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Synthesis of Methyl 2-Isocyano-3-[3(1*H*)-indolyl]acrylate and Related Compounds from 3-(Aminomethylene)-3*H*-indoles

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Methyl 2-isocyano-3-[3(1*H*)-indolyl]acrylate (1) was synthesized in 73—75% yield by the reaction of 3-(aminomethylene)-3*H*-indoles (5) with methyl α-isocyanoacetate (3) in pyridine or dimethylformamide, while the reaction in methanol afforded selectively 2-(aminomethyleneamino)-3-[3(1*H*)-indolyl]acrylates (**6a**—**e**) in 63—100% yields. The mechanisms of formation of **1** and **6** are discussed. Both **1** and **6a**—**e** were hydrolyzed to N-formyl-α,β-dehydrotryptophan (**8**) and/or its methyl ester (**2**).

Keywords——isocyanides; amidines; 3-(aminomethylene)-3*H*-indoles; α,β-dehydrotryptophans; conjugated enamine; condensation; solvent effect; hydrolysis; antibacterial activity; inhibiting activity of blood platelet aggregation

The indole skeleton is found in many naturally occurring compounds of great pharmaceutical interest. Of these, α,β-dehydrotryptophan derivatives have recently been isolated from natural sources. For example, aplysinopsines isolated from marine sponge,[1] echinulines obtained from metabolites of fungi,[2] and telomycin[3] and A-128-OP[4] found as peptide antibiotics contain the α,β-dehydrotryptophan residue in their structures. Furthermore, *cis*-3-(2-isocyanovinyl)-1*H*-indole (B-371)[5] has also been isolated from culture broth of a species of pseudomonas (NCIB-11237) and possesses antifungal activity.

On the other hand, α-isocyanocinnamic acid derivatives, which seem to correspond to α,β-dehydroamino acid derivatives, have been synthesized in our laboratory not only as antimicrobial agents[6] but also as useful synthetic intermediates for pharmaceuticals such as pyrrole compounds.[7]

We were next interested in synthesizing 2-isocyano-3-[3(1*H*)-indolyl]acrylate as a tryptophan analog which would be a useful intermediate for the preparation of biologically active compounds.

With regard to the synthesis of 2-isocyanoacrylic acid derivatives, dehydration of the corresponding 2-formylamino derivatives using phosphoryl chloride seems to be a convenient method in practice. Therefore, first of all an attempt to synthesize *N*-formyl-α,β-dehydrotryptophan methyl ester (2) according to Schöllkopf's method[8] was made. Actually, the reaction of methyl α-isocyanoacetate (3) with 3(1*H*)-indolecarbaldehyde (4) was carried out in the presence of sodium hydride or potassium tertiary butoxide. However, the desired product was not obtained, but the raw material (4) was largely recovered in the conditions of Schöllkopf's reaction. The lower reactivity is presumably due to the contribution of the enolate form of **4**.[9]

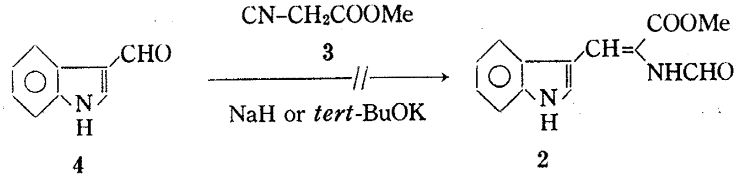

Chart 1

Concerning the reactivity of **4**, we previously reported[10] that 3-(aminomethylene)-3*H*-indole (**5**) having a reactive vinylogous amidine moiety, was useful as a 1,4-dipolar synthon for introducing the indole skeleton. For example, a reaction of **5** with active methylene compounds proceeds smoothly without any additional base to afford the corresponding 3-vinyl-1*H*-indoles in good yields. For the synthesis of methyl 2-isocyano-3-[3(1*H*)-indolyl]acrylate (**1**), the reaction using **5** was extended in this study.

Results and Discussion

The reaction of 3-(1-pyrrolidinylmethylene)-3*H*-indole (**5a**) with methyl α-isocyanoacetate (**3**) was carried out in methanol under the conditions used for the condensation of **5** with active methylene compound. Surprisingly, the desired compound (**1**) was not formed but methyl (*Z*)-2-(1-pyrrolidinylmethyleneamino)-3-[3(1*H*)-indolyl]acrylate (**6a**) was obtained in quantitative yield. The compound (**6a**) formed yellow prisms having mp 186—188°C and its hydrochloride was also crystalline solid having mp 203°C (dec.). The structure of **6a** was confirmed by spectral and analytical data as follows. The mass spectrum (MS) of **6a** showed a molecular ion peak at *m/e* 297. The infrared (IR) spectrum exhibited intense absorption at 1700 cm^{-1} and broad absorption at 1605 cm^{-1} attributable to the ester carbonyl and C=C and C=N double bonds, respectively. The proton magnetic resonance (^{1}H-NMR) spectrum in deuterochloroform ($CDCl_3$) showed sharp singlets at 3.80, 7.45, and 8.12 ppm attributable to ester methyl, olefinic proton of the side-chain, and a proton of the formamidine moiety, respectively. Multiplets of α- and β-methylene protons in the pyrrolidinyl group appeared at 3.2—3.7 and 1.6—2.0 ppm. A doublet at 8.15 ppm which coalesced to a singlet on deuterium oxide (D_2O) exchange was recognized as the C-2 proton of the indole nucleus, and a broad signal at 8.9—9.2 ppm due to the N-1 proton of indole was also observed. The sp^2 carbon region in the ^{13}C nuclear magnetic resonance (^{13}C-NMR) spectrum of **6a** measured in the nuclear Overhauser effect (NOE) mode is shown in Fig. 1. The absorptions at 151.5 and 132.5 ppm were attributable to carbon of the formamidine group (C_{11}) and to the α-carbon (C_9) of the acrylic ester moiety, respectively. The carbonyl carbon of the ester group appeared at 166 ppm as a quintet in which the spin coupling constant was about 4 Hz in its fine structure (NOE mode measurement). This splitting was interpreted as a doubled quartet due to three-bond long-range coupling between carbon (C_{10}) and hydrogen (C_8–H) nuclei for the following reason: the doublet[11] coupled with β-hydrogen of the acrylic ester moiety split into quartets by coupling with the methyl ester protons ($^3J_{C-O-C-H}$).[12] From the coupling constant, 4 Hz, between the carbonyl carbon

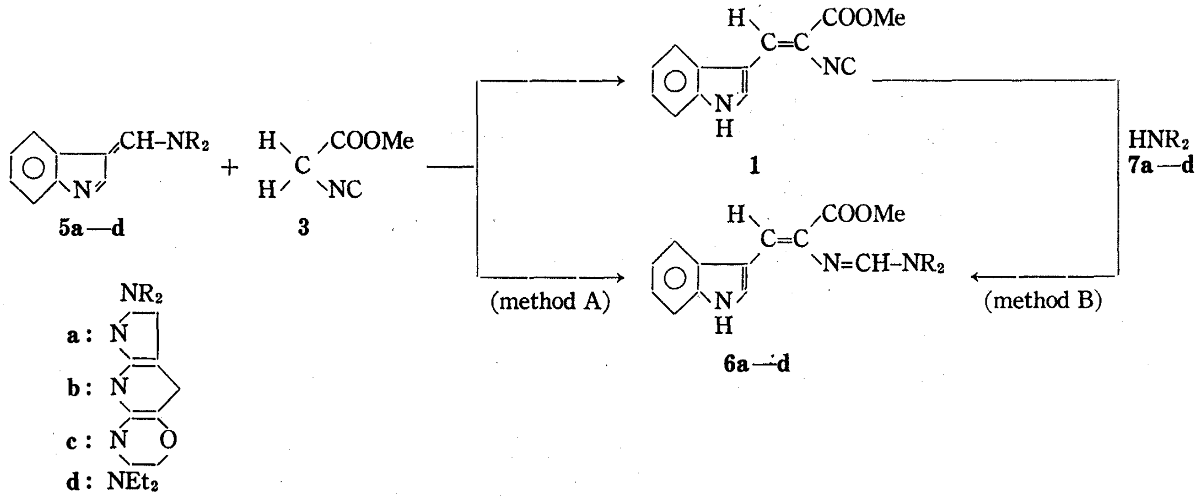

Chart 2

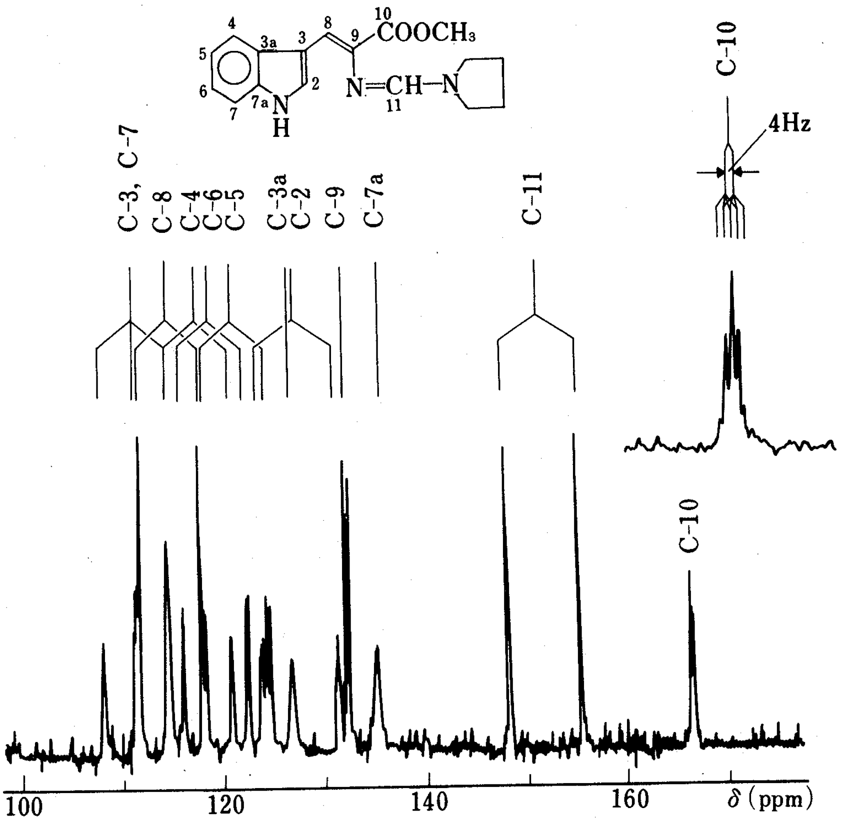

Fig. 1. ^{13}C-NMR Spectrum of **6a** in DMSO-d_6 (Sp^2 Carbon Region in the NOE Mode)[a]

[a] Pulse width, 8 μs (45°); repetition time between pulses, 3 s; No. of pulses, 25000; spectral width, 5 kHz.

and the vicinal olefinic H_β proton ($^3J_{C-C=C-H}$), the stereochemisrty of **6a** was suggested to be *Z*-form.[11]

To obtain the desired isocyano compound (**1**), the reaction conditions were investigated. When tetrahydrofuran (THF) was used as a solvent, the reaction afforded, interestingly, a mixture of **6a** and the desired 2-isocyanoacrylate (**1**) in 45 and 40% yields, respectively. The structural elucidation of **1** (mp 168—168.5°C, pale yellow prisms) was carried out on the basis of spectral data and elemental analysis as follows. The MS of **1** showed the molecular ion peak at *m/e* 226 as the base peak. The IR spectrum revealed the presence of an isocyano group at 2100 cm^{-1}, and of an ester group conjugated with a double bond at 1705, 1600, and 1270 cm^{-1}. In the ^{1}H-NMR spectrum in dimethyl sulfoxide-d_6 (DMSO-d_6), the methyl groups of the ester moiety and the olefinic proton appeared at 3.86 and 8.04 ppm as sharp singlets. A doublet at 8.33 ppm having a coupling constant of 3 Hz (coalesced to a singlet on D_2O exchange) and a D_2O-exchangeable broad absorption at 12.3 ppm were assigned to C-2 and N-1 protons in the 1*H*-indole skeleton, respectively. The ^{13}C-NMR spectrum of **1** showed three characteristic singlets at 172.1, 161.9, and 107.2 ppm attributable to the α-carbon (C_9), carbonyl carbon (C_{10}) of the acrylic ester moiety and the terminal carbon (C_{11}) of the isocyano group (NOE mode measurement), respectively, as shown in Fig. 2. The carbonyl carbon signal split into a pattern similar to that of **6a** in its fine structure. The *Z*-configuration of **1** was also suggested from the coupling constant of 4 Hz, attributable to three-bond long-range coupling ($^3J_{C-C=C-H}$).

In order to investigate the optimum conditions for the formation of the isocyano compound (**1**), various solvents were employed. In the reaction using pyridine or *N*,*N*-dimethylformamide (DMF) as a solvent, **1** was obtained in up to 75% yield, while in nitrobenzene the amidine compound (**6a**) was the major product as shown in Table I. From the above result it was

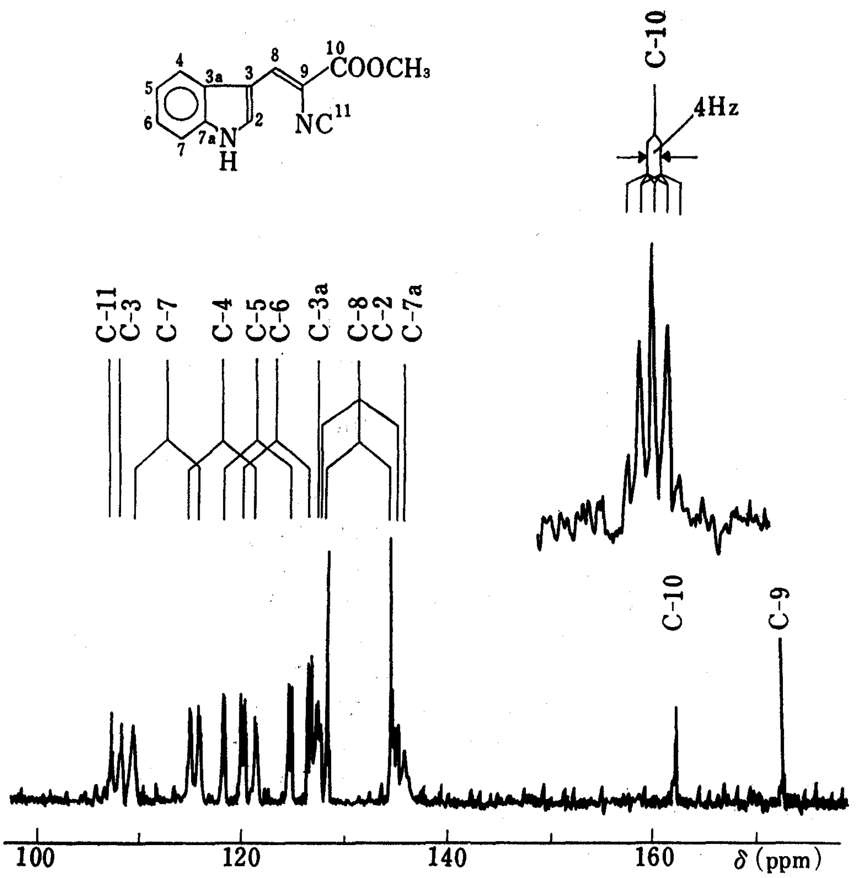

Fig. 2. ^{13}C-NMR Spectrum of **1** in DMSO-d_6 (sp^2 Carbon Region in the NOE Mode)[a]

[a] See Fig. 1.

Table I. Solvent Effect on the Reaction[a] of **5a** with **3**

Solvent	Yield (% isolated)	
	1	**6a**
Pyridine	75	10
DMF	73	10
THF	40	45
CH_2Cl_2	28	61
$PhNO_2$	9	68
MeOH	0	100

[a] **5a** (8 mmol), **3** (10 mmol), solvent (20 ml) at 25°C for 1 h.

deduced that **1** was the predominant product in the reaction using nucleophilic or amphoteric solvents, whereas **6** was formed predominantly in the reaction using electrophilic and/or protic solvents.

This selectivity in the synthesis of the amidine compound (**6**) and the 2-isocyanoacrylate (**1**) interested us in relation to the suggestion in our previous paper[13] that the 2-isocyanoacrylate derivative was an intermediate of a congener amidine formed by a reaction of **3** with aromatic aldehydes in the presence of a cyclic secondary amine such as pyrrolidine. Therefore, it was of interest to determine whether the isocyano compound (**1**) is also the intermediate of the amidine (**6**) obtained here or not. Assuming that **1** is the intermediate, the reaction of **5** with **3** would proceed as shown in the following equation.

$$\mathbf{5} + \mathbf{3} \longrightarrow (\mathbf{1} + \mathrm{HNR_2}) \longrightarrow \mathbf{6}$$

From the equation, it was expected that the direct reaction of **1** with the secondary amine would be superior or at least equal to the reaction of **5** with **3** for the synthesis of the amidine compound (**6**). Therefore, the yields of **6a**—**d** formed by the reaction of **5a**—**d** with **3** in methanol (method A) were compared with those of the reaction of **1** with the corresponding amines (**7a**—**d**) under the same reaction conditions in methanol (method B). As shown in Table II, the yields of **6a**—**d** in method A were all fairly good but the yields in method B were generally poor. Particularly in the case of the acyclic amine (**7d**), **6d** was hardly detected even by thin-layer chromatography. Moreover, the reaction of **1** with the amines (**7**) in DMF gave no product, but the starting materials were recovered. From these results, it was suggested that the isocyanoacrylate derivative (**1**) was not an intermediate in the formation of the amidine compound (**6**) in this reaction. Therefore, the course of the reaction of **5** with **3** was proposed to be as shown in Chart 3. At the first step, the Michael type adduct (A), postulated in the previous paper,[13] should be formed by 1-4 addition of **3** to the vinylogous amidine moiety of **5**. Next, β-elimination of the labile amino group of the adduct **A** would yield **1**. At this stage, the insertion of the liberated amine into the isocyano group may be prevented by solvation of the isocyano group in a nucleophilic or amphoteric solvent. On the other hand, in a protic solvent or aprotic electrophilic solvent such as nitrobenzene, the isocyano group, which is a strong proton acceptor,[14] would abstract a proton from the solvent and/or **3** to form a cationic intermediate (B). Subsequently, synchronous migration of the amino group would yield the amidine compounds (**6a**—**e**). It was also suggested that the equilibrium between adduct **A** and a mixture of **1** and secondary amine (**7**) was inclined largely to the latter side in a nucleophilic or amphoteric solvent.

Table II. A Comparison of the Yields of Amidine Compounds (**6a**—**d**) obtained in Method A[a] and Method B[b]

Prod. No.	$\mathrm{NR_2}$	Yield (%)		mp (°C)
		Method A	Method B	
6a	1-Pyrrolidinyl	100	20	186—188
6b	Piperidino	63	5	167—169
6c	Morpholino	69	2	184—186
6d	Diethylamino	82	—	117.5—118.5

a) **5a**—**d** (8 mmol), **3** (8 mmol), MeOH (10 ml), at 25°C for 1 h.
b) **1** (8 mmol), **7a**—**d** (16 mmol), MeOH (10 ml), at 25°C for 1 h.

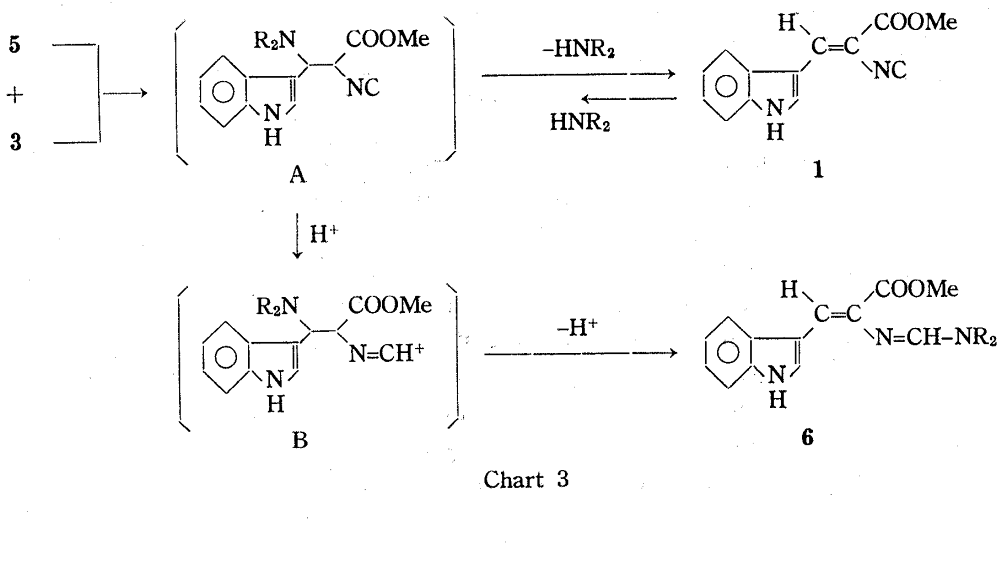

Chart 3

For the more convenient preparation of **1**, a one-pot synthesis from indole (**9**) was carried out in DMF, used as both a reagent and a solvent. The reaction of **9** with Vilsmeier–Haack reagent, prepared from phosphoryl chloride and DMF, provided a 3*H*-indolium salt (**10e**) and subsequent neutralization with sodium carbonate afforded the reactive intermediate **5e** *in situ*.[15] Then **3** was directly reacted with the intact **5e** in the reaction mixture to obtain **1** in 60% yield. When methanol was added as a co-solvent to the reaction mixture before the addition of **3**, **6e** was alternatively obtained in 80% yield (method C).

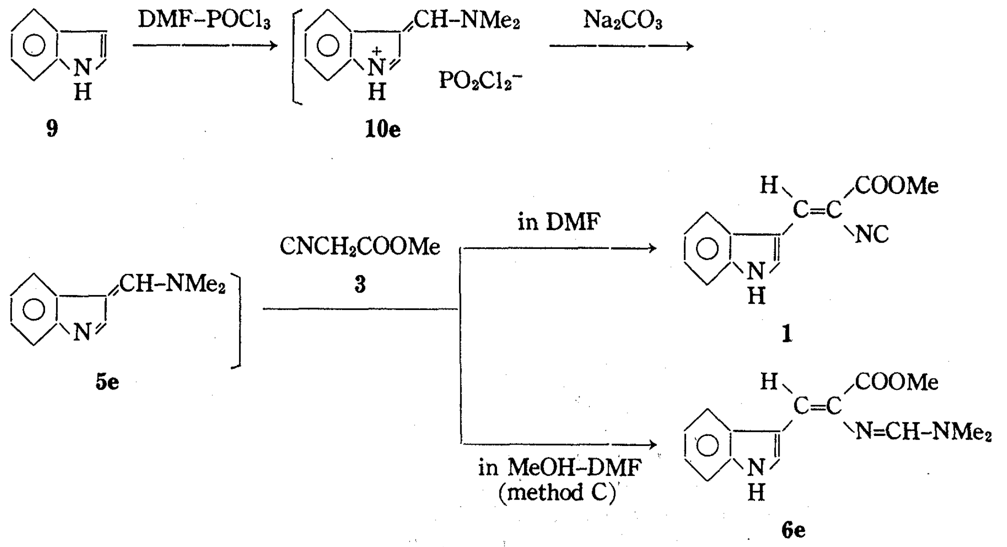

Chart 4

The compounds **1** and **6** were easily converted to *N*-formyl dehydrotryptophan derivatives by hydrolysis. Partial hydrolysis of **1** with aqueous formic acid in ether at room temperature, afforded (*Z*)-*N*-formyl-α,β-dehydrotryptophan methyl ester (**2**) in 90% yield. Further hydrolysis of **2** with sodium hydroxide in aqueous methanol gave (*Z*)-*N*-formyl-α,β-dehydrotryptophan (**8**) in 95% yield. Hydrolysis of **6a** with a slight excess of sodium hydroxide in refluxing aqueous methanol afforded **8** in 80% yield. Interestingly, partial hydrolysis of the amidine moiety of **6a** proceeded selectively on treatment with silica gel in chloroform saturated with water to afford **2** in 75% yield.

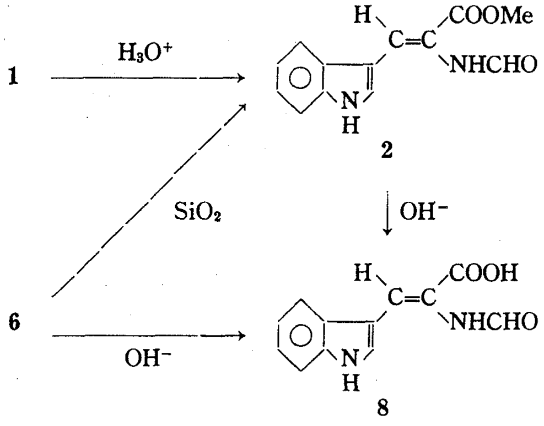

Chart 5

The geometry of these *N*-formyl derivatives (**2** and **8**) was deduced to be *Z*-form from the following observations. The starting materials (**1** and **6a**) were *Z*-isomers and the hydrolyzed products (**2** and **8**) thus obtained by the routes described above were identical with each other. Liquid chromatography (HPLC) analysis[16] also showed a single peak. The splittings of the absorptions of the formyl and amide protons in ^{1}H-NMR were distinctly assignable to rotational conformers of the amide group[11c,17] in single geometrical isomer. Additionally, it was reported that the thermodynamic stability of the *Z*-isomer is greater than that of the *E*-isomer even in the more bulky *N*-acetyl analog of the α,β-dehydrotryptophan derivative.[11c]

The amidine compounds (**6a**—**e**) and the isocyano compound (**1**) were screened for biological activities, and **1** showed weak antibacterial activity against *Tricophyton mentagrophytes*. The amidine compounds possessed inhibitory activity on blood platelet aggregation, and compounds **6a**, **b**, **e** showed activity comparable to that of aspirin. Further investigations on the activities of the congeners are in progress.

Experimental

All the melting points are uncorrected. IR spectra were obtained on a Shimadzu IR-27G spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi R-20A instrument, using tetramethylsilane (TMS) as the internal standard. ^{13}C-NMR spectra were measured with a JEOL FX-100 spectrometer in the pulsed Fourier transform mode using TMS as the external reference at 24.5°C. MS were taken on a Hitachi RMU-6M spectrometer at an ionizing potential of 30 eV.

Elemental analysis data for new compounds are listed in Table IV.

Reaction of 3-(1-Pyrrolidinylmethylene)-3*H*-indole (5a) with Methyl α-Isocyanoacetate (3) in DMF: Synthesis of Methyl (*Z*)-2-(1-Pyrrolidinylmethyleneamino)-3-[3(1*H*)-indolyl]acrylate (6a) and Methyl (*Z*)-2-Isocyano-3-[3(1*H*)-indolyl]acrylate (1)——Compound 3 (0.99 g, 10 mmol) was added to a solution of **5a** (1.59 g, 8 mmol) in DMF (20 ml) at 0°C with stirring. After being stirred at room temperature (25°C) for 1 h, the reaction mixture was shaken with a mixture of cracked ice (20 g), 0.2 N HCl (55 ml), and ether (50 ml × 2). The organic layer was dried and concentrated, and then the residue was crystallized from benzene to afford pale yellow prisms of **1** (1.32 g, 73%). mp 168—168.5°C. IR $\nu^{\text{KBr}}_{\text{max}}$ cm^{-1}: 3370 ($\nu_{\text{N-H}}$), 2100 ($\nu_{\text{N=C:}}$), 1705 ($\nu_{\text{C=O}}$), 1600 ($\nu_{\text{C=C}}$), 1270 ($\nu_{\text{C-O}}$). ^{1}H-NMR (DMSO-d_6) δ: 3.86 (3H, s, CH$_3$), 7.1—8.0 (4H, m, C-4, 5, 6, 7H), 8.04 (1H, s, olefinic H), 8.33 (1H, d, J=3.0 Hz, coalesced to a singlet on D$_2$O exchange, C-2H), 12.3 (1H, broad, D$_2$O-exchangeable, NH). MS *m/e*: 226 (M$^+$). ^{13}C-NMR (DMSO-d_6) δ: 52.8 (1C, q, CH$_3$), 107.2 (1C, s, NC), 108.2 (1C, s, C-3), 112.5 (1C, d, C-7), 118.2 (1C, d, C-4), 121.5 (1C, d, C-5), 123.2 (1C, d, C-6), 126.8 (1C, s, C-3a), 131.2 (1C, d, C-8), 131.3 (1C, d, C-2), 135.7 (1C, s, C-7a), 161.9 (1C, s, COO), 172.1 (1C, s, C-9).

The acidic aqueous layer was made alkaline with 2.5 N NaOH (5 ml) and extracted with AcOEt (50 ml × 2). The extract was dried and concentrated, and then the residue was crystallized from aqueous methanol to give yellow prisms of **6a** (0.24 g, 10%). mp 186—188°C. MS *m/e*: 297 (M$^+$). ^{13}C-NMR (DMSO-d_6) δ: 24.5 (2C, t, β-CH$_2$ of pyrrolidinyl group), 47.9 (2C, broad t, α-CH$_2$ of pyrrolidinyl group), 51.4 (1C, q, OCH$_3$), 111.5 (2C, s, C-3 and d, C-7), 114.7 (1C, d, C-8), 117.9 (1C, d, C-4), 119.3 (1C, d, C-6), 121.5 (1C, d, C-5), 126.9 (1C, s, C-3a), 127.9 (1C, d, C-2), 132.4 (1C, d, C-9), 135.4 (1C, s, C-7a), 151.9 (1C, d, C-11), 166.2 (1C, s, CO). The IR and ^{1}H-NMR spectral data are listed in Table III.

The reaction of **5a** with **3** was carried out similarly in other solvents, and the results are shown in Table I.

Methyl (*Z*)-2-(1-Pyrrolidinylmethyleneamino)-3-[3(1*H*)-indolyl]acrylate Hydrochloride (6a·HCl)——mp 203°C (dec.). The IR and ^{1}H-NMR spectral data are listed in Table III.

Syntheses of Methyl 2-(Aminomethyleneamino)-3-[3(1*H*)-indolyl]acrylates (6a—e)——The reactions were achieved according to the following three methods (A, B, and C).

Table III. Spectral Data for Methyl (*Z*)-2-(Aminomethyleneamino)-3-[3(1*H*)-indolyl]acrylates (**6a**—**e**)

No.	IR ($\nu^{\text{Nujol}}_{\text{max}}$, cm^{-1})	NMR (δ, ppm, in CDCl$_3$)							
		CH=C	N=CH–N	COOCH$_3$	C-2[a)]	C-4	C-5-7	NH[b)]	Others
6a	3150, 1700, 1605, 1235	7.45	8.12	3.80	8.15	7.9—8.0	7.0—7.4	8.9—9.2	1.6—2.0 (4H, m), 3.2—3.7 (4H, m)
6a·HCl	3330, 3160, 1680, 1620	7.99	7.5[c)]	3.83	7.09	7.1—7.9		10.4—11.0	1.7—2.4 (4H, m), 3.5—4.0 (4H, m), 12.1—12.3[b)] (1H, br)
6b	3400, 1700, 1630, 1220	7.42	7.78	3.80	8.00	7.6—8.0	7.0—7.4	8.5—8.9	1.3—2.0 (6H, m), 3.1—3.7 (4H, m)
6c	3410, 1695, 1630, 1250	7.47	7.82	3.85	8.00	7.7—8.0	7.0—7.4	8.5—8.9	3.3—3.9 (8H, m)
6d	3320, 1670, 1610, 1215	7.39	7.83	3.81	8.02	7.7—8.0	7.0—7.4	8.5—8.8	1.19 (6H, t, J=7.1), 3.40 (6H, q, J=7.1)
6e	3150, 1690, 1630, 1235	7.42	7.78	3.80	8.02	7.6—7.9	7.0—7.4	8.8—9.1	2.90 (6H, s)

a) Doublet, J=2.5—5.0 Hz. Coalesced to a singlet on D$_2$O exchange.
b) D$_2$O-exchangeable.
c) Broad, sharpened on D$_2$O exchange

Table IV. Elemental Analysis Data for New Compounds

No.	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Calcd Cl	Found C	Found H	Found N	Found Cl
1	$C_{13}H_{10}N_2O_2$	69.02	4.46	12.38		68.82	4.78	12.57	
6a	$C_{17}H_{19}N_3O_2$	68.66	6.44	14.13		68.45	6.56	14.22	
6a·HCl	$C_{17}H_{19}ClN_3O_2$	61.16	6.04	12.59	10.62	61.26	6.12	12.59	10.60
6b	$C_{18}H_{21}N_3O_2$	69.42	6.79	13.49		69.27	6.88	13.42	
6c	$C_{17}H_{19}N_3O_3$	65.15	6.11	13.41		65.10	6.29	13.42	
6d	$C_{17}H_{21}N_3O_2$	68.20	7.07	14.04		68.08	7.09	14.01	
6e	$C_{15}H_{17}N_3O_2$	66.40	6.31	15.48		66.56	6.56	15.47	
2	$C_{13}H_{12}N_2O_3$	63.93	4.93	11.47		63.63	5.17	11.32	
8	$C_{12}H_{10}N_2O_3 \cdot 1/6H_2O$	61.80	4.47	12.01		61.87	4.58	11.96	

Method A. Typical Procedure for the Reaction of 3-(Aminomethylene)-3*H*-indoles (**5a**—**d**) with **3** in Methanol: Compound **3** (2.08 g, 21 mmol) was added to a solution of **5a** (3.97 g, 20 mmol) in MeOH (20 ml) at 25°C with stirring. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with water (80 ml). The resulting yellow prisms were collected and washed with a small amount of MeOH to afford **6a** (5.94 g, 100%). mp 186—188°C.

Similar reactions of **5b**—**d** with **3** in MeOH gave the corresponding amidine compounds (**6b**—**d**).

Method B. Typical Procedure for the Reaction of **1** with Secondary Amines (**7a**—**d**): A mixture of **1** (1.81 g, 8 mmol) and pyrrolidine (**7a**) (1.14 g, 16 mmol) in MeOH (10 ml) was stirred at 25°C for 1 h. After concentration of the reaction mixture below 10°C under reduced pressure, the residue was shaken with 0.5 N HCl (40 ml) and $CHCl_3$ (100 ml). The aqueous layer was made alkaline with 2.5 N NaOH (10 ml) and then extracted with AcOEt (50 ml × 2). The extract was dried and concentrated to afford **6a** (0.48 g, 20%). mp 186—188°C.

Similar reactions of **1** with other secondary amines **7b**—**d** were carried out and the results are shown in Table II.

Method C. One-pot Synthesis of Methyl (*Z*)-2-(Dimethylaminomethyleneamino)-3-[3(1*H*)-indolyl]-acrylate (**6e**) from Indole (**9**): A solution of **9** (3.51 g, 30 mmol) in DMF (20 ml) was added dropwise to the Vilsmeier–Haack reagent [prepared from DMF (30 ml) and phosphoryl chloride (5.06 g, 33 mmol) at −5°C] at 0°C with stirring and the reaction mixture was kept at 35—40°C for 1 h. Anhydrous sodium carbonate (14.00 g, 132 mmol), MeOH (50 ml), and **3** (2.97 g, 30 mmol) were added successively to the reaction mixture with sufficient stirring at −5—0°C. After being stirred at room temperature (25°C) for 1 d, the reaction mixture was concentrated *in vacuo*, and treated as described in the case of the reaction of **5** with **3** in DMF. From the basic part, the desired **6e** (6.51 g, 80%, mp 163—164°C) was obtained, while **4** (0.39 g, 9%, mp 195—197°C) was also isolated from the neutral part as a by-product.

All amidine derivatives obtained were yellow prisms and were recrystallized from aqueous MeOH. The yields and melting points of **6a**—**d** obtained by method A and method B are summarized in Table II. The spectral data for **6a**—**e** are listed in Table III.

One-pot Synthesis of 1 from Indole (9)——Anhydrous sodium carbonate (14.00 g, 132 mmol) was added to the indolium salt **10e** (30 mmol in DMF 50 ml) [prepared as described in the synthesis of **6e** by method C] with sufficient stirring at 0°C, and then a solution of **3** (2.97 g, 30 mmol) in DMF (20 ml) was added at the same reaction temperature. After being stirred for 1 d at room temperature (25°C), the reaction mixture was treated as described in the case of the reaction of **5** with **3** in DMF to afford **1** (4.07 g, 60%, mp 166—168°C).

Synthesis of (*Z*)-*N*-Formyl-α,β-dehydrotryptophan Methyl Ester (2) by Partial Hydrolysis of 1——A solution of **1** (1.13 g, 5 mmol) in ether (100 ml) was vigorously stirred with 50% HCOOH (40 ml) at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The residue was diluted with water (30 ml) and then extracted with AcOEt (30 ml × 2). The organic layer was dried and concentrated, and the residue was crystallized to give **2** (1.10 g, 90%, mp 190—196°C), which was recrystallized from MeOH to afford pale yellow prisms having mp 196—198°C. IR ν_{max}^{KBr} cm^{-1}: 3350, 3210 (ν_{N-H}), 1700, 1660 ($\nu_{C=O}$), 1610 ($\nu_{C=C}$) ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 3.76 and 3.80 [3H (5 : 2),[18] s each, CH_3], 7.1—8.0 (4H, m, C-4, 5, 6, 7H), 7.78 (1H, s, olefinic H), 8.00 (1H, d, J = 3 Hz, coalesced to a singlet on D_2O exchange, C-2H), 8.05 and 8.31 [1H (2 : 5),[18] d (J = 12 Hz, coalesced to a singlet on D_2O exchange) and s, respectively, N–CHO], 9.22 and 9.63 [1H (2 : 5),[18] d (J = 12 Hz) and s, respectively, D_2O-exchangeable, NH–CO], 11.6—12.0 (1H, broad, D_2O-exchangeable, NH of indole). MS *m*/*e*: 244 (M^+).

Synthesis of 2 by Treatment of 6a with Silica Gel——A solution of **6a** (4.00 g, 13.5 mmol) in $CHCl_3$ (40 ml) was absorbed on a silica gel column (Merck, Kiesel Gel 60, 0.063—0.200 mm, 50 g), and the column was eluted with $CHCl_3$ saturated with water (1 l). From the eluate, 0.45 g (11%) of **6a** was recovered. The silica gel was extracted with hot MeOH (200 ml). The methanolic extract was concentrated and the residue was crystallized from aqueous methanol to afford **2** (2.48 g, 75%) as pale yellow prisms, mp 196—198°C.

Synthesis of (*Z*)-*N*-Formyl-*α*,*β*-dehydrotryptophan (8) by Hydrolysis of 2——A mixture of **2** (7.32 g, 30 mmol) and NaOH (1.60 g, 40 mmol) in 50% MeOH (100 ml) was stirred at 60°C for 8 h. After concentration, the reaction mixture was acidified with 10% HCl to obtain yellow prisms of **8** (6.56 g, 95%, mp 217°C (dec.)). An analytical sample was recrystallized from 65% EtOH, mp 219—220°C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3350, 3230 (ν_{N-H}), 1665 ($\nu_{C=O}$), 1610 ($\nu_{C=C}$). ^1H-NMR (DMSO-d_6) δ: 7.0—8.0 (4H, m, C-4, 5, 6, 7H), 7.79 (1H, s, olefinic H), 7.93 (1H, d, $J=3$ Hz, coalesced to a singlet on D_2O exchange, C-2H), 8.10 and 8.31 [1H (1: 2),[18] d ($J=12$ Hz, coalesced to a singlet on D_2O exchange) and s, respectively, N-CHO], 9.13 and 9.42 [1H (1: 2),[18] broad d ($J=12$ Hz) and broad s, respectively, D_2O-exchangeable, NH-CO], 11.6—12.0 and 12.5—13.0 (1H each, broad, D_2O-exchangeable, NH of indole and COOH), MS *m/e*: 230 (M^+).

Hydrolysis of 6a to 8——A suspension of **6a** (7.43 g, 25 mmol) and NaOH (1.60 g, 40 mmol) in 50% MeOH (100 ml) was refluxed for 1 h. Compound **8** was obtained from the reaction mixture by the same treatment as described above (4.60 g, 65%), mp 216—218°C (dec.).

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16) The *E* and *Z*-isomers in *N*-acetyl and *N*-benzoyl-*α*,*β*-dehydrotryptophan esters and *N*-formyl-*α*,*β*-dehydrophenylalanine esters were clearly observed as separated peaks on HPLC analysis (unpublished data): column, LS-410; mobile phase, MeOH-1% AcOH (1: 1); flow rate, 0.8 ml/min; detector 254 nm.
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18) These paired signals were due to rotational isomers of the formamido group, as shown in Chart 6. The minor conformer was assigned as the *cis*-amide conformation on the basis of the coupling constant, 12 Hz, between the formyl and amido protons.

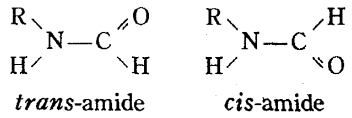

Chart 6