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INTERACTION OF 2-AMINOINDOLES WITH TETRACYANOETHYLENE.

1. 2-AMINO-3,4-DICYANO-α-CARBOLINES AND RELATED COMPOUNDS

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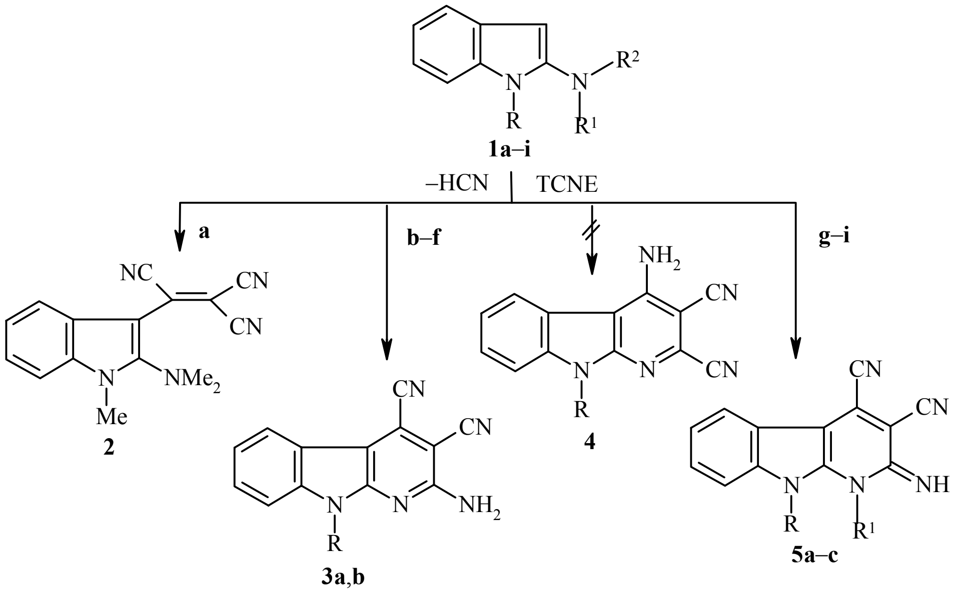
2-Aminoindoles are subject to attack by tetracyanoethylene at position 3 with, when possible, subsequent ring closure.

Keywords: 2-aminoindoles, carboline.

The presence in the 2-aminoindole molecule of a minimum of three positions capable of electrophilic attack enables the preparation from it of various condensed systems. Thus with β-dicarbonyl compounds 2-aminoindoles form derivatives of either pyrimido[1,2-*a*]indole or pyrido[2,3-*b*]indole [1]. We have investigated the interaction of 2-aminoindoles **1a-i** with tetracyanoethylene (TCNE) in neutral or weakly basic medium.



1 a $R = R^1 = R^2 = Me$; **b** $R = R^1 = R^2 = H$; **c** $R = Me, R^1 = R^2 = H$; **d** $R = H, R^1 = Ts, R^2 = H$; **e** $R = Me, R^1 = Ts, R^2 = H$; **f** $R = H, R^1 = COOBu, R^2 = H$; **g** $R = Me, R^1 = COOBu, R^2 = H$; **h** $R = Me, R^1 = COOMe, R^2 = H$; **i** $R+R^1 = –(CH_2)_3–, R^2 = H$; **3 a** $R = H$; **b** $R = Me$; **a** $R = Me, R^1=COOBu$; **b** $R = Me, R^1 = COOMe$; **c** $R+R^1= –(CH_2)_3–$

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When all the substituents R, R^1, and R^2 are alkyl groups, as in compound **1a**, the intense red 2-dimethylamino-1-methyl-3-tricyanovinylindole (**2**), which is readily soluble in the majority of the usual solvents, is formed. There are bands in its IR spectrum (Table 1) for the absorption of conjugated C≡N groups. In the ^{1}H NMR spectrum the singlet for the proton in position 3 of the indole ring was absent, but partially split doublets were present for the 4-H and 7-H protons and a multiplet for the 5-H and 6-H protons, and also two singlets for three methyl groups with an intensity ratio of 3:6 (Table 2). The mass spectrum also corresponded to that expected. Compound **2** is therefore the first example known to us when the tricyanovinyl group is directed to the ortho position relative to the dialkylamino group.

If one of the substituents R^1 or R^2 is a H atom, attack by TCNE may be effected either at position 3 of the indole ring or at the amino group in position 2. By reacting aminoindoles **1b,c** with TCNE in the presence of base we obtained yellow high-melting compounds, capable of being sublimed in vacuum and poorly soluble in the usual organic solvents, which clearly distinguishes them from compound **2**. In their mass spectra the most intense peak was the molecular ion $M^{+\cdot}$, there were peaks for doubly charged ions M^{++} and fragment ions $(M\text{-}CN)^+$ and $(M\text{-}HCN)^{+\cdot}$. The intensity of the peaks of each of the fragment ions did not exceed 5% of *I* for $(M^{+\cdot})$, which confirms the condensed aromatic character of the heterocycle. The IR and ^{1}H NMR spectra were compatible with the alternative structures **3** and **4**.

Since the spectral data proved to be insufficient for an indisputable choice between structures **3** and **4** we carried out a chemical determination of the structure of the compounds obtained. For this, the product **3a** of the reaction of **1b** with TCNE was subjected to prolonged alkaline hydrolysis in aqueous alcoholic medium. The dicarboxylic acid obtained (**6**) was decarboxylated by heating with CuO in quinoline. The IR spectrum of the compound obtained proved to be completely identical, including the finger-print region, to the spectrum of 2-amino-α-carboline **7**, a strong natural carcinogen, isolated previously by Japanese investigators from roasted beans and then synthesized by them [2,3]. The melting points also practically coincided (lit. 202, exp. 196-197°C). A different mp (238-240°C) has been reported for the alternative compound **8**.

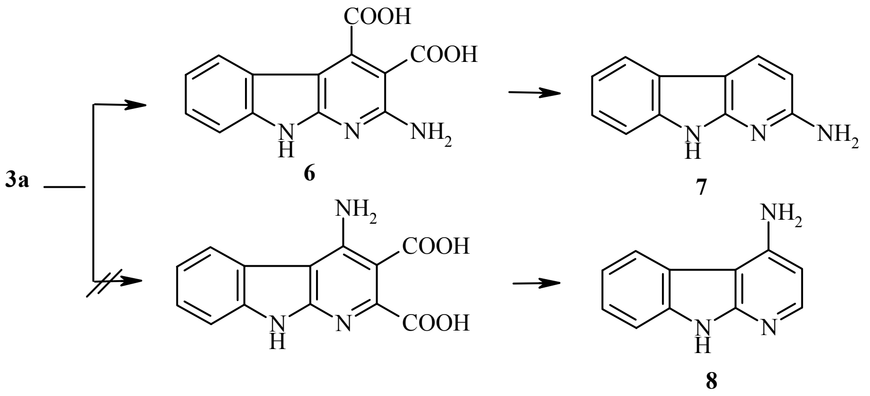
TABLE 1. IR Spectra of the Compounds Obtained, cm^{-1}

Compound	$\nu_{C\equiv N}$	ν_{NH}	$\nu_{C=O}$	Other
2	2220, 2210 (sh.)	—	—	1650 (sh., $\nu_{C=C}$)
3a	2215, 2210	3470, 3320, 3180	—	—
3b	2210	3455, 3315, 3180	—	—
5a	2230	3390, 3345, 3230, 3145	1690	—
5b	2235	3290, 3190 (br.)	1740	—
5c	2220	3320	—	—
6	—	3520 (sh.), 3420 (br.), 3330 (br.), 3200 (br.)*	1675	—
7	—	3400, 3300	—	1625 (br.), 1605, 1570, 1455, 1420, 1365, 1305, 1235, 1120, 740

* N–H + O–H

TABLE 2. ^{1}H NMR Spectrum of Compounds **2**, **3b**, and **5b,c**

Compound	δ, ppm
2	3.25 (6H, s, $N(CH_3)_2$); 3.75 (3H, s, NCH_3); 7.25-7.70 (4H, m, arom.)
3b	3.8 (3H, s, NCH_3); 7.2-8.1 (6H, m, arom. + NH_2)
5b	3.8 (3H, s, NCH_3); 4.0 (3H, s, OCH_3); 7.5-8.3 (4H, m, arom.); 10.55 (1H, br. s, NH)
5c	2.4 (2H, m, C–CH_2–C); 4.05 (2H, t), 4.2 (2H, t, 2 groups N–CH_2–C); 7.1 (1H, br. s, NH); 7.25-7.4 (2H, m, 6-H + 7-H); 7.5 (1H, d, *J* = 7 Hz); 7.85 (1H, d, *J* = 7 Hz, 5-H + 8-H)



The same products **3a,b** were also obtained from aminoindoles **1d-f**. It is interesting to note that fission of the tosyl group was effected in this way independent of the structure of the remaining part of the molecule, while fission of the ester group (compound **1f**) occurred only when the N atom in position 1 of the indole ring is unsubstituted.

In those cases when substituent R^1 was an ester group and substituent R on the indole nitrogen was alkyl (compounds **1g,h**), fission of the ester group did not occur and pale yellow 9-R-1-R^1-3,4-dicyano-2-imino-1,2-dihydro-α-carbolines **5** were isolated. An additional absorption band appeared in their IR spectra for a carbonyl group and in the ^{1}H NMR spectra the signals for the side groups were retained. There were peaks in the mass spectra for the molecular ion M$^{+·}$, and in addition, in difference to compound **3**, fairly intense peaks appeared for fragment ions. Similarly the substituted dihydro-α-carboline **5c** was also formed when both groups R and R^1 were alkyl (compound **1i**).

Attack by TCNE on aminoindoles in neutral or weakly basic medium is therefore directed to position 3 of the indole ring, and the structure of the products is determined by the number and character of the substituents R, R^1, and R^2.

TABLE 3. Characteristics of the Compounds Obtained

Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	M$^{+·}$	Yield, %
2	$C_{16}H_{13}N_5$	69.58 69.80	4.61 4.76	24.93 25.44	227-230	275	28
3a	$C_{13}H_7N_5$	66.73 66.95	3.05 3.03	29.96 30.03	>300 (dec.)	233	34*; 30*^{2}; 95*^{3}
3b	$C_{14}H_9N_5$	68.41 68.01	3.53 3.67	27.95 28.32	>300 (dec.)	247	39*; 33*^{2}
5a	$C_{19}H_{17}N_5O_2$	66.18 65.70	4.55 4.93	19.74 20.16	>250 (dec.)	347	99
5b	$C_{16}H_{11}N_5O_2$	63.43 62.95	3.16 3.63	23.08 22.94	>300 (dec.)	305	56
5c	$C_{16}H_{11}N_5$	70.59 70.32	3.78 4.06	25.19 25.63	>300 (dec.)	273	54*^{2}
6	$C_{13}H_9N_3O_4$	57.99 57.57	2.88 3.34	15.92 15.49	>300 (dec.)	—	53
7	$C_{11}H_9N_3$	71.97 72.11	5.12 4.95	22.74 22.94	196-197	183	12

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* Method A.

*^{2} Method B.

*^{3} Method C

EXPERIMENTAL

A check on the progress of reactions and the purity of the products synthesized was effected by TLC on Silufol UV 254 plates with visualization with UV radiation or iodine vapor. The IR spectra were taken on a UR 20 instrument in thin films (nujol suspension). The ^{1}H NMR spectra were taken on Bruker MV 250 or AM 300 instruments, solvent was DMSO-d_6 or $CDCl_3$. The mass spectra were obtained on a Varian MAT 111 (70 eV) instrument with insertion of samples into the ion source.

Aminoindole **1a** was synthesized by the procedure of [5], the hydrochloride **1b·HCl** by the procedure of [1], **1c·HCl** and **1i·HCl** by the procedure of [6], and compounds **1f-h** as described in [7].

2-Dimethylamino-1-methyl-3-tricyanovinylindole (2). TCNE (0.62 g, 4.8 mmol) was added in small portions to a solution of 2-dimethylamino-1-methylindole (**1a**) (0.77 g, 4.4 mmol) in ether (5 ml). The mixture became colored and boiled. After the end of the exothermic reaction the mixture was boiled 1 h further under reflux, and then the reaction mixture was left for a week to crystallize. The precipitated dark semicrystalline solid was filtered off, washed with ether, and purified by crystallization from glacial acetic acid. For the final purification the compound was subjected to flash chromatography on a dry column [8] in the system benzene–chloroform with dry application, to give dark-red needles, poorly soluble in ether, readily soluble in the majority of other organic solvents.

2-Amino-3,4-dicyano-α-carboline (3a). A. Triethylamine (5.5 mmol) was added to a suspension of **1b** HCl (5 mmol) in 2-propanol (10 ml). A warm solution of TCNE (5.5 mmol) in 2-propanol (5 ml) was added dropwise to the resulting solution of **3a**. The mixture was stirred with gentle heating for a further 1 h, the precipitated solid was filtered off, washed with 2-propanol, and air-dried. The compound was recrystallized from DMF or subjected to sublimation in vacuum. **2-Amino-3,4-dicyano-9-methyl-α-carboline (3b)** was obtained similarly from **1c**·HCl, and **1,2-dicyano-3-imino-5,6-dihydro-3H,4H-3a,6a-diazafluoranthene (5c)** from **1i**·HCl.

B. TCNE (5.5 mmol) was added in small portions with stirring to a suspension of **1d** (5 mmol) in hot dioxane (15 ml) containing Et_3N (2-3 drops). The mixture was boiled for 3 h, cooled, the precipitated solid **3a** was filtered off, and purified as indicated above. Compound **3b** was obtained analogously from **1e**.

C. Compound **3a** was also obtained from 2-butoxycarbonylaminoindole **1f** by an analogous procedure.

1-Butoxycarbonyl-3,4-dicyano-2-imino-9-methyl-1,2-dihydro-α-carboline (5a). TCNE (5.5 mmol) was added in small portions with stirring to a warm solution of 2-butyloxycarbonylamino-1-methylindole (**1g**) (5 mmol), containing 2-3 drops Et_3N. The mixture was boiled for 1 h, cooled, the precipitated solid was filtered off, washed with dioxane, dried, and recrystallized from dioxane for purification. **3,4-Dicyano-2-imino-1-methoxycarbonyl-9-methyl-1,2-dihydro-α-carboline (5b)** was obtained analogously from 2-methoxycarbonylamino-1-methylindole **1h**.

2-Amino-α-carboline-3,4-dicarboxylic acid (6). A 20% solution (40 ml) of KOH was added to a suspension of **3a** (0.43 g, 1.8 mmol) in ethanol (10 ml) and the mixture obtained was boiled under reflux until complete solution of the starting material (about 30 h). The reaction mixture was carefully neutralized with 20% HCl. The precipitated solid, containing a significant quantity of silicic acid (from dissolution of the glass), was filtered off, and treated with 5% Na_2CO_3 solution. The solution obtained was separated from the precipitate of silicic acid, and the solid was washed several times more with Na_2CO_3 solution. The filtrates were combined, once again neutralized with hydrochloric acid, and the operation described above was repeated several times. The carbonate solution obtained was slowly neutralized by the dropwise addition of glacial acetic acid with stirring. The precipitated solid was filtered off, washed with distilled water, and dried over $CaCl_2$. Yield of the product was 0.26 g.

2-Amino-α-carboline (7). Powdered CuO (25 mg) was added to compound **6** (0.23 g, 0.87 mmol) in quinoline (1.5 ml) and the mixture obtained was heated under reflux. The course of the reaction was observed by the change in volume of gas evolved. After 2 h the mass was cooled, ether (5 ml) was added, and the mixture stirred. The yellow solution was decanted from the resinous solid, and the solid was washed sequentially with hexane, ether, and acetone. The extracts were combined with the quinoline solution, the solvents were distilled off in vacuum. The residue was dissolved in ethyl acetate, the solution washed with 5% KOH solution, with water, and the organic layer dried over $CaCl_2$. The drying agent was removed, and the solution evaporated to dryness. The residue was subjected to column chromatography (silica gel, benzene–ethyl acetate), and for the final purification a sample was sublimed in vacuum. Practically colorless product (0.022 g) was obtained.

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