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Preparation and Reactions of 3-(Aminomethylene)-3H-indoles

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A series of 3-(aminomethylene)-3H-indoles (**1a**—**e** and **6a**—**8a**) was prepared by the condensation of 3-indolecarbaldehydes (**2**—**5**) with secondary amines. Among them, 3-(1-pyrrolidinylmethylene)-3H-indoles (**1a** and **6a**—**8a**) were obtained as stable colorless prisms, while 3-(piperidinomethylene)-3H-indole (**1b**) and 3-(morpholinomethylene)-3H-indole (**1c**) readily polymerized in refluxing benzene. Reaction of **1** with electrophiles, such as alkyl and acyl halides, gave 1-substituted 3-aminomethylene-3H-indolium salts, which were converted to the corresponding 1-substituted 3-indolecarbaldehydes by hydrolysis. Reaction of **1** with active methylene compounds proceeded under mild reaction conditions to afford the corresponding condensation products in good yields. Successive reaction of **1** with electrophiles and nucleophiles provided a convenient route to 1,3-disubstituted indole derivatives.

Keywords——conjugated enamine; 3-indolecarbaldehyde; 3-(aminomethylene)-3H-indole; 3-(aminomethylene)-3H-indolium salt; active methylene compounds; 3-(substituted vinyl)indole; gramine; electrophilic reaction; condensation

Conjugated enamines have recently been found to be reactive species for the preparation of various physiologically active compounds, such as alkaloids,[2] steroids,[3] and heterocyclic compounds.[4] Velluz *et al.*[3a] reported a synthesis of 13-propyl-nor-estradiol by the reaction of dienamine with alkyl halide as an electrophile. Further, Büchi *et al.*[2a] described a new synthesis of an indole alkaloid by the condensation of 1-dimethylamino-2-nitroethylene with indole as a nucleophile.

However, there have been few studies yet concerning the reactivity of an enamine conjugated with an electron-withdrawing iminomethyl group, that is, a vinyloguos amidine.[5] Among the vinylogous amidines, we were particularly interested in 3-(aminomethylene)-3H-indoles, which would be useful intermediates for the preparation of indole alkaloids and derivatives of amino acids such as tryptophan. In the present paper, we describe a new preparation procedure and some reactions of 3-(aminomethylene)-3H-indoles with both electrophiles and nucleophiles.

1. Preparation of 3-(Aminomethylene)-3H-indoles

With regard to the preparation of 3-(aminomethylene)-3H-indoles (**1**), Smith[6] obtained 3-(dimethylaminomethylene)-3H-indole (**1f**) by the reaction of indole with Vilsmeier-Haack

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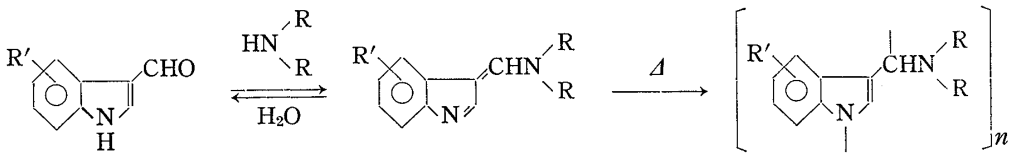
[2] *a*) G. Büchi and C.P. Mak, *J. Org. Chem.*, **42**, 1784 (1977); *b*) T. Onaka, *Tetrahedron Lett.*, **1971**, 4395; *c*) G. Büchi, D.L. Coffen, K. Kocsis, P.E. Sonnet, and F.E. Ziegler, *J. Amer. Chem. Soc.*, **87**, 2073 (1965); *d*) J. Auerbach and S.M. Weinreb, *ibid.*, **94**, 7172 (1972).

[3] *a*) L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, and Ph. Dufay, *Tetrahedron Lett.*, **1961**, 127; *b*) H. Singh, T.R. Bhardwaj, N.K. Ahuja, and D. Paul, *J. Chem. Soc. Perkin I*, **1979**, 305.

[4] *a*) P.S. Mariano, D.D. Mariano, and P.L. Huesmann, *J. Org. Chem.*, **44**, 124 (1979); *b*) T.A. Bryson and R.B. Gammill, *Tetrahedron Lett.*, **1974**, 3963; *c*) R. Gompper and R. Sobotta, *Synthesis*, **1979**, 385; *d*) J. Geevers, G.W. Visser, and D.N. Reinhoudt, *Rec. Trav. Chem.-J. Roy, Neth. Chem.*, **98**, 251 (1979).

[5] *a*) G.A. Youngdale, D.G. Anger, W.C. Anthony, J.P. DaVanzo, M.E. Greig, R.V. Heinzelman, H.H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964); *b*) M. Sekiya, and T. Morimoto, *Chem. Pharm. Bull.*, **23**, 1241 (1975).

[6] G.F. Smith, *J. Chem. Soc.*, **1954**, 3842.



2—5 **1a—e, 6a—8a** **9b, c**

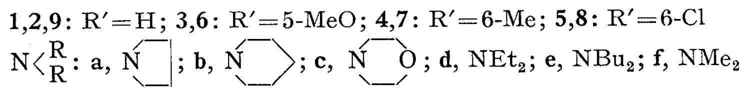
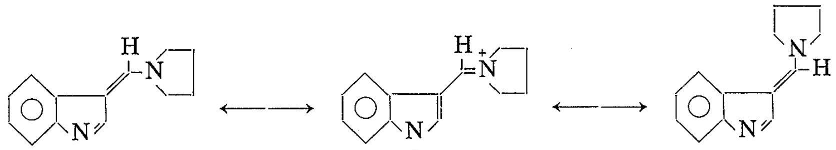


Chart 1

reagent, followed by careful deprotonation of the iminium salt with sodium hydroxide. However, this method was not satisfactory for the isolation of **1**, because hydrolysis of **1** could not be avoided during the deprotonation.[7] In this study, we prepared **1** by the dehydration of indolecarbaldehyde (**2**) with various secondary amines in refluxing benzene.[8]

In the reaction of **2** with pyrrolidine, 3-(1-pyrrolidinylmethylene)-3H-indole (**1a**) was formed as stable colorless prisms, mp 185—190°. The spectra of **1a** showed a molecular ion peak at *m/e* 198, a characteristic absorption of the exo-methylene-3H-indole system[5a,6] at 362 nm, and a broad strong band at 1635 cm^{-1} attributable to C=N and C=C double bonds, but no N-H stretching absorption band of indole was observed. The nuclear magnetic resonance (NMR) spectrum exhibited two sharp singlets at δ 8.10 and 7.61 ppm attributable to the C-2 proton of indole and a side-chain olefinic proton, and the signals due to α- and β-methylene groups of pyrrolidine at 3.0—3.6 and 1.6—2.3 ppm, respectively. Although *E* and *Z* isomers of **1a** exist, as shown in Chart 2, the NMR spectrum of **1a** suggested a single isomer, possibly the less hindered *Z* isomer. In contrast to 6-(1-pyrrolidinyl)-1-azafulvenes, which were reported by Sonnet *et al.*[9] to be a mixture of *E* and *Z* isomers, the formation of the zwitterion of **1a** would facilitate isomerization to the desired isomer. Congeners (**6a**—**8a**) of **1a** with substituents on the indole nucleus were also obtained from the corresponding indolecarbaldehydes (**3**—**5**).



Z-**1a** *E*-**1a**

Chart 2

With piperidine or morpholine, **2** gave a benzene-soluble amorphous solid (**1b**, **c**), which readily polymerized on heating. The polymers (**9b**, **c**) having high melting points were sparingly soluble in organic and inorganic solvents, and were stable in both acids and bases. The mass (MS) spectra of **9b**, **c** showed ion peaks corresponding to the monomer molecular weight that resembled molecular ion peaks. The infrared (IR) spectra were similar to those of 3-(aminomethyl)indoles (**30b**, **c**) except for the N-H stretching band of the indole, and the ultraviolet (UV) spectra resembled those of 1,3-dialkylindoles.[10]

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[7] The 3-(dimethylaminomethylene)-3H-indole (**1f**) prepared according to Smith's method was considerably contaminated with **2** (based on the NMR spectrum).

[8] Although this preparative method for **1** is the conventional method for the preparation of enamines, it has not previously been applied to the present compounds. T. Kobayashi, S. Kajigaeshi, and S. Kanemasa, *Bull. Chem. Soc. Jpn.*, **48**, 3255 (1975).

[9] P.E. Sonnet, J.L. Flippen, and R.D. Gilardi, *J. Heterocyclic Chem.*, **11**, 811 (1974).

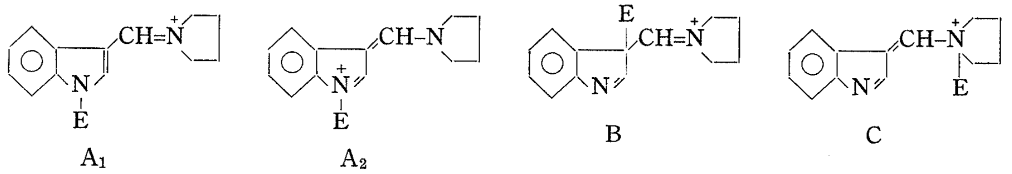
[10] See W.J. Houliham, "The Chemistry of Heterocyclic Compounds, Indoles Part I," John Wiley and Sons, Inc., New York, 1972, pp. 19—21.

On the other hand, the condensation reaction of **2** with acyclic secondary amines, such as diethylamine and dibutylamine, proceeded much more slowly than that with the cyclic amines[11] to give the corresponding 3-(aminomethylene)-3H-indole (**1d**, **e**) as colorless prisms, which were readily susceptible to hydrolysis.

Such a remarkable difference of reactivities among secondary amines towards **2** was also observed by Herz and Brasch[12] in the reactions of 2-pyrrolecarbadehydes. The significantly greater stabilities of **1a** and **6a**—**8a**, having the 1-pyrrolidinyl group, would be attributable to the greater overlap between the electron pair on the nitrogen atom and the π electrons of the double bond.[13]

2. Reaction of 3-(Aminomethylene)-3H-indole with Electrophiles

The reaction sites of vinylogous amidines with attacking electrophiles depends on the properties of the enamine and the reaction conditions.[14] In the case of the reaction of **1**, four types of iminium salts might be formed with various electrophiles, as shown in Chart 3. To clarify the iminium form involved here, protonation and alkylation with alkyl halides were examined using **1a**, a typical stable vinylogous amidine in this study.



A_1 A_2 B C

Chart 3

With a Brønsted acid, such as hydrochloric acid and picric acid, **1a** gave stable iminium salts (**10a**, **b**). With alkyl halides such as methyl iodide, *p*-chlorobenzyl chloride, and ethyl α-bromoacetate, **1a** also gave the iminium salts (**11**, **12**, and **13**, respectively) at room temperture in ethanol, chloroform, or tetrahydrofuran. The structure of the iminium salts thus obtained was confirmed by hydrolysis to give 1-alkyl-3-indolecarbaldehydes (**14**, **15** and **16**). Similarly, with benzoyl chloride and *p*-toluenesulfonyl chloride, 1-benzoyl and 1-(*p*-toluenesulfonyl)-3-indolecarbaldehyde (**17**, **18**) were obtained after hydrolysis. Further, these iminium salts showed maxium absorption in the UV spectra at 346—348 nm, in good accord with those of exomethylene-3H-indolium salts.[5a] These results show that the alkyl halides attack the nitrogen atom of the indole nucleus selectively, so that the iminium salt formed should be A_2 type, having the 1-alkyl-exomethylene-3H-indolium structure.

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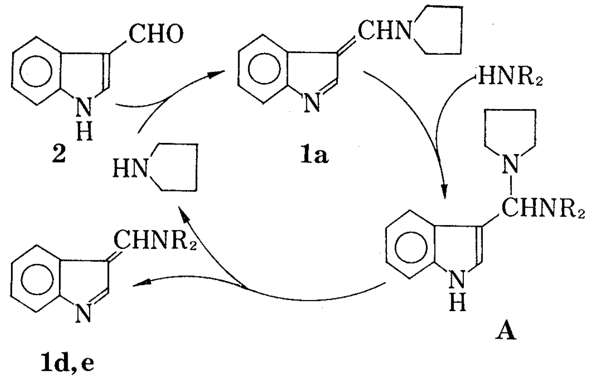
[11] However, this condensation was promoted by the addition of catalytic amounts of **1a**. The catalytic action of **1a** suggests the existence of the reaction cycle shown in Scheme. Namely, Michael-type addition of acyclic secondary amine to **1a** occurs first to form an intermediate (A). Subsequent 1—4 elimination of the labile 1-pyrrolidinyl group of A then produces **1d**, **e**, and the liberated pyrrolidine condenses with **2** to regenerate **1a**.

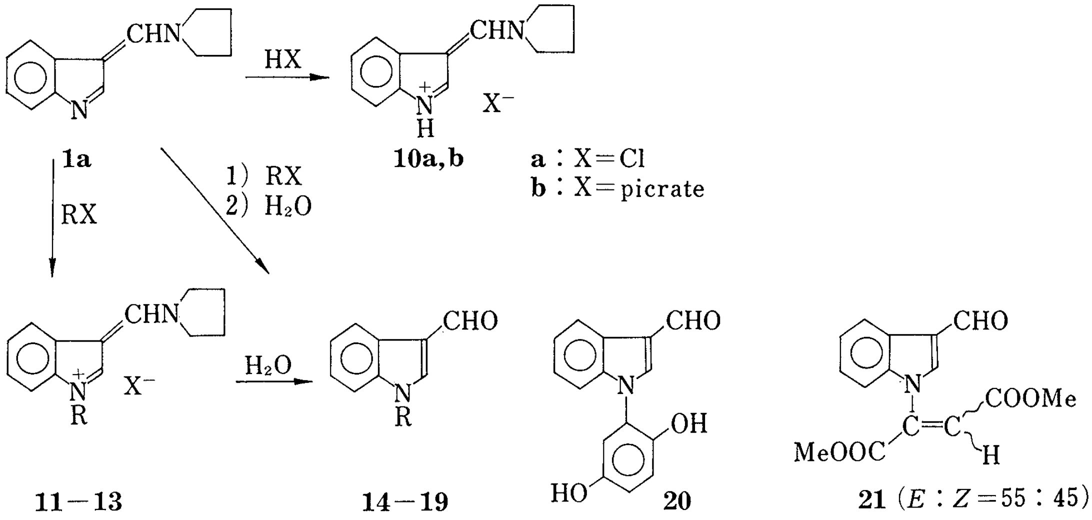


Scheme

[12] W. Herz and J. Brasch, *J. Org. Chem.*, 23, 711 (1958).

[13] See S.K. Malhotra "Enamines: Synthesis, Structure, and Reactions," ed. by A.G. Cook, Marcel Dekker, Inc., New York, 1969, pp. 8—9.

[14] See G.H. Alt "Enamines: Synthesis, Structure, and Reactions," ed. by A.G. Cood, Marcel Dekker, Inc., New York, 1969, pp. 115—168.



11: R=Me, X=I
12: R=p-$ClC_6H_4CH_2$, X=Cl
13: R=CH_2COOEt, X=Br

14: R=Me
15: R=p-$ClC_6H_4CH_2$
16: R=CH_2COOEt
17: R=COC_6H_5
18: R=p-$MeC_6H_4SO_2$
19: R=$CONHC_6H_5$

Chart 4

Reaction of **1a** with other electrophiles such as phenyl isocyanate, *p*-quinone, and dimethyl acetylenedicarboxylate also gave the 1-substituted indolecarbaldehydes (**19**, **20**, and **21**, respectively). It is of interest that Youngdale *et al.*[5a] reported the formation of A_2 type indolium salt in the reaction of 3-(1-methyl-2-pyrrolidinylidene)-3H-indole with methyl iodide.

3. Reaction of 3-(Aminomethylene)-3H-indole with Nucleophiles

Recently Alt and Gallegos[15] reported a condensation of 1-morpholinocyclohexene with cyanoacetic acid to afford α-cyanocyclohexylideneacetic acid, and this reaction was developed by Prout[16] using other active methylene compounds. Severin and Brück[17] reported that an enamine conjugated with a nitro group reacted with active methylene compounds. Prior to our investigation, Dobeneck *et al.* briefly described[18] the formation of 3-(2-oxo-3-indolinylidenemethyl)indole by a condensation of 3-(dimethylaminomethylene)-3H-indole (**1f**) with 2-indolinone in the presence of sodium methoxide in refluxing methanol.

The reaction of **1a** with active methylene compounds proceeded smoothly to give the corresponding condensation products (**22**—**27**) in good yields, as shown in Table I. For example, 3-(3-indolyl)-2-phenylacrylonitrile (**22**) was obtained in 92% yield by the condensation with benzyl cyanide at room temperature without any additional base. It should be noted that 1-morpholinocyclohexene[16] did not react with benzyl cyanide under the same reaction conditions, showing that **1a** is the more reactive enamine.

In contrast to the case of 1-morpholinocyclohexene[16] and 1-dimethylamino-2-nitroethylene,[2a] however, the reactivity of **1a** was greatly reduced in acidic media or even in the reaction with nucleophiles having an acidic moiety, such as cyanoacetic acid. In the latter case, the reactivity was restored by the addition of an equivalent amount of base. In view of these results, **1** may act as a strong base to eliminate a proton from the active methylene compound

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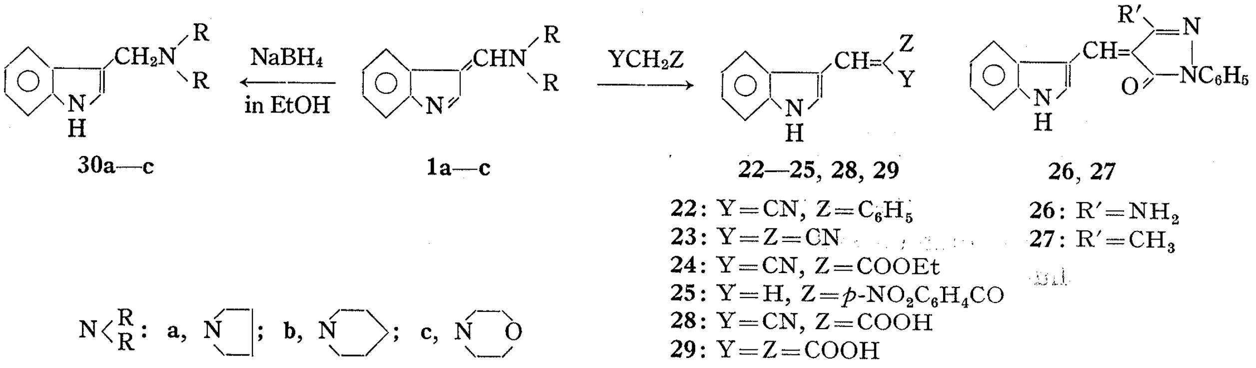
15) G.H. Alt and G.A. Gallegos, *J. Org. Chem.*, **36**, 1000 (1971).
16) F.S. Prout, *J. Org. Chem.*, **38**, 399 (1973).
17) T. Severin and B. Brück, *Chem. Ber.*, **98**, 3847 (1965).
18) H. von Dobeneck, D. Wolkenstein, and G. Blankenstein, *Chem. Ber.*, **102**, 1347 (1969).



22: Y=CN, Z=C_6H_5
23: Y=Z=CN
24: Y=CN, Z=COOEt
25: Y=H, Z=p-$NO_2C_6H_4CO$
28: Y=CN, Z=COOH
29: Y=Z=COOH

26: R′=NH_2
27: R′=CH_3

Chart 5

Table I. Condensation of **1a** with Active Methylene Compounds

Y-CH_2-Z	Reaction[a] time (hr)	Products No.	Yield (%)	mp (°C)
$NCCH_2C_6H_5$	0.5	**22**[b]	92	185
$NCCH_2CN$	0.5	**23**	97	219—220
$NCCH_2COOEt$	0.5	**24**[b]	97	164—165
p-$NO_2C_6H_4COCH_3$	0.5	**25**	90	226—227
3-Amino-1-phenylpyrazoline-5-one	0.5	**26**	94	260—261[d]
3-Methyl-1-phenylpyrazoline-5-one	0.5	**27**	85	235—236
$NCCH_2COOH$	5.0	**28**	11 72[c]	260—261[d]
$HOOCCH_2COOH$	5.0	**29**	15 60[c]	207—208[d]

[a] Reacted in EtOH at 25°.
[b] R.B. van Order and H.G. Lindwall, *J. Org. Chem.*, **10**, 128 (1945).
[c] Reacted in pyridine.
[d] Decomposed.

at the first reaction step. Thus, the condensation of the iminium ion of **1** with the carbanion formed can proceed under mild reaction conditions. However, in the reaction with cyanoacetic acid, the iminium ion can easily be formed by proton donation from the acidic moiety, thus leaving the active methylene compound unactivated. In this case, addition of an equivalent amount of base may be necessary to form the carbanion.

To elucidate the reason for the high reactivity of **1** in the preparation of 3-substituted indoles, the condensation of **1a** with malonic acid was compared with that of **2**. Previously, Rodionov *et al.*[19] and Shaw *et al.*[20] reported that condensation of **2** with excess malonic acid in pyridine using a catalytic amount of piperidine at 40° for 40—45 hours gave decarboxylated 3-(3-indolyl)acrylic acid as a main product, in 32—50% yield. Moffatt[21] reported that the reaction of 1-acetyl-3-indolecarbaldehyde[22] with malonic acid followed by deacylation afforded (3-indolylmethylene)malonic acid (**29**) in 32% yield. In our experiment, the reaction of **1a** with malonic acid in the presence of twice the equimolar amount of triethyl amine gave **29** in 68% yield under mild reaction conditions (in ethanol at room temperature for 5 hours).

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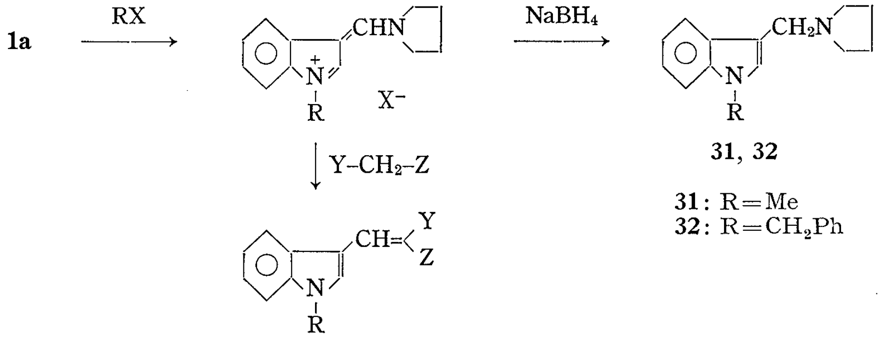
19) V.M. Rodionov and T.K. Veselovskaya, *Zhur. Obshschei Khim.*, **20**, 2202 (1950).
20) K.N.F. Shaw, A. McMillan, A.G. Gudmundson, and K.D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).
21) J.S. Moffatt, *J. Chem. Soc.*, **1957**, 1442.
22) The acetyl substituent at the 1-position activates the carbonyl group. See R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, pp. 405—406.

Further, as the other example of nucleophilic reaction of **1**, the reduction of **1a**—**c** with sodium borohydride in ethanol gave the corresponding gramine derivatives (**30a**—**c**) in good yields.

4. Preparation of 1,3-Disubstituted Indole Derivatives by the Reaction of 3-(Aminomethylene)-3H-indole with Electrophiles and Nucleophiles

As described above, the reaction of **1** with electrophiles gave 1-substituted indolium salts. Since the reaction of iminium salts with nucleophiles is well known,[23] the reaction of nucleophile with the indolium salts was examined.



31, 32

31: R=Me
32: R=CH_2Ph

33—**36**

33: R=CH_2COOEt, Y=C_6H_5, Z=CN
34: R=CH_2COOEt, Y=$CONH_2$, Z=CN
35: R=$CH_2C_6H_4$-*p*-Cl, Y=Z=CN
36: R=COC_6H_5, Y=$CONH_2$, Z=CN

Chart 6

Table II. Preparation of 1,3-Disubstituted Indoles (**33**—**36**)

R–X	Y–CH_2–Z	Base	Reaction conditions			Product		
			solvent	temp (°C)	time (hr)	No.	Yield (%)	mp (°C)
$BrCH_2COOEt$	$C_6H_5CH_2CN$	NaOEt	EtOH-$CHCl_3$	25	6	**33**	72	156—157
$BrCH_2COOEt$	$C_6H_5CH_2CN$	—	DMF	110	70	**33**	60	156—157
$BrCH_2COOEt$	H_2NCOCH_2CN	NaOEt	EtOH-$CHCl_3$	25	1	**34**	95	244—245
p-$ClC_6H_4CH_2Cl$	$NCCH_2CN$	NaOEt	EtOH-$CHCl_3$	25	1	**35**	90	201—202
C_6H_5COCl	H_2NCOCH_2CN	—	EtOH	80	2	**36**	56	216—217

The iminium salts of **1a** were used with or without isolation from the reaction mixture. For example, isolated **11** and 1-benzyl-3-(1-pyrrolidinylmenthylene)-3H-indolium chloride prepared *in situ* gave the 1-alkyl gramines **31** and **32** respectively, on reduction with sodium borohydride. With active methylene compounds, the iminium salt **13** prepared *in situ* from **1a** and ethyl α-bromoacetate reacted with benzyl cyanide in the presence of an equimolar amount of sodium ethoxide to give ethyl 3-(2-cyano-2-phenylvinyl)-1-indolylacetate (**33**) in 72% yield. The reaction proceeded smoothly at room temperature for 6 hours in a mixed solvent (ethanol and chloroform). It should be noted that much more drastic reaction conditions (at 110°, 70 hr) are required for the same reaction if the base is not used.

Thus, various 1,3-disubstituted indole derivatives (**34**, **35**, and **36**) were obtained under the above mild reaction conditions in good yields, as summarized in Table II.

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[23] See J.V. Paukstelis, "Enamines: Synthesis, Structure, and Reactions," ed. by A.G. Cook, Marcel Dekker, Inc., New York, 1969, pp. 169—209.

Experimental[24]

General Procedure for the Preparation of 3-(1-Pyrrolidinylmethylene)-3H-indoles (1a and 6a—8a)——A suspension of 3-indolecarbaldehyde (**2**—**5**, 0.1 mol) and pyrrolidine (8.6 g, 0.12 mol) in benzene (200 ml) was refluxed for 2 hr using a Dean-Stark apparatus to remove the liberated water. On heating, the reaction mixture first became clear, then prisms appeared. The resulting crystals were collected by filtration, washed with benzene, and dried in a desiccator under reduced pressure at room temperature. Analytical samples were recrystallized from dry THF. Yields and physicochemical data of the products were as follows.

3-(1-Pyrrolidinylmethylene)-3H-indole (1a)——Yield 96%. Colorless prisms, mp 185—190° (dec.). *Anal.* Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.11; N, 14.13. Found: C, 78.57; H, 7.35; N, 14.22. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 276.5 (4.24), 282 (4.29), and 362 (4.45). IR ν_{max}^{Nujol} cm^{-1}: 1635. NMR ($CDCl_3$) δ: 1.6—2.3 (4H, m, C–CH_2), 3.0—3.6 (4H, m, N-CH_2), 7.0—7.9 (4H, m, C-4,5,6,7H), 7.61 and 8.10 (1H each, s, olefinic and C-2H). MS *m/e*: 198 M^+.

5-Methoxy-3-(1-pyrrolidinylmethylene)-3H-indole (6a)——Yield 82%. Pale yellow prisms, mp 170—175°. *Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.07; N, 12.27. Found: C, 73.44; H, 7.28; N, 12.05. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 287 (4.28), 294 sh (4.06), 357 (4.38). IR ν_{max}^{Nujol} cm^{-1}: 1630. NMR ($CDCl_3$) δ: 1.5—2.3 (4H, m, C–CH_2), 3.0—3.7 (4H, m, N–CH_2), 3.83 (3H, s, OCH_3), 6.77 (1H, dd, J=8.7 and 2.3 Hz, C-6H), 6.94 (1H, d, J=2.3 Hz, C-4H), 7.47 (1H, s, =CH–N), 7.55 (1H, d, J=8.7 Hz, C-7H), 7.94 (1H, s, C-2H). MS *m/e*: 228 M^+.

6-Methyl-3-(1-pyrrolidinylmethylene)-3H-indole (7a)——Yield 85%. Colorless prisms, mp 175—185° (dec.). *Anal.* Calcd for $C_{14}H_{16}N_2$: C, 79.20; H, 7.59; N, 13.19. Found: C, 79.06; H, 7.55; N, 12.89. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 282 sh (4.26), 287 (4.31), 366 (4.43). IR ν_{max}^{Nujol} cm^{-1}: 1620. NMR ($CDCl_3$) δ: 1.6—2.2 (4H, m, C–CH_2), 3.0—3.7 (4H, m, N–CH_2), 2.46 (3H, s, CH_3), 6.96 (1H, broad d, J=8.0 Hz, C-5H), 7.36 (1H, d, J= 8.0 Hz, C-4H), 7.50 (2H, broad s, C-7H and =CH–N), 8.00 (1H, s, C-2H), MS *m/e*: 212 M^+.

6-Chloro-3-(1-pyrrolidinylmethylene)-3H-indole (8a)——Yield 66%. Pale yellow prisms, mp 170—175° (dec.). *Anal.* Calcd for $C_{13}H_{13}ClN_2$: C, 67.09; H, 5.62; Cl, 15.23; N, 12.03. Found: C, 67.42; H, 5.81; Cl, 15.22; N, 12.05. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 284 sh (4.24), 289 (4.31), 364 (4.49). IR ν_{max}^{Nujol} cm^{-1}: 1640. NMR ($CDCl_3$) δ: 1.7—2.4 (4H, m, C–CH_2), 3.0—3.9 (4H, m, N–CH_2), 7.06 (1H, dd, J=8.0 and 2.0 Hz, C-5H), 7.33 (1H, d, J=8.0 Hz, C-4H), 7.51 (1H, s, =CH–N), 7.64 (1H, d, J=2.0 Hz, C-7H), 8.01 (1H, s, C-2H). MS *m/e*: 234 M^+.

Preparation of 3-(Piperidinomethylene)- and 3-(Morpholinomethylene)-3H-indole (1b, c)——A suspension of **2** (1.45 g, 10 mmol) in piperidine (1.28 g, 15 mmol) and benzene (25 ml) was refluxed for 1.5 hr, removing the liberated water. Concentration of the resulting clear solution to dryness *in vacuo* afforded **1b** as an amorphous solid in quantitative yield. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 276 sh (4.07), 282 (4.11), 364 (4.13). IR ν_{max}^{Nujol} cm^{-1}: 1630, 1610. NMR ($CDCl_3$) δ: 0.8—2.0 (6H, m, C–CH_2), 3.0—3.6 (4H, m, N–CH_2), 6.7—8.5 (6H, m, aromatic H, C-2H, and =CH–N); no signal was observed for a formyl group. MS *m/e*: 212 M^+.

Compound **1c** was similarly prepared as an amorphous solid in quantitative yield: UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 277 sh (3.96), 283 (4.02), 364 (4.02). IR ν_{max}^{Nujol} cm^{-1}: 1630, 1610. NMR ($CDCl_3$) δ: 2.2—3.0 (4H, m, C–CH_2), 3.3—4.0 (4H, m, O–CH_2), 6.1—8.5 (6H, m, aromatic H, C-2H, and =CH–N); no signal was observed for a formyl group. MS *m/e*: 214 M^+.

3-(Diethylaminomethylene)-3H-indole (1d)——A suspension of **2** (5.80 g, 40 mmol) in diethylamine (7.30 g, 100 mmol) and benzene (80 ml) was refluxed for 7 hr in the presence of **1a**[11] (0.05 g, 0.25 mmol), removing the liberated water. After concentration of the resulting clear solution, the residue was crystallized from diisopropyl ether, giving pale yellow prisms (**1d**) (2.96 g, 37%): mp 120—124° (dec.). UV λ_{max}^{Nujol} nm (log ε): 277 sh (4.21), 282 (4.30), 364 (4.30). IR ν_{max}^{Nujol} cm^{-1}: 1640, 1620. NMR (DMSO-d_6) δ: 1.31 (6H, t, J=7.0 Hz, CH_2–$\underline{CH_3}$), 3.69 (4H, q, J=7.0 Hz, $\underline{CH_2}$–CH_3), 7.0—8.0 (4H, m, C-4,5,6,7H), 8.18 (1H, s, =CH–N), 8.30 (1H, s, C-2H).

3-(Dibutylaminomethylene)-3H-indole (1e)——A mixture of **2** (1.45 g, 10 mmol), dibutylamine (2.59 g, 20 mmol), and **1a**[11] (0.05 g, 0.25 mmol) in benzene (80 ml) was refluxed for 7 hr, removing the liberated water. The reaction mixture was then concentrated to yield colorless prisms of **1e** (2.20 g, 86%): mp 80—85° (dec.). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 277 sh (4.27), 282 (4.33), 364 (4.29). IR ν_{max}^{Nujol} cm^{-1}: 1660, 1630. NMR (DMSO-d_6) δ: 0.7—2.3 (14H, m, C–$CH_2CH_2CH_3$), 3.4—4.0 (4H, m, N–CH_2), 7.0—8.0 (4H, m, C-4,5,6,7H), and 8.18 (2H, s, C-2H and =CH–N).

Formation of 3-(Piperidinomethylene)- and 3-(Morpholinomethylene)-3H-indole Polymer (9b, c)——A suspension of **2** (1.45 g, 10 mmol) in piperidine (1.28 g, 15 mmol) and benzene (25 ml) was refluxed for 7 hr, removing the liberated water. The reaction mixture first became clear, then yielded colorless fine crystals of **9b** (1.87 g, 88%): mp 199—201° (dec.). *Anal.* Calcd for $(C_{14}H_{16}N_2)_n$: C, 79.21; H, 7.60; N, 13.20. Found:

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[24] All melting points are uncorrected. IR spectra were obtained on a Shimadzu IR-27G spectrophotometer. H^1-NMR spectra were recorded on a Hitachi R-20A instrument, using TMS as an internal standard. UV spectra were taken on a Hitachi EPS-3T spectrophotometer. MS spectra were measured with a Hitachi RMU-6M spectrometer.

C, 79.18; H, 7.60; N, 12.92. UV $\lambda_{\max}^{CHCl_3}$ nm (log ε)[25]: 278 (3.89), 287 (3.61). IR $\nu_{\max}^{Nujol}$ cm^{-1}: 1105, 745. MS (30 eV) *m/e* (rel intensity); 212 (88), 129 (100).

Compound **9c** was similarly prepared in 71% yield: colorless fine crystals, mp 209—214°. *Anal.* Calcd for $(C_{13}H_{14}N_2O)_n$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.64; H, 6.72; N, 12.79. UV $\lambda_{\max}^{CHCl_3}$ nm (log ε)[25]: 279 sh (3.80), 286 (3.86). IR $\nu_{\max}^{Nujol}$ cm^{-1}: 1115, 1105, 750. MS (30 eV) *m/e* (rel intensity): 214 (100), 129 (95).

General Procedure for the Preparation of Indolium Salts (10—13) by Reaction of 1 with Electrophiles——A solution of **1a** in EtOH was treated with 1.1 times the equimolar amount of acid or alkyl halide at room temperature with stirring. After stirring overnight, the precipitated indolium salts were isolated, washed with EtOH and recrystallized from $CHCl_3$–EtOH. The electrophiles used, yields, and physicochemical properties of the products were as follows.

3-(1-Pyrrolidinylmethylene)-3H-indolium Chloride (10a)——Hydrochloric acid, yield 95%. Colorless prisms, mp 260° (dec.). *Anal.* Calcd for $C_{13}H_{15}ClN_2$: C, 66.52; H, 6.44; Cl, 15.11; N, 11.94. Found: C, 66.11; H, 6.37; Cl, 14.94; N, 11.94. UV $\lambda_{\max}^{MeOH}$ nm (log ε): 348 (4.29), 275.5 (3.82), 268 sh (3.87), 258 (4.04) 249 sh (3.98). IR $\nu_{\max}^{KBr}$ cm^{-1}: 3170, 3100, 1645. NMR (DMSO-d_6) δ: 1.9—2.4 (4H, m, C–CH_2), 3.7—4.5 (4H, m, N–CH_2), 7.2—7.8 (3H, m, C-5,6,7H), 8.0—8.3 (1H, m, C-4H), 8.62 (1H, s, C-2H); 9.28 (1H, s, =CH–N).

3-(1-Pyrrolidinylmethylene)-3H-indolium Picrate (10b)——Picric acid, yield 100%. Yellow prisms, mp 234—235° (dec.). *Anal.* Calcd for $C_{19}H_{17}N_5O_7$: C, 53.40; H, 4.01; N, 16.39. Found: C, 53.49; H, 4.15; N, 16.55.

1-Methyl-3-(1-pyrrolidinylmethylene)-3H-indolium Iodide (11)——Methyl iodide, yield 86%. Colorless prisms, mp >280°. *Anal.* Calcd for $C_{14}H_{17}IN_2$: C, 49.43; H, 5.04; I, 37.30; N, 8.23. Found: C, 49.31; H, 5.09; I, 37.32; N, 8.38. UV $\lambda_{\max}^{MeOH}$ nm (log ε): 348 (4.36), 275.5 (3.92), 268 sh (3.97), 258 (4.18), 249 sh (4.12). IR $\nu_{\max}^{KBr}$ cm^{-1}: 1635, 1530. NMR (DMSO-d_6) δ: 1.9—2.4 (4H, m, C–CH_2), 3.7—4.4 (4H, m, N–CH_2), 4.05 (3H, s, N–CH_3), 7.2—7.8 (3H, m, C-5,6,7H), 8.0—8.3 (1H, m, C-4H), 8.75 (1H, s, C-2H), 9.41 (1H, s, =CH–N).

1-(*p*-Chlorobenzyl)-3-(1-pyrrolidinylmethylene)-3H-indolium Chloride (12)——*p*-Chlorobenzyl chloride, yield 84%. Colorless prisms, mp 187—189°. *Anal.* Calcd for $C_{20}H_{20}Cl_2N_2 \cdot H_2O$: C, 66.85; H, 5.61; Cl, 19.74; N, 7.80. Found: C, 67.05; H, 5.88; Cl, 19.70; N, 8.09. UV $\lambda_{\max}^{MeOH}$ nm (log ε): 348 (4.33), 276 (3.82), 269 sh (3.79), 257.5 (4.07), 250 sh (4.06). IR $\nu_{\max}^{KBr}$ cm^{-1}: 1640, 1525. NMR (DMSO-d_6) δ: 2.0—2.48 (4H, m, C–CH_2), 3.8—4.5 (4H, m, N-CH_2), 5.85 (2H, s, $\overset{+}{N}$–$\underline{CH_2}C_6H_4Cl$), 7.3—7.9 (3H, m, C-5,6,7H), 7.43 (4H, s, C_6H_4Cl), 8.0—8.3 (1H, m, C-4H), 9.10 (1H, s, C-2H), 9.54 (1H, s, =CH–N).

1-Ethoxycarbonylmethyl-3-(1-pyrrolidinylmethylene)-3H-indolium Bromide (13)——Ethyl bromoacetate, yield 80%. Colorless prisms, mp 222° (dec.). *Anal.* Calcd for $C_{17}H_{21}BrN_2O_2$: C, 55.90; H, 5.80; Br, 21.88; N, 7.67. Found: C, 56.01; H, 5.95; Br, 21.75; N, 7.53. UV $\lambda_{\max}^{MeOH}$ nm (log ε): 346 (4.37), 275.5 (3.86), 269 (3.90), 256 (4.15), 248.5 (4.17). IR $\nu_{\max}^{KBr}$ cm^{-1}: 1750, 1640, 1535. NMR (DMSO-d_6-$CDCl_3$) δ: 1.27 (3H, t, J=7.3 Hz, $CH_2\underline{CH_3}$), 1.8—2.4 (4H, m, C–CH_2), 3.6—4.2 (4H, m, N–CH_2), 4.20 (2H, q, J=7.3 Hz, $\underline{CH_2}CH_3$), 5.41 (2H, s, N–CH_2CO), 7.2—7.5 (3H, m, C-5,6,7H), 8.0—8.4 (1H, m, C-4H), 9.10 (1H, s, C-2H), 9.68 (1H, s, =CH–N).

General Procedure for the Hydrolysis of Indolium Salts (11—13)——The indolium salt (**11**—**13**) was stirred with 1% aqueous NaOH at room temperature for 30 minutes then extracted with AcOEt. The organic layer was washed successively with dil. HCl, sat. $NaHCO_3$, and sat. NaCl and then concentrated to yield 1-substituted-3-indolecarbaldehyde (**14**—**16**). Yields and physicochemical properties of the products were as follows.

1-Methyl-3-indolecarbaldehyde (14)——Yield 90%. Pale yellow scales (iso-PrOH), mp 68—69° (lit[26] 69—70°).

1-(*p*-Chlorobenzyl)-3-indolecarbaldehyde (15)——Yield 85%. Pale-yellow needles (iso-PrOH), mp 99—102°. *Anal.* Calcd for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.48; Cl, 13.14; N, 5.19. Found: C, 71.40; H, 4.53; Cl, 12.98; N, 5.20. IR $\nu_{\max}^{Nujol}$ cm^{-1}: 1655, 1530. NMR ($CDCl_3$) δ: 5.32 (2H, s, $\underline{CH_2}C_6H_4Cl$), 7.20 (4H, $A_2'B_2'$, C_6H_4Cl), 7.2—7.5 (3H, m, C-5,6,7H), 7.67 (1H, s, C-2H), 8.2—8.5 (1H, m, C-4H), 10.0 (1H, s, CHO).

1-Ethoxycarbonylmethyl-3-indolecarbaldehyde (16)——Yield 76%. Colorless syrup (purified by silica gel column chromatography). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.38; H, 5.75; N, 5.97. IR $\nu_{\max}^{film}$ cm^{-1}: 1760, 1640, 1530. NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 4.18 (2H, q, J=7.0 Hz, $\underline{CH_2}CH_3$), 4.80 (2H, s, CH_2CO_2), 7.1—7.5 (3H, m, C-5,6,7H), 7.65 (1H, s, C-2H), 8.15—8.45 (1H, m, C-4H), 9.93 (1H, s, CHO).

General Procedure for the Preparation of 1-Substituted 3-Indolecarbaldehydes (14, 17, 18) from 1a——The electrophilic reagent (11 mmol) was added to a solution of **1a** (1.98 g, 10 mmol) in EtOH (10 ml) at room temperature. After stirring overnight, the reaction mixture was poured into 1% aqueous NaOH solution, concentrated under reduced pressure, and extracted with AcOEt. The extract was washed successively with dil. HCl, sat. $NaHCO_3$, and sat. NaCl and then concentrated to yield 1-substituted 3-indolecarbaldehydes (**14**, **17**, **18**). The electrophiles used, yields and physicochemical properties of the products were as follows.

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25) The ε values were calculated on the basis of the monomeric molecular weight.

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1-Methyl-3-indolecarbaldehyde (14)——Methyl iodide, yield 93%. Dimethyl sulfate, yield 90%. Pale yellow scales (iso-PrOH), mp 66—69°.[26]

1-Benzoyl-3-indolecarbaldehyde (17)——Benzoyl chloride, yield 95%. Benzoyl anhydride, yield 70%. Colorless prisms, mp 86—88°. (lit.[27] mp 85—86°).

1-(*p*-Toluenesulfonyl)-3-indolecarbaldehyde (18)——*p*-Toluenesulfonyl chloride, yield 65%. Colorless needles, mp 147—148° (lit.[28] mp 148—150°).

3-Formyl-N-phenylindole-1-carboxamide (19)——A solution of **1a** (1.98 g, 10 mmol) in $CHCl_3$ (30 ml) was treated with phenylisocyanate (1.79 g, 15 mmol) at $-10°$ and the reaction mixture was allowed to stand at room temperature overnight with stirring. After addition of water (30 ml), the reaction mixture was stirred for one hour and extracted with AcOEt (100 ml × 2). The organic layer was dried, chromatographed on silica gel (Kieselgel 60, 0.063—0.200 mm, Merck) with C_6H_6–AcOEt (100: 3) as an eluent to give colorless needles of **19** (1.30 g, 49%), mp 139—140° (dec.). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.75; H, 4.72; N, 10.46. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280, 1730, 1650, 1530. NMR (DMSO-d_6) δ: 7.2—7.9 and 8.15—8.4 (7H and 2H, respectively, m, aromatic H), 8.96 (1H, s, C-2H), 10.18 (1H, s, CHO), 10.60 (1H, broad s, D_2O–exchangeable, NH).

1-(2,5-Dihydroxyphenyl)-3-indolecarbaldehyde (20)——A solution of 1,4-benzoquinone (1.08 g, 10 mmol) in CH_2Cl_2 (50 ml) was mixed with a solution of **1a** (1.98 g, 10 mmol) in CH_2Cl_2 (50 ml) at 0°. After stirring for one hour at room temperature, the resulting precipitate was boiled in 50% aqueous AcOH (30 ml) for an hour and extracted with AcOEt. The organic layer was washed successively with water, sat. $NaHCO_3$, and sat. NaCl, concentrated *in vacuo*, and then chromatographed on silica gel (Kieselgel 60, 0.063—0.200 mm, Merck) with $CHCl_3$–EtOH (40: 1) as an eluent to give colorless prisms of **20** (1.12 g, 44%), mp 242—243°. *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53. Found: C, 70.88; H, 4.48; N, 5.59. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3250, 3100, 1635, 1530, 1510. NMR (DMSO-d_6-$CDCl_3$) 6.6—7.0 (2H, m, C-3′,4′H of Ph), 6.80 (1H, s, C-6′H of Ph), 7.0—7.5 (3H, m, C-5,6,7H), 7.91 (1H, s, C-2H), 8.1—8.4 (1H, m, C-4H), 8.70 and 8.75 (1H, each, s, D_2O-exchangeable, OH), 9.95 (1H, s, CHO).

Dimethyl (3-Formyl-1-indolyl)butenedioate (21)——Dimethyl acetylenedicarboxylate (0.71 g, 5 mmol) was added to a solution of **1a** (0.99 g, 5 mmol) in $CHCl_3$ (10 ml) at 5—6°. After stirring at room temperature for 3 hr, the reaction mixture was shaken with 10% aqueous AcOH. The organic layer was dried, concentrated and chromatographed on silica gel (Kieselgel 60, 0.063—0.200 mm, Merck) with C_6H_6–AcOEt (100: 3) as an eluent, yielding two fractions. From the first fraction of the eluate, TLC *Rf* 0.50 (SiO_2, C_6H_6: AcOEt: EtOH = 8: 2: 1), *Z*-**21** (0.31 g, 22%) was obtained as a pale brown paste: *Anal.* Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.83; H, 4.80; N, 4.79. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3100, 2950, 1730, 1670, 1540. NMR ($CDCl_3$) δ: 3.85 (3H, s, OMe), 3.98 (3H, s, OMe), 6.43 (1H, s, vinylic H), 7.2—7.6 (3H, m, C-5,6,7H), 7.77 (1H, s, C-2H), 8.2—8.5 (1H, m, C-4H), 10.06 (1H, s, CHO). The second fraction of the eluate, TLC *Rf* 0.35 (SiO_2, C_6H_6: AcOEt: EtOH = 8: 2: 1), was crystallized from (iso-Pr_2O to provide colorless prisms of *E*-**21** (0.39 g, 27%): mp 104—105.5°. *Anal.* Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.74; H, 4.65; N, 4.77. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3100, 2800, 1720, 1650, 1515. NMR ($CDCl_3$) δ: 3.55 (3H, s, OMe), 3.87 (3H, s, OMe), 6.9—7.5 (3H, m, C-5,6,7H), 7.28 (1H, s, vinylic H), 7.75 (1H, s, C-2H), 8.2—8.5 (1H, m, C-4H), 10.10 (1H, s, CHO).

General Procedure for the Preparation of Condensation Products (22—27) of 1a with Active Methylene Compounds——A mixture of **1a** (1.98 g, 10 mmol) and active methylene compound (10 mmol) in EtOH (20 ml) was stirred at 25° for 0.5 hr. After addition of 10% aqueous AcOH (10 ml) to the reaction mixture, the resulting precipitates were collected and washed with a small amount of EtOH to afford the practically pure condensation product (**22**—**27**). The yields and melting points of the products are listed in Table I. The physicochemical properties of new compounds were as follows.

2-Cyano-3-(3-indolyl)acrylonitrile (23)——Fine yellow crystals, mp 219—220°. *Anal.* Calcd for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.60; H, 3.95; N, 22.01. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3290, 2230, 1530. NMR (DMSO-d_6) δ: 7.1—7.8 (3H, m, C-5,6,7H), 7.9—8.2 (1H, m, C-4H), 8.63 and 8.51 (1H each, s, C-2H and olefinic H), 12.7 (1H, broad, D_2O–exchangeable, NH).

3-[2-(4-Nitrobenzoyl)vinyl]indole (25)——Yellow prisms, mp 226—227°. *Anal.* Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.82; H, 4.12; N, 9.56. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3350, 1650, 1560, 1510, 1340. NMR (DMSO-d_6) δ: 7.1—7.8 (3H, m, C-5,6,7H), 7.61 and 8.61 (1H each, d, J = 15.5 Hz, vinylic H), 7.9—8.3 (1H, m, C-4H), 8.18 (1H, s, sharpened on D_2O exchange, C-2H), 8.34 (4H, s, $C_6H_4NO_2$).

3-Amino-4-(3-indolylmethylene)-1-phenylpyrazolin-5-one (26)——Reddish-brown prisms, mp 260—261° (dec.). *Anal.* Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.22; H, 4.89; N, 18.29. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3420, 3150, 1655, 1640, 1605. NMR (DMSO-d_6) δ: 6.30 (2H, broad s, D_2O-exchangeable, NH_2), 7.0—7.8 (6H, m, C-5,6,7H and C-3′,4′,5′H of Ph), 8.0—8.3 (3H, m, C-4H and C-2′,6′H of Ph), 8.32 (1H, s, C-2H), 9.76 (1H, s, olefinic H), 12.5 (1H, broad s, D_2O-exchangeable, NH).

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4-(3-Indolylmethylene)-3-methyl-1-phenylpyrazolin-5-one (27)[29]——Reddish-brown prisms, mp 235—236°. *Anal.* Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.50; H, 5.30; N, 13.65. IR ν_{max}^{KBr} cm^{-1}: 3250, 1650. NMR (DMSO-d_6) δ: 2.43 (3H, s, CH_3), 7.0—7.8 (9H, m, aromatic H), 8.11 (1H, s, C-2H), 9.06 (1H, s, olefinic H).

2-Cyano-3-(3-indolyl)acrylic Acid (28)——a) A solution of cyanoacetic acid (0.43 g, 5 mmol) and **1a** (0.99 g, 5 mmol) in EtOH (10 ml) was allowed to stand at 25° for 5 hr with stirring. The reaction mixture was made alkaline (pH 12) with 3% NaOH, and concentrated under reduced pressure. The resulting aqueous solution was washed with AcOEt and acidified with 10% HCl to precipitate fine yellow crystals of **28** (0.12 g, 11%), mp 260—261° (dec.). (lit.[30] mp 260°).

b) A solution of **1a** (0.99 g, 5 mmol) in pyridine (10 ml) was treated with cyanoacetic acid (0.43 g, 5 mmol) at 25° with stirring. After stirring for 5 hr, the reaction mixture was poured into water (50 ml) and washed with AcOEt. The aqueous layer yielded **28** (0.76 g, 72%), mp 260—261° (dec.).

(3-Indolylmethylene)malonic Acid (29)——a) A mixture of **1a** (0.99 g, 5 mmol) and malonic acid (0.52 g, 5 mmol) in EtOH (10 ml) was reacted and treated as described for the preparation of **28** (method a) to give fine yellow crystals of **29** (0.17 g, 15%), mp 207—208° (dec.).[31] (lit.[20] mp 195°).

b) Addition of twice the equimolar amount of triethylamine to the reaction mixture of method a increased the yield of **29**[31] to 68%.

c) Reaction of **1a** (0.99 g, 5 mmol) with malonic acid (0.52 g, 5 mmol) in pyridine (10 ml) was carried out as described for the preparation of **28** (method b) to give **29**[31] (0.68 g, 60%, mp 207—208° (dec.).

Reduction of 1a—c with Sodium Borohydride——A stirred solution of **1a** (1.98 g, 10 mmol) in EtOH (30 ml) was treated with sodium borohydride (0.38 g, 10 mmol) at room temperature. After stirring for 3 hr, the reaction mixture was concentrated. The resulting residue was dissolved in dil. HCl, then shaken with AcOEt. The aqueous layer was made alkaline with aqueous NaOH, and extracted with ether. Concentration of the extract furnished crystals, which were washed with hexane and collected by suction to give **30a** as colorless prisms (1.88 g, 94%), mp 127°. (lit.[32] mp 127—128°).

In a similar manner, **1b** and **1c** were reduced to the corresponding 3-(aminomethyl)indole **30b** (77%, mp 160°, lit.[32] mp 160—161°) and **30c** (78%, mp 121°, lit.[33] mp 121°), respectively.

1-Methyl-3-(1-pyrrolidinylmethyl)indole (31)——A suspension of **11** (1.70 g, 5 mmol) in EtOH (10 ml) was treated with sodium borohydride (0.38 g, 10 mmol) at room temperature with stirring. After stirring for 3 hr, the reaction mixture was quenched with water (50 ml) and extracted with ether. The extract was dried and concentrated, then the residual oil was chromatographed on alumina (Aluminiumoxid 90. Aktiv. basisch. Merck) with C_6H_6–AcOEt (100: 3) as an eluent to give **31** as a colorless oil (0.53 g, 49%). *Anal.* Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.28; H, 8.20; N, 12.85. IR ν_{max}^{film} cm^{-1}: 2930, 2700, 1475, 1325, 1125, 735. NMR (CCl_4) δ: 1.5—1.9 (4H, m, C–CH_2), 2.3—2.7 (4H, m, N–CH_2), 3.45 (3H, s, CH_3), 3.65 (2H, s, C-3 CH_2–N), 6.70 (1H, s, C-2H), 6.8—7.2 (3H, m, C-5,6,7H), 7.4—7.7 (1H, m, C-4H).

1-Benzyl-3-(1-pyrrolidinylmethyl)indole (32) **Hydrochloride**——Benzyl chloride (1.27 g, 10 mmol) was added to a solution of **1a** (1.98 g, 10 mmol) in EtOH (25 ml) at room temperature. After stirring overnight, sodium borohydride (0.57 g, 15 mmol) was added to the reaction mixture and the whole was stirred for a day. The reaction mixture was quenched with water (50 ml), concentrated, and extracted with ether. The ether extract was worked up as described for the preparation of **31** to give **32** as a colorless oil, which crystallized with 30% HCl in EtOH as colorless prisms of the hydrochloride (2.10 g, 64%), mp 198—199°. *Anal.* Calcd for $C_{20}H_{22}N_2 \cdot HCl$: C, 73.49; H, 7.09; N, 8.57; Cl, 10.85. Found: C, 73.25; H, 7.01; N, 8.49; Cl, 10.72. IR ν_{max}^{KBr} cm^{-1}: 1545, 1470, 1355, 1165, 735. NMR ($CDCl_3$) δ: 1.7—2.5 (4H, m, C–CH_2), 2.5—4.0 (4H, m, N–CH_2), 4.45 (2H, d, $J=5$ Hz, collapses to a singlet on D_2O exchange, C-3 CH_2–N), 5.33 (2H, s, N–CH_2–Ph), 7.0—7.9 (9H, m, aromatic H), 7.78 (1H, s, C-2H).

General Procedure for the Preparation of 1,3-Disubstituted Indole Derivatives (33—36) **by Successive Reaction of 1a with Electrophiles and Nucleophiles**——A solution of **1a** (10 mmol) in $CHCl_3$ (10 ml) was treated with alkyl halide or acyl halide (10 mmol) at room temperature and the reaction mixture was allowed to stand for a day with stirring. A solution of active methylene compound (10 mmol) in EtOH (10 ml) and sodium ethoxide (10 mmol) were added successively at room temperature to the resulting iminium salt. The whole was stirred under the reaction conditions shown in Table II. When the reaction was complete, 1 N HCl (15 ml) was added to isolate the products. The electrophiles and nucleophiles used, yields and the physicochemical properties of the products were as follows.

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Ethyl 3-(2-Cyano-2-phenylvinyl)-1-indolylacetate (33)——Ethyl bromoacetate, benzyl cyanide, yield 72%. Pale-yellow prisms (EeOH), mp 156—157°. *Anal.* Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.13; H, 5.65; C, 8.34. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2200, 1740, 1525. NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7.2$ Hz, CH_3), 4.24 (2H, q, $J=7.2$ Hz, $\underline{CH}_2CH_3$), 4.88 (2H, s, N–CH_2CO), 7.2—7.9 (9H, m, aromatic H), 7.85 and 8.46 (1H each, s, C-2H and olefinic H).

Ethyl 3-(2-Carbamoyl-2-cyanovinyl)-1-indolylacetate (34)——Ethyl bromoacetate, cyanoacetamide, yield 95%. Yellow prisms (EeOH), mp 244—245°. *Anal.* Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.65; H, 5.11; N, 14.30. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3460, 3130, 2200, 1745, 1700, 1583, 1570, 1520, 1200. NMR (DMSO-d_6) δ: 1.22 (3H, t, $J=7.1$ Hz, $CH_2\underline{CH}_3$), 3.18 (2H, q, $J=7.1$ Hz, $\underline{CH}_2CH_3$), 5.48 (2H, s, CH_2CO), 7.2—8.1 (6H, m, two of these protons are D_2O-exchangeable, C-4,5,6,7H and NH_2), 8.43 and 8.49 (1H, each, s, C-2H and olefinic H).

3-[1-(*p*-Chlorobenzyl)-3-indolyl]-2-cyanoacrylonitrile (35)——*p*-Chlorobenzyl chloride, malononitrile, yield 90%. Yellow prisms ($CHCl_3$–EtOH), mp 201—202°. *Anal.* Calcd for $C_{19}H_{12}ClN_3$: C, 71.81; H, 3.81; Cl, 11.16; N, 13.22. Found: C, 71.63; H, 4.03; Cl, 11.11; N, 13.06. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2250, 1590, 1580, 1513, 1365, 1190, 744. NMR (DMSO-d_6) δ: 5.66 (2H, s, $\underline{CH}_2C_6H_4Cl$), 7.2—8.2 (8H, m, aromatic H), 8.69 (2H, s, C-2H and olefinic H).

3-(1-Benzoyl-3-indolyl)-2-cyanoacrylamide (36)——Benzoyl chloride, cyanoacetamide (without NaOEt), yield 56%. Yellow prisms (EtOH), mp 216—217°. *Anal.* Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.46; H, 4.20; N, 13.31. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3400, 3170, 2210, 1705, 1690, 1580, 1535, 1360, 1220. NMR ($CDCl_3$–DMSO-d_6) δ: 7.2—8.0 (10H, m, aromatic H and NH_2), 8.2—8.5 (1H, m, C-7H), 8.42 and 8.47 (1H each, s, C-2H and olefinic H).

Condensation of 13 with Benzyl Cyanide——A suspension of **13** (3.65 g, 10 mmol) and benzyl cyanide (1.17 g, 10 mmol) in DMF (10 ml) was stirred at 110° for 70 hr. Water (100 ml) was then added and the resulting yellow prisms were washed with EtOH to afford **33**. Yield 1.98 g, (60%), mp 156—157°.

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