Sublimation at 100 °C (0.065 mm) afforded 1.5 g (75%) of a light yellow solid. A second sublimation afforded analytically pure, colorless crystals: mp 135–137 °C; IR ($CHCl_3$) 3505–2755 (br, w, OH), 1713 (s, C=O), 1687 (s, C=O), 1485 (s), 1435 (m), 1412 (m), 1390 (m), 1330 (m), 1280 (m), 1250 (s), 1200 (s), 1140 (s), 1062 (m), 925 (w), 725 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H, CH_3), 2.82 (AA′, t, 2 H, apparent J = 7.5 Hz, CH_2CO_2H), 3.80 (s, 3 H, OCH_3), 4.53 (BB′, t, 2 H, apparent J = 7.5 Hz, NCH_2), 5.91 (d, 1 H, J = 3.9 Hz, C_4 pyrrole H), 6.91 (d, 1 H, J = 3.9 Hz, C_3 pyrrole H), 10.85–11.15 (br s, 1 H, OH). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.97; H, 5.88; N, 6.57.

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Registry No. 2a, 86129-38-6; **2b**, 86129-39-7; **2c**, 86129-40-0; **2d**, 86129-41-1; **2e**, 86129-42-2; **2f**, 86129-43-3; **3a**, 43227-83-4; **3b**, 86129-44-4; 4 ($R^1 = R^3 = R^4 = H$), 78-94-4; 4 ($R^1 = CH_2CH_2CH_3$; $R^3 = R^4 = H$), 2918-13-0; 4 ($R^1 = R^3 = H$; $R^4 = CH_3$), 814-78-8; **5a**, 83483-17-4; **5b**, 86129-45-5; **5c** (isomer 1), 86129-46-6; **5c** (isomer 2), 86129-47-7; **5d** (isomer 1), 86129-48-8; **5d** (isomer 2), 86129-49-9; (*E*)-3-hexen-2-one, 4376-23-2; (*Z*)-3-hexen-2-one, 86129-50-2; dimethoxyethylamine, 22483-09-6; (*R*)-(−)-2-aminobutanol, 5856-63-3; methyl nitroacetate, 2483-57-0; 3-aminopropanol, 156-87-6; benzylamine, 100-46-9; β-alanine, 107-95-9.

Indoles as Dipolarophiles toward 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide

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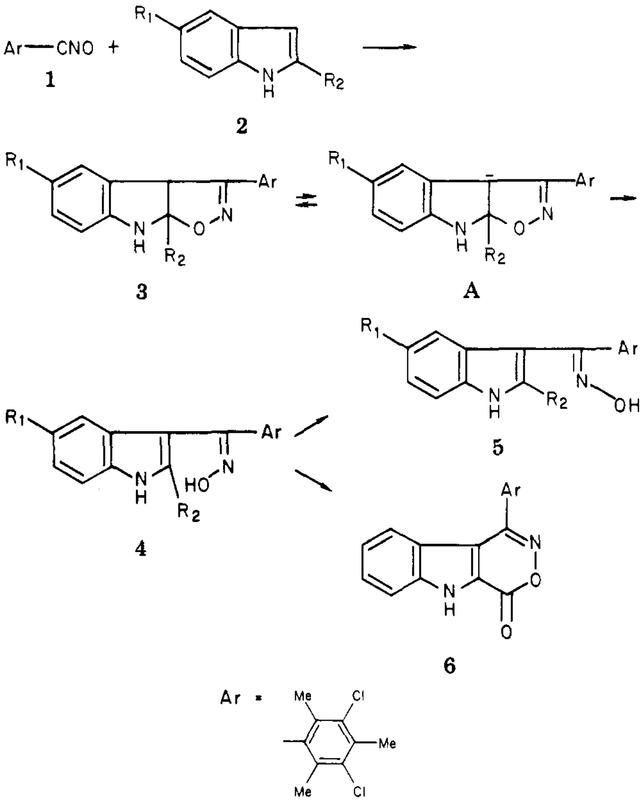
In spite of the well-known propensity of aromatic heterocycles to undergo substitution rather than addition reactions, 1,3-dipolar cycloadditions to five-membered, electron-rich heteroaromatics are documented in the chemical literature.[1-10] Our previous contribution in this area was concerned with the behavior of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (1) toward furan, thiophene, and their benzoderivatives.[9] Recently, a report appeared dealing with the reaction of benzonitrile and mesitonitrile oxides with indole and N-substituted indoles.[11] This paper prompted us to report the results obtained in our laboratory upon treatment of 1 with the indole derivatives **2a–e**.

Scheme I



[a] **a**, $R_1 = R_2 = H$; **b**, R_1 = OMe, R_2 = H; **c**, $R_1 = NO_2$, R_2 = H; **d**, R_1 = H, R_2 = Me; **e**, R_1 = H, R_2 = COOEt;

The reaction between 1 and 2 was carried out in boiling benzene by using a large excess of the potential dipolarophile to minimize side reactions of 1. Heating was continued until the disappearance of the starting nitrile oxide; reaction times, products, and yields are collected in Table I.

Although both oximes **4a** and **5a** could be isolated in pure form by column chromatography, the *Z* isomer **4a** was found to rearrange completely to the stable *E* form **5a** (Scheme I) on heating for a few hours or by standing at room temperature for several days. It was ascertained that the tricyclic compounds **3c** and **3e** are not stable in boiling benzene but change slowly to give **5c** and **6**, respectively. In harmony with this trend, the TLC analyses of the reaction mixtures showed that **5c** and **6** were practically absent at short times, thus suggesting that these compounds are secondary products. On the other hand, when the reaction of **2a** was monitored by periodic TLC analyses, an intermediate product became evident, the isolation of which through chromatographic procedures was precluded by its lability. This goal, however, was reached upon treatment of 1 with a modest excess of **2a** followed by removal in vacuo of the volatile components and fractional recrystallization of the resulting mixture. The new product, which was formulated as **3a**, was shown to originate on heating a mixture of **4a** and **5a**; the same oximes were obtained when passing **3a** through a silica gel column. Interestingly, the rearrangement of the cycloadducts **3a,c** to ring-opened oximes was greatly accelerated by the presence of triethylamine, being complete within 1 h at

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Table I. Reaction of Nitrile Oxide 1 with Indoles 2

compd	time, h	product(s)[a]	yield, %	mp,[b] °C	solvent: NMR,[c] δ
2a	9	**5a**	63	200 (CCl_4)	CD_3COCD_3: 2.22 (6 H, s), 2.54 (3 H, s), 6.88 (1 H, d, *J* = 3),[d] 7.0–7.6 (3 H, m), 8.2–8.4 (1 H, m), 9.5 (1 H, br s),[e] 10.4 (1 H, br s)[e]
		4a	17	187 (benzene)	CD_3COCD_3: 2.18 (6 H, s), 2.58 (3 H, s), 6.2–6.4 (1 H, m), 6.7–7.2 (2 H, m), 7.3–7.5 (1 H, m), 8.72 (1 H, d, *J* = 3),[d] 9.9 (1 H, br s),[e] 10.8 (1 H, br s)[e]
		3a	*f*	157 (acetone)	C_6D_6: 1.70 (3 H, s), 2.16 (3 H, s), 2.36 (3 H, s), 4.5 (1 H, br s),[e] 4.39 (1 H, d, *J* = 8), 6.02 (1 H, dd, *J* = 8 and 3),[g] 6.2–6.5 (3 H, m), 6.8–7.0 (1 H, m)
2b	5	**5b**	64	210 (benzene)	CD_3COCD_3: 2.18 (6 H, s), 2.52 (3 H, s), 3.78 (3 H, s), 6.76 (1 H, d, *J* = 3),[d] 6.84 (1 H, dd, *J* = 8.5 and 2.5), 7.30 (1 H, d, *J* = 8.5), 7.72 (1 H, d, *J* = 2.5), 9.4 (1 H, br s),[e] 9.8 (1 H, br s)[e]
2c	24	**5c**	10	290 dec (acetone)	CD_3SOCD_3: 2.14 (6 H, s), 2.59 (3 H, s), 7.36 (1 H, d, *J* = 2.5), 7.60 (1 H, d, *J* = 8.5), 7.94 (1 H, dd, *J* = 8.5 and 2.5), 8.54 (1 H, d, *J* = 3),[d] 10.1 (1 H, br s),[e] 10.7 (1 H, br s)[e]
		3c	42	243 (acetone)	CD_3SOCD_3: 1.46 (3 H, s), 2.40 (3 H, s), 2.51 (3 H, s), 5.34 (1 H, d, *J* = 8), 6.74 (1 H, d, *J* = 8.5), 6.80 (1 H, dd, *J* = 8 and 3),[g] 7.3–7.4 (1 H, m), 8.04 (1 H, dd, *J* = 8.5 and 2.5), 8.8 (1 H, br s)[e]
2d	13	**5d**	59	209 (benzene)	CD_3COCD_3: 1.98 (3 H, s), 2.24 (6 H, s), 2.52 (3 H, s), 6.8–7.4 (3 H, m), 7.7–7.9 (1 H, m), 9.9 (1 H, br s),[e] 10.2 (1 H, br s)[e]
2e	10	**3e**	40	179 (chloroform)	$CDCl_3$: 1.38 (3 H, t), 1.64 (3 H, s), 2.46 (3 H, s), 2.54 (3 H, s), 4.38 (2 H, q), 5.30 (1 H, s), 5.8 (1 H, br s),[e] 6.4–6.8 (3 H, m), 7.0–7.2 (1 H, m)
		6	25	280 dec (acetone)	CD_3SOCD_3: 2.14 (6 H, s), 2.64 (3 H, s), 6.5–6.7 (1 H, m), 7.1–7.8 (3 H, m), 13.6 (1 H, br s)[e]

[a] The products listed are new compounds; all of them gave satisfactory elemental analyses (C, H, N ±0.3%) and correct molecular peaks in the mass spectra. [b] Recrystallization solvent in parentheses. [c] *J* in hertz. [d] Singlet after deuteriation of the NH group. [e] Exchangeable with D_2O. [f] See text. [g] Doublet after deuteriation of the NH group (*J* = 8 Hz).

room temperature; some acceleration was also observed in the presence of hydrogen chloride. Similar effects were found for the conversion of **3e** to **6**.

For the structures of the above products, we rely upon analytical data, spectral properties, and chemical behavior. In particular, the vicinal coupling between CH and NH protons in the oximes **4a** and **5a–c** provides clear-cut evidence which excludes isomeric formulas due to bond formation between the carbon of the nitrile oxide and the 2-position of the indole ring. Although such evidence is not available for **5d**, the latter structure is firmly established by the close analogy of its NMR and mass spectra with those of **5a**. That the *E* structures **5** are stable configurations is not surprising in the light of literature data for imines[12] and oximes[11] of mesityl ketones. Structural assignments to the cycloadducts **3a,c,e**, were suggested by the spectral evidence and confirmed by their conversion to **5a,c** and **6**, respectively. The formation of **6** from **3e** clearly involves the intermediacy of a ring-opened oxime, which then undergoes an intramolecular displacement of the ethoxy group. Such a process has precedent in the construction of the 1,2-oxazine ring.[13]

Examination of the above results indicates that the isolated oximes are in reality not substitution products but derive from first-formed cycloadducts of type **3**. This means that the indoles undergo concerted 1,3-dipolar cycloaddition in which the carbon of the nitrile oxide bonds to the 3-position of the heterocyclic ring. Such behavior matches what has recently been found for indole and N-substituted indoles toward benzonitrile and mesitonitrile oxides;[11] it is proven to be general in the light of the results presented here. Interestingly, the regiospecificity observed in the case of the indole system is at variance with the finding of both possible regioisomers in the reaction of nitrile oxides with benzofuran and benzothiophene.[8,9]

It remains to be noted that the stability of the tricyclic compounds **3** is dependent on the substituents, being greater in the case of electron-withdrawing groups. This effect may perhaps be ascribed to kinetic stabilization of the anionic species A, which represents a plausible intermediate in the ring-opening of **3** (see Scheme I).

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Varian HA-100 instrument with Me_4Si as an internal standard.

General Procedure for the Reaction of Nitrile Oxide 1 with Indoles 2. A solution of **1**[14] (3 mmol) and **2** (15 mmol) in benzene (30 mL) was refluxed for the time given in Table I. After evaporation of the solvent, the mixture was chromatographed on a silica gel column by eluting first with benzene to separate the excess of **2** and then with benzene–ethyl acetate (9:1) to afford the products indicated in the table (in order of elution).

Isolation of Cycloadduct 3a. A solution of **1** (1 mmol) and **2a** (1.5 mmol) in benzene (10 mL) was refluxed for 10 h. After evaporation of the solvent under reduced pressure, the excess of **2a** was removed in vacuo at 40 °C. Two fractional recrystallizations of the residue from acetone gave **3a** in the pure state (35%).

General Procedure for the Reaction of Cycloadducts 3 with Triethylamine. A mixture of **3** (1 mmol), triethylamine (5 mL), and benzene (5 mL) was left at room temperature for 1 h. After removal of the volatile components under reduced pressure, the residue was taken up with diisopropyl ether and filtered to give practically pure product, namely, **4a**, **5c**, and **6** from **3a**, **3c**, and **3e**, respectively.

Registry No. 1, 13456-86-5; **2a**, 120-72-9; **2b**, 1006-94-6; **2c**, 6146-52-7; **2d**, 95-20-5; **2e**, 3770-50-1; **3a**, 86120-01-6; **3c**, 86120-02-7; **3e**, 86120-03-8; **4a**, 86120-04-9; **5a**, 86120-05-0; **5b**, 86120-06-1; **5c**, 86120-07-2; **5d**, 86120-08-3; **6**, 86120-09-4.

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