr, rt[b]	74	*i*-PrOH–acetone	122–123	
CH_3	*p*-NO_2Ph	(1b)	10 min, rt	98	EtOH–acetone	219–220	Orange needles
CH_3	*o*-OHPh	(1c)	46 hr, rt	34	*i*-PrOH	180–182	Yellow needles
Ph	Ph	(1d)	4 hr, rt	93	50% aq EtOH	167–168	Yellow needles
o-OHPh	*o*-OHPh	(1e)	24 hr, rt	60	*i*-PrOH	182–183 dec	Yellow crystals
CH_3	β-Naph	(1f)	30 min, rt	79	EtOH	187–188	Yellow needles
Ph	β-Naph	(1g)	37 hr, ref[c]	46	20% aq EtOH	179–181	Yellow powder
9-Fluorenylidene		(1h)	2.5 hr, ref[c]	68	Benzene	155–156	Red crystals
CH_3	2-Thienyl	(1i)	2 hr, rt	77	EtOH	177–178	Yellow plates
CH_3	2-Furyl	(1j)	1 hr, rt	73	EtOH	174–175	Yellow crystals
CH_3	3-Pyridyl	(1k)	1 hr, rt	82	EtOH	228–230	Yellow crystals
Ph	3-Pyridyl	(1l)	1 hr, ref[c]	71	EtOH	215–216 dec	Yellow crystals
CH_3	CN	(5a)	10 min, rt	41	aq MeOH	222–224	Colorless flakes
C_2H_5	CN	(5b)	10 min, rt	60	aq MeOH	198–199	Colorless needles
$CH(CH_3)_2$	CN	(5c)	10 min, rt	76	aq MeOH	150–152	Colorless flakes
Ph	CN	(5d)	15 min, rt	52	MeOH	184–185	Yellow powder

[a] The molecular structures are supported by spectroscopic data (ir, NMR, and MS) of each compound. [b] Excess of the ketone with several drops of ethanol was used as the medium (rt = room temperature). [c] Refluxed in ethanol. [d] Satisfactory analytical data (±0.2% for C, H, and N) for all compounds in this table and in Tables II and III were submitted for review. Ed.

singlet at δ 6.45 (2 H), and the NH proton singlet at δ 8.78 (1 H) in the NMR (in acetone-d_6 solution with Me_4Si) exhibited by the product.[9] Other enamines similarly prepared are given in Table III.

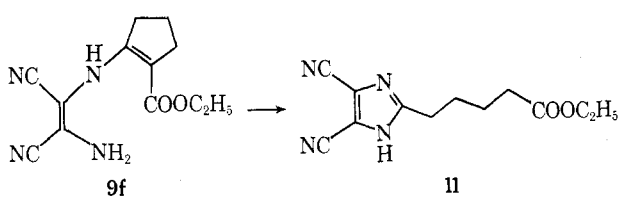


9a, R = CH_3; Y = OC_2H_5
b, R = CH_3; Y = morpholino
c, R = C_2H_5; Y = OC_2H_5
d, R = $CH(CH_3)_2$; Y = OC_2H_5
e, R = Ph; Y = OC_2H_5



10a, R = CH_3
b, R = C_2H_5
c, R = $CH(CH_3)_2$
d, R = Ph

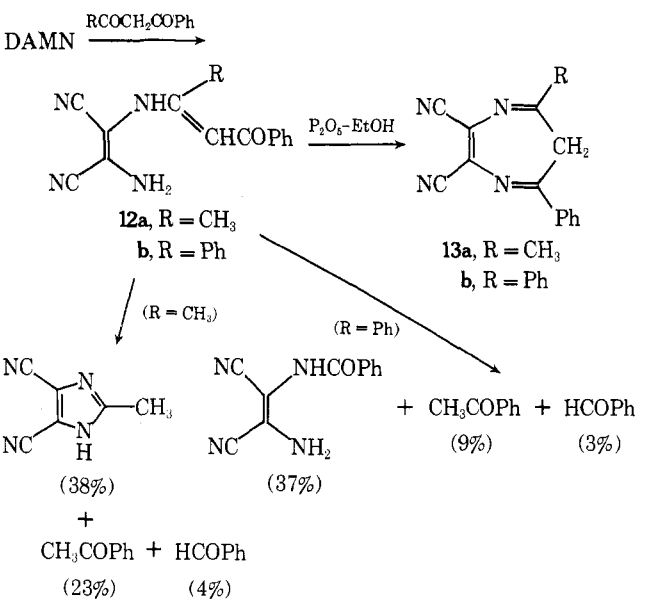
It was found that **9a–e** can be converted to the corresponding 4,5-dicyanoimidazoles (**10a–d**) by refluxing ethanol or butanol. Enamine **9f** gave the corresponding 2-valerate **11**. 4,5-Dicyanoimidazoles, **10** and **11**, are important intermediates for the synthesis of purine derivatives,[10] and



9f **11**

this reaction gives the pure products in good yield by a simple procedure. Similar reaction, a sort of reverse Claisen reaction, has been observed with several aromatic enamines.[11] A reaction of DAMN and ethyl acetoacetate with phosphorus oxychloride gives tetrahydro-6*H*-1,4-diazepine.[2]

Condensation of DAMN with benzoylacetone or dibenzoylmethane in phosphorus pentoxide–ethanol at room temperature gave enamines **12a** and **12b** (Table III), re-



12a, R = CH_3
b, R = Ph

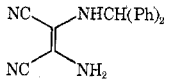
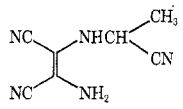
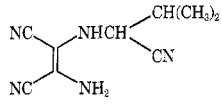
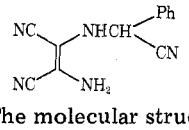
13a, R = CH_3
b, R = Ph

(R = CH_3): (38%) + CH_3COPh + HCOPh (23%) (4%)

(R = Ph): (37%) + CH_3COPh (9%) + HCOPh (3%)

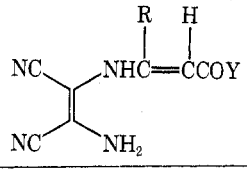
spectively. The structure of **12b**, for example, was evidenced by the vinyl proton singlet at δ 6.38 (1 H), the NH_2 protons broad singlet at δ 7.8 (2 H), and the NH proton singlet at δ 11.50 (1 H) in the NMR (in dimethyl sulfoxide-d_6 solution with Me_4Si). In chemical reactions, however, **12** showed rather ambiguous character. When **12a** or **12b** was heated with phosphorus pentoxide in ethanol 1,4-diazepine **13a** and **13b** were obtained, respectively. Upon heating **12a**

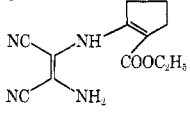
Table II
Alkyl Derivatives of Diaminomaleonitrile

Compd[a]	Starting compd	Yield, %	Mp, °C	Crystn solvent
 (3)	1d	93	217–219	EtOH
 (7a)	5a	54	224–226	aq MeOH
 (7b)	5c	68	229–231	aq MeOH
 (7c)	5d	59	203–204 dec	aq MeOH

[a] The molecular structures are supported by spectroscopic data (ir, NMR, and MS) of each compound.

Table III
Enamine Derivatives of Diaminomaleonitrile



Compd[a] R	Y	Reaction conditions	Yield, %	Crystn solvent	Mp, °C
CH_3	OC_2H_5 (9a)	1 hr, rt	97	*i*-PrOH	152–153
CH_3	 (9b)	5 min, rt	98	EtOH	167–168
C_2H_5	OC_2H_5 (9c)	4 hr, rt[b]	91	*i*-PrOH	133–134[c]
$CH(CH_3)_2$	OC_2H_5 (9d)	30 min, 40°C[b]	62	*i*-PrOH	134–136
C_6H_5	OC_2H_5 (9e)	1 hr, rt	94	*i*-PrOH	141–142
	(9f)	20 min, rt	79	EtOH	188–189
CH_3	C_6H_5 (12a)	1 hr, rt	87	*i*-PrOH	159–160
C_6H_5	C_6H_5 (12b)	1 hr, rt	86	EtOH	158–160

[a] The molecular structures are supported by spectroscopic data (ir, NMR, and MS) of each compound. [b] Neat reaction. [c] Crystal turns brown on standing in moist air.

in wet butanol,[12] 4,5-dicyano-2-methylimidazole (**10a**), acetophenone, and benzaldehyde were isolated. Similar treatment of **12b** gave benzoyl DAMN and hydrolyzed products. In the latter reactions, the process giving the different type of products is unclear, but both **12a** and **12b** undergo their C–C bond cleavage by the treatment.

Experimental Section

Infrared spectra were obtained with KBr disks on a Hitachi Model EPI-G3 spectrometer. NMR determinations were carried out either on a Hitachi Perkin-Elmer R-20B or on a Varian HA-100 spectrometer. The NH and NH_2 proton signals in the spectra were identified from the diminution of the intensity by addition of deuterium oxide. Mass spectra were determined at 70 eV on a Hitachi RMU-6E spectrometer using a solid sample inlet (at 100–150°C). Melting points were measured on a micro hot-stage apparatus and were corrected.

General Procedure of Condensation of Diaminomaleonitrile and Ketones with Phosphorus Pentoxide in Ethanol. Preparation of 1 (Table I), 9 and 12 (Table III). To a solution of DAMN (3.0 g) and the ketone (an equimolecular weight or an excess) in ethanol (80 ml) was added portionwise phosphorus pentoxide (1.3 g). After the reaction (listed in tables), the insoluble products were collected by filtration, washed with cold water, and dried. The soluble products were isolated after concentration of the reaction mixture by a rotary evaporator followed by treatment of the residue with ice–water (50–100 ml).

Preparation of Alkyl Diaminomaleonitrile (3 and 7a–c in Table II). Schiff bases (**1d, 5a, 5c,** and **5d**) were reduced by three equivalents of sodium borohydride in their solution in methanol–tetrahydrofuran mixtures.[2] After stirring at room temperature for 15 min, reaction mixtures were poured into ice–water, giving the corresponding products as fine crystals.

Reaction of Schiff Bases with Methyl Vinyl Ketone. *N*-Diphenylmethylene-*N'*-(3-oxobutyl)diaminomaleonitrile (4a). A mixture of **1d** (3.0 g), methyl vinyl ketone (70 ml), and phosphorus pentoxide (1.5 g) was stirred for 20 min at room temperature. The resulting semisolids were dissolved in ethyl ether (300 ml). The ether solution was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The resulting oil was chromatographed by a column (silica gel–ether) to give yellow crystals, mp 151–153°C from 2-propanol, in 21% yield (0.8 g): NMR (Me_2SO-d_6) δ 2.11 (s, 3, CH_3), 2.72 (t, 2, CH_2), 3.58 (q, 2 CH_2), 7.2 and 7.5 (m, total 10, C_6H_5); ir 2215, 2180, 1718 cm^{-1}.

Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.66; H, 5.30; N, 16.36. Found: C, 73.39; H, 5.35; N, 16.14.

***N*-Benzylidene-*N'*-(3-oxobutyl)diaminomaleonitrile (4b)** was obtained similarly from benzylidene DAMN[13] (2.0 g), methyl

vinyl ketone (20 ml), and phosphorus pentoxide (0.5 g), as yellow needles: mp 156–157°C (from ethanol); yield 37% (1.0 g); NMR (Me_2SO-d_6) δ 2.15 (s, 3, CH_3), 2.88 (t, 2, CH_2), 3.60 (q, 2, CH_2), 7.44 and 7.94 (m, total 6, C_6H_5), 8.23 (s, 1, CH); ir 2230, 2220, 1740 cm^{-1}; MS *m/e* 266 (M^+, rel intensity 26), 223 (11), 209 (20), 208 (17).

Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.55; H, 5.30; N, 21.04. Found: C, 67.74; H, 5.32; N, 20.86.

Condensation of Diaminomaleonitrile with Acyl Cyanides[14] (Table I). α-Cyanoethylidenediaminomaleonitrile (5a). Method A. DAMN (10.8 g) and acetyl cyanide (10.0 g) were added successively to a solution of *p*-toluenesulfonic acid (1.9 g) in dry ether (100 ml). The resultant yellow solids were filtered and dried. The crude product was dissolved in acetone (600 ml) and undissolved solids were removed by filtration. Addition of water (900 ml) to the filtrate gave **5a.**

Method B. To a mixture of acetyl cyanide (22.1 g) and DAMN (16.3 g) was added dropwise a solution of phosphorus pentoxide (0.5 g) in ethanol (3 ml). The crude product was recrystallized from aqueous methanol to give **5a** in 26% yield (6.3 g). **5b** and **5c** were prepared by method B.

α-Cyanobenzylidenediaminomaleonitrile (5d). Benzoyl cyanide (10.8 g) and then DAMN (5.4 g) were added to a solution of phosphorus pentoxide (1.3 g) in methanol (50 ml). The resultant yellow crystals were filtered. Cooling the filtrate gave an additional crop.

2-Amino-5,6-dicyano-3-phenylpyrazine (6). 5d (1.5 g) was refluxed in ethanol (80 ml) for 19 hr and then concentrated. The residue was recrystallized from toluene to give colorless needles, mp 166–167°C, in almost quantitative yield: ir 3410, 3305, 3200, 2230, 1630, 1540, 1500 cm^{-1}; MS (150°C) *m/e* (rel intensity) 222 (9), 221 (M^+, 70), 220 (100).

Anal. Calcd for $C_{12}H_7N_5$: C, 65.15; H, 3.19; N, 31.66. Found: C, 65.17; H, 3.18; N, 31.72.

Cyclization of α-Cyanoalkyldiaminomaleonitrile (7a and 7d). 5,6-Dicyano-3-methyl-1,2,3,4-tetrahydropyrazin-2-one (8a). Phosphorus pentoxide (0.3 g) and **7a** (1.0 g) were refluxed in ethanol (30 ml) for 19 hr. Concentration of the mixture gave **8a** as a colorless powder: mp 241–243°C (from aqueous ethanol); yield 72%; ir 2210, 1700–1690, 1660, 1630 cm^{-1}; MS *m/e* 162 (M^+).

Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.37; N, 34.55. Found: C, 51.63; H, 3.78; N, 34.80.

5,6-Dicyano-3-phenyl-1,2,3,4-tetrahydropyrazin-2-one (8b) was obtained similarly from **7d** in 94% yield as a yellow-orange powder: mp 220–222°C (from aqueous methanol); NMR (Me_2SO-d_6) δ 5.08 (d, 1, CH), 7.35 (s, 5, C_6H_5), 8.31 (d, 1, NH), 10.94 (s, 1, NH).

Anal. Calcd for $C_{12}H_8N_4O$: C, 64.28; H, 3.59; N, 24.98. Found: C, 64.12; H, 3.60; N, 24.97.

Preparation of Imidazoles 10a–d and 11. General Method. The precipitate obtained from the reaction mixture of DAMN and ethyl acylacetates or *N*-acetoacetylmorpholine (see the preparation of 1) was washed with cold water and rapidly dried in vacuo. The solid thus obtained was almost pure compound **9** (Table III) and was refluxed in butanol (ca. 5 g/100 ml) for 24 hr. The reaction mixture was concentrated under reduced pressure.[15] *N*-Acetylmorpholine was removed at 60–80°C (2 mmHg). The resultant tan solid was washed with chloroform and recrystallized. **10a** (R = CH_3)[10a] was prepared in 83% yield from **9a** and in 92% yield from **9b**, the adduct of DAMN and *N*-acetoacetylmorpholine. **10b** (R = C_2H_5)[16] was prepared in 84% yield from **9c**, the adduct of DAMN and ethyl propionylacetate.[17] **4,5-Dicyano-2-isopropylimidazole [10c, R = $CH(CH_3)_2$]** was prepared in 33% yield from **9d**, the adduct of DAMN and ethyl γ-methyl-β-oxovalerate.[17] Recrystallization from water gave colorless flakes: mp 156–157°C; NMR (Me_2SO-d_6) δ 1.29 and 3.0 (total 7, isopropyl protons), 8.0 broad s, 1); MS (100°C) *m/e* (rel intensity) 160 (M^+, 20), 159 (12), 145 ([M – CH_3]$^+$, 100, M* 131.4).

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 60.00; H, 4.87; N, 34.92.

10d (R = Ph)[13] was prepared in 77% yield from **9e**, the adduct of DAMN and ethyl benzoylacetate.

Ethyl 4,5-Dicyanoimidazole-2-valerate (11). 9f prepared from DAMN and 2-ethoxycarbonylcyclopentanone was refluxed in butanol. The evaporated residue was a syrup which was purified by a column (silica gel, benzene–ethyl acetate) to give a colorless oil in 46% yield. A 44% yield of **11** was estimated separately from its silver salt, which was obtained from a methanol solution of the crude syrup and aqueous silver nitrate. The silver salt is insoluble and can be purified by washing with hot ethanol. The ir spectum of the silver salt is similar to that of **11**. The silver salt was heated in an excess of trimethylsilyl chloride for 2 hr. Filtration and treatment of the evaporated filtrate with methanol gave **11** as a colorless liquid.

Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.75; H, 5.64; N, 22.88.

One-step preparations of imidazoles **10** from DAMN and acylacetates gave less satisfactory results. When a mixture of ethyl acetoacetate, DAMN, and phosphorus pentoxide was heated in ethanol without separation of **9a, 10a** was obtained in a 38% yield. The yields by the treatment using other carbonyl compounds follow: 35% (**10a**) from *N*-acetoacetylmorpholine; 64% (**10b**) from ethyl propionylacetate; trace (**10c**) from ethyl γ-methyl-β-oxovalerate; 70% (**10d**) from ethyl benzolyacetate.

2,3-Dicyano-5-methyl-7-phenyl-1,4,6*H*-diazepine (13a). A mixture of **12a** (6.1 g), prepared from DAMN and benzoylacetone (Table III), and phosphorus pentoxide (1.3 g) in ethanol (100 ml) was refluxed for 16 hr and then evaporated. The residual brown syrup was treated with water and extracted with chloroform. The extract was dried with sodium sulfate and the solvent was removed. The residue was crystallized from a small quantity of 2-propanol to give light-tan crystals: yield 18% (1.2 g); mp 126–127°C (from 2-propanol); NMR (Me_2SO-d_6) δ 2.17 (s, 3), 7.5–7.7 and 8.1–8.3 (m, total 5); ir 3050, 2220, 1594, 1530 cm^{-1}; MS (100°C) *m/e* (rel intensity 234 (M^+, 100), 219 ([M – CH_3]$^+$, 76).

Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.54; H, 4.04; N, 23.84.

2,3-Dicyano-5,7-diphenyl-1,4,6*H*-diazepine (13b). A mixture of DAMN (24 g), dibenzoylmethane (50 g), and phosphorus pentoxide (10.5 g) in ethanol (700 ml) was stirred for 1 hr at room temperature. Additional phosphorus pentoxide (10.5 g) was added and the mixture was refluxed for 2 hr. The mixture was concentrated and cooled to give **13b** as crystals. Recrystallization from benzene or acetonitrile gave yellowish plates, mp 249–251°C, yield 73% (48 g). **13b** can be obtained also from **12b** (Table III) and phosphorus pentoxide: ir 3080, 2250, 1607, 1593, 1540, 1460, 1333, 1262, 1200 cm^{-1}; MS (100°C) *m/e* (rel intensity) 219 (11), 193 (3), 103 (100).

Anal. Calcd for $C_{19}H_{12}N_4$: C, 77.01; H, 4.08; N, 18.91. Found: C, 76.89; H, 3.87; N, 18.75.

Fragmentation Reaction of 12. One gram of **12a** or **12b** was refluxed in 20 ml of commercial butanol (containing water, ca. 0.5%) for 24 hr. The reaction mixtures were analyzed by GLC (2-m column Pora Pak Q, 225°C) and the presence of benzaldehyde and acetophenone was detected. Evaporation of the mixtures left solids, which were crystallized from water and identified as **10a** (from **12a**) and benzoyl DAMN (from **12b**) by comparison of spectroscopic data with authentic samples, respectively.

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Registry No.—**1a,** 51802-34-7; **1b,** 55752-07-3; **1c,** 55752-08-4; **1d,** 55752-09-5; **1e,** 57443-93-3; **1f,** 55752-10-8; **1g,** 55752-11-9; **1h,** 55752-12-0; **1i,** 55752-13-1; **1j,** 55752-14-2; **1k,** 55752-15-3; **1l,** 55752-16-4; **3,** 57443-94-4; **4a,** 57443-95-5; **4b,** 57443-96-6; **5a,** 57443-97-7; **5b,** 57443-98-8; **5c,** 57443-99-9; **5d,** 57444-00-5; **6,** 57444-01-6; **7a,** 57444-02-7; **7b,** 57444-03-8; **7c,** 57444-04-9; **8a,** 57444-05-0; **8b,** 57444-06-1; **9a,** 57444-07-2; **9b,** 57444-08-3; **9c,** 57484-04-5; **9d,** 57444-09-4; **9e,** 57444-10-7; **9f,** 57444-11-8; **10c,** 52685-70-8; **11,** 57444-12-9; **12a,** 57444-13-0; **12b,** 57444-14-1; **13a,** 56984-06-6; **13b,** 56984-07-7; DAMN, 1187-42-4; phosphorus pentoxide, 1314-56-3; acetophenone, 98-86-2; *p*-nitroacetophenone, 100-19-6; *o*-hydroxyacetophenone, 118-93-4; benzophenone, 119-61-9; 2,2′-dihydroxybenzophenone, 835-11-0; methyl β-naphthalenyl ketone, 941-98-0; phenyl β-naphthalenyl ketone, 642-29-5; 9*H*-fluoren-9-one, 486-25-9; methyl 2-thienyl ketone, 88-15-3; methyl 2-furyl ketone, 1192-62-7; methyl 3-pyridyl ketone, 350-03-8; phenyl 3-pyridyl ketone, 5424-19-1; acetyl cyanide, 631-57-2; 2-oxobutyronitrile, 4390-78-7; 3-methyl-2-oxobutyronitrile, 42867-39-0; benzoyl cyanide, 613-90-1; ethyl acetoacetate, 141-97-9; *N*-acetoacetylmorpholine, 16695-54-8; ethyl β-oxovalerate, 4949-44-4; ethyl γ-methyl-β-oxovalerate, 7152-15-0; ethyl 3-oxo-3-phenylpropionate, 94-02-0; benzoylacetone, 93-91-4; dibenzoylmethane, 120-46-7; methyl vinyl ketone, 78-94-4; 2-ethoxycarbonylcyclopentanone, 611-10-9.

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Contribution to the Chemistry of Indole. About the 5-(1-Indolyl)-2-pentanone System

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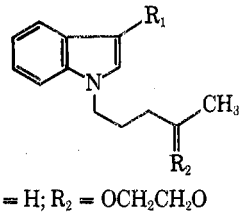
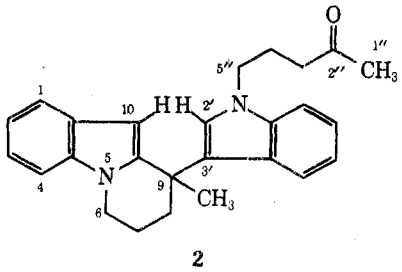
Alkylation of indole with 5-chloro-2-pentanone ethylene ketal gave **1a**. Attempts to hydrolyze the ketal gave **2** instead. The 3-substituted indoles **1b** and **1d** were hydrolyzed to the corresponding ketones **1c** and **1e**. Skatole was alkylated with the same alkylating agent to give **1f**. Hydrolysis gave the pyrido[1,2-*a*]indole **3**.

The alkylation of indole[1] on nitrogen is a well-documented reaction in organic chemistry. As a model for further studies we were interested in the preparation of 5-(1-indolyl)-2-pentanone. It was our intention to obtain this compound from the corresponding ethylene ketal via mild hydrolysis in acidic medium. For this purpose indole was treated with sodium hydride in absolute DMF followed by the addition of 5-chloro-2-pentanone ethylene ketal. The product of this alkylation, 5-(1-indolyl)-2-pentanone ethylene ketal (**1a**), was obtained in 98% yield and gave ir, NMR, and mass spectral data in agreement with the expected structure **1a**.

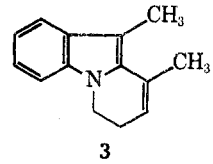
Chart I



1a, $R_1 = H$; $R_2 = OCH_2CH_2O$
b, $R_1 = COOMe$; $R_2 = OCH_2CH_2O$
c, $R_1 = COOMe$; $R_2 = O$
d, $R_1 = CH_2COOMe$; $R_2 = OCH_2CH_2O$
e, $R_1 = CH_2COOMe$; $R_2 = O$
f, $R_1 = CH_3$; $R_2 = OCH_2CH_2O$



2



3

Attempts to remove the protecting group in **1a** via hydrolysis in aqueous acetic acid did not yield the expected ketone. Instead compound **2** of the molecular composition $C_{26}H_{28}N_2O$ (*m/e* 384, M^+) was isolated in 63% yield. This formally represents a condensation between 2 mol of the product of the deketalization less 1 mol of water. One oxygen atom was retained as a saturated keto group as indicated by the presence of an ir band at 1713 cm^{-1} in the spectrum of **2** excluding the presence of an α,β-unsaturated ketone formed via an aldol condensation.

The ^1H NMR spectrum of **2** indicated ten aromatic protons and no vinylic protons, ruling out a double bond in the side chain and pointing to the structure **2**. This product was assumed to arise by intramolecular condensation of the carbonyl group liberated in the hydrolysis of **1a** at the indole 2 position followed by alkylation at C-3 of a second indole unit. Although electrophilic substitution should occur more readily in the β position of indole[1] and particularly of N-alkylated indoles, the ^1H NMR spectrum of **2** did not allow a definitive assignment of the position of the attachment of the second indole nucleus. Thus it was decided to study the ^{13}C NMR of **2** in the hope of establishing the substitution patterns of the two indole nuclei.

Discussion of the ^{13}C NMR Spectrum of 2. The fully proton decoupled spectrum of **2** gave a total of 26 peaks accounting for all the 26 carbon atoms of the product, indicating at the same time that the product on hand consisted of a single isomer.

Shift theory[2] and models from the literature[2a] (the compounds **1a**, **1f**, and **3**, see below, serving as additional models) were used for the calculations. Peaks at 126.7 and 97.7 ppm (see Experimental Section) were assigned to the carbon atoms at position 2' and 10, respectively, based upon the following arguments. The chemical shift for C_2 of an unsubstituted indole[2a] is documented to occur at 125.2 ppm. Methyl substituents in positions 1 and 3 are known to shift the absorption by +4.1 and −2.5 ppm. This is in good agreement with the observed value of 126.7 ppm (calcd