Dyes and Pigments 2 (1981) 11–20

A NOVEL CYCLISATION OF *o*-CYANODIARYLAZO-COMPOUNDS†

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SUMMARY

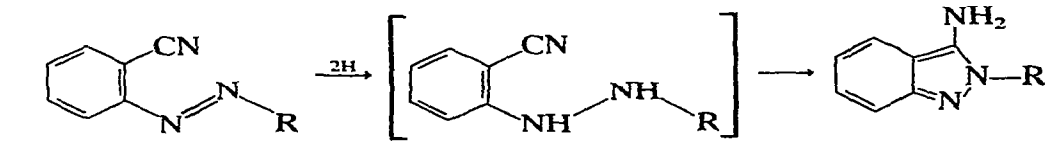
In the presence of strongly basic primary, secondary and tertiary amines having α-methylene- or methyl- groups, certain o-cyanodiarylazo-compounds, including the commercially important 3-acetylamino-4-(2-cyano-4,6-dinitrophenylazo)-NN-diethylaniline (11), *undergo reductive cyclisation to the corresponding 3-aminoindazoles. The scope of the reaction is described and a possible mechanism is discussed. The reverse reaction can be accomplished by passing a stream of air through a nitrobenzene solution of the 3-aminoindazole in the presence of a copper salt and certain tertiary bases.*

1. INTRODUCTION

o-Cyanodiarylazo-compounds (1; R = aryl) are reduced by stannous chloride in boiling ethanol[1] to the hydrazo-compounds (2; R = aryl) which cyclise spontaneously to the 3-amino-2-arylindazoles (3; R = aryl). The few *o*-cyanodiarylazo-compounds and *o*-cyanophenylazo-heterocyclic compounds (1; R = heterocyclic residue) resistant to stannous chloride in ethanol readily undergo reductive cyclisation with zinc in acetic acid.[2] Similar reductive cyclisations of *o*-cyanodiarylazo- and *o*-cyanophenylazo-heterocyclic compounds have also been achieved[3] with sodium dithionite in alkaline medium. For obvious reasons, however, all these methods are restricted to *o*-cyanoarylazo-compounds devoid of easily reducible substituents, e.g. nitro groups. The direct

† The content of this paper was originally the subject of a lecture given at the 7th International Dyestuffs Symposium, Interlaken, Switzerland, September 1979.

Dyes and Pigments 0143-7208/81/0002-0011/$02·50



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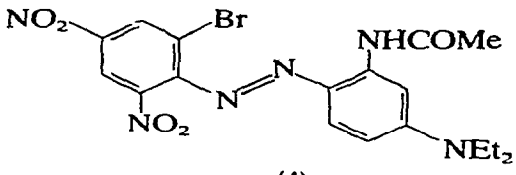

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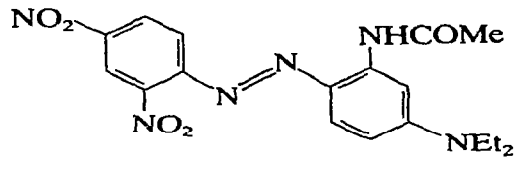

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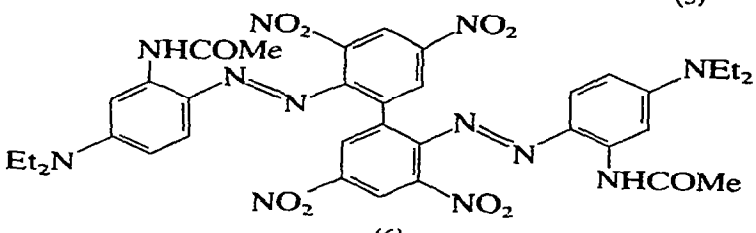

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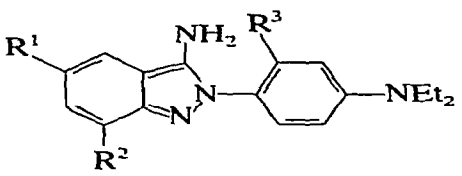
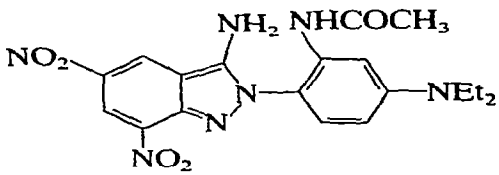


(7) $R^1 = R^2 = NO_2$, $R^3 = NHCOMe$
(8) $R^1 = R^2 = NO_2$, $R^3 = H$
(9) $R^1 = R^2 = NO_2$, $R^3 = NMeCOMe$
(10) $R^1 = NO_2$, $R^2 = CN$, $R^3 = H$

preparation of certain nitrated 3-amino-2-arylindazoles, otherwise difficult to obtain,[4] from the corresponding *o*-cyanodiarylazo-compounds is now reported.

2. RESULTS AND DISCUSSION

In the course of an investigation[5] of the copper-promoted conversion of (4) into the commercially important (11) by reaction with formaldoxime and a base in nitrobenzene the formation of a brown impurity was observed under certain conditions. In the presence of triethylamine the latter was effectively the sole product of the reaction and was identified as the aminoindazole (7). Thin-layer



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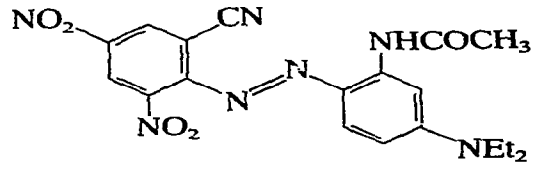


(11)

TABLE 1

RESULTS OF TREATING (11) WITH VARIOUS BASES IN NITROBENZENE AT 90°C

Base	pK_a[a]	*Time* (h)	*Results*
Piperidine	11·1	24	complete conversion to (7)-1-nitrobenzene[b]
Diethylamine	11·04	24	complete conversion to (7)-1-nitrobenzene[b]
Triethylamine	10·75	24	complete conversion to (7)-1-nitrobenzene[b]
Benzylamine	9·33	30	complete conversion to (7)-1-nitrobenzene[b]
Imidazole	6·93	48	no reaction
2,6-Lutidine	6·6	48	no reaction
Pyridine	5·21	48	no reaction
Aniline	4·63	48	no reaction

[a] pK_a of conjugate acid.[6]

[b] The reaction mixtures were cooled and filtered. After washing with nitrobenzene and drying, the products had infrared spectra identical with that of authentic (7)-1-nitrobenzene.

chromatography suggested that (11) was an intermediate in the conversion of (4) into (7) and further work revealed that (11) is smoothly converted into (7) on heating with triethylamine in nitrobenzene. This surprising observation prompted a further investigation of this reaction and the results of heating (11) with various organic bases in nitrobenzene are summarised in Table 1. From these it can be seen that the conversion of (11) into (7) proceeds only in the presence of strong bases which may be primary, secondary or tertiary amines. With weaker bases no aminoindazole formation occurs, even on very prolonged heating. In the absence of nitrobenzene, (11) is converted into (7) even more readily (Table 2) and in certain bases the reaction takes place effectively instantaneously at room temperature. Again the conversion of (11) into (7) proceeds only in strongly basic primary, secondary or tertiary amines. Under these conditions, however, the reaction fails with di- and tri-ethylamine; this is attributed to the fact that (11) is completely insoluble in these bases.

The scope of the reaction with regard to *o*-cyanodiarylazo-compounds is relatively limited and is illustrated by the results summarised in Table 3. It is significant that the reaction occurs only with those *o*-cyanodiarylazo-compounds [(11), (17), (19), (20)] in which the aryl residue containing the cyano-group has at least two strongly electronegative substituents in *ortho* and *para* positions relative to the azo group. Reaction proceeds most readily when both of these are nitro-groups and the *ortho'* position of the *o*-cyanodiarylazo-compound is unsubstituted (19), and, in this case, is complete when the temperature of the reaction mixture reaches 90°C. The first step in the reaction

TABLE 2
RESULTS OF TREATING (11) WITH VARIOUS BASES IN THE ABSENCE OF SOLVENT

Base	pK_a[a]	*Temp* (°C)	*Time* (h)	*Results*
Pyrrolidine	11·27	20	0·05	complete conversion to (7)[b]
Piperidine	11·1	20	0·05	complete conversion to (7)[b]
Diethylamine[c]	11·04	90	18	no reaction
Ethylamine	10·81	20	0·3	complete conversion to (7)
Triethylamine[c]	10·75	90	18	no reaction
N-ethyl benzylamine	9·4	90	0·5	complete conversion to (7)[b]
Benzylamine	9·33	20	0·05	complete conversion to (7)[b]
NN-dimethyl benzylamine	8·6	90	18	complete conversion to (7)[b]
Morpholine	8·33	90	0·5	complete conversion to (7)[b]
NN-diethylaniline	6·61	90	18	no reaction
2,6-lutidine	6·6	90	18	no reaction
Pyridine	5·21	90	18	no reaction
Aniline	4·63	90	18	no reaction

[a] pK_a of conjugate acid.
[b] Infrared spectrum of isolated product identical with that of authentic material.
[c] (11) is insoluble in these bases.

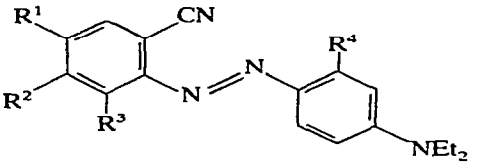
(Scheme 1) is seen as a one-electron transfer from the strongly basic triethylamine to the highly polarised (19) giving rise to the radical anion (26). There is an increasing amount of experimental evidence to indicate[7] that this is a fairly general reaction pathway which is particularly common in reactions involving nitro compounds having the ability to delocalise the unpaired electron. Various canonical forms of the radical anion are possible but (26) is favoured[8] since the negative charge on the α-nitrogen atom is stabilised by the multiplicity of electronegative groups on ring A of the molecule and the electron deficient radical on the β-nitrogen atom by the *p*-diethylamino-group on ring B. Hydrogen transfer from the triethylamine radical cation to the radical anion then leads to the ion pair (27). Hydrogen abstraction from the α-carbon atom of alkylamines by radicals is well established[9] and, in this context, it is noteworthy (Tables 1 and 2) that only those amines having α-methylene or methyl groups are effective in converting *o*-cyanodiarylazo-compounds into the corresponding 3-aminoindazoles. Further reaction could follow several pathways, the most likely being that outlined in Scheme 1, viz. proton transfer to give the hydrazine (28) which then undergoes spontaneous cyclisation[1-3] to the 3-aminoindazole (8).

Introduction of substituents in the *ortho* position of ring B markedly reduces the rate of the reaction (Table 3). Thus the conversion of (17) into (9) is considerably slower than that of (19) into (8), and that of (11) into (7) even slower. This result is in keeping with the proposed mechanism since it is known[10] that the *N*-methylacetylamino-group is twisted out of the plane of the molecule and is weakly electronegative in character, reducing the overall

polarisation of the molecule. The even greater retarding effect of the acetylamino-group is attributed to deprotonation[10] of the latter in the strongly basic medium generating an anionic species and thereby suppressing the first step in the overall reaction, electron transfer from the base to the azo-compound. The slower reaction of (20) relative to (19) and the failure of (12) and (18) to undergo conversion of the corresponding 3-aminoindazoles in the

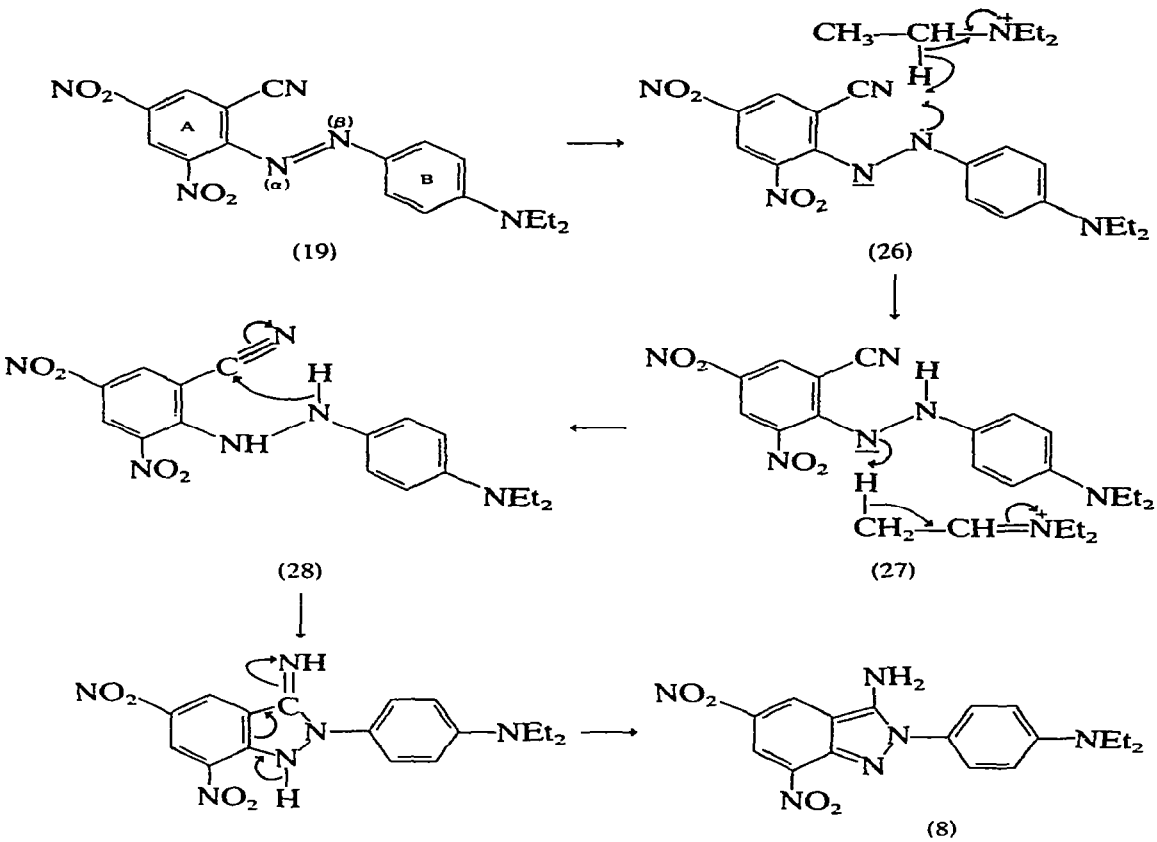
TABLE 3

RESULTS OF TREATING THE *o*-CYANODIARYLAZO-COMPOUNDS (11)–(25) WITH TRIETHYLAMINE IN NITROBENZENE AT 90°C



(12) $R^1 = NO_2$, $R^2 = H$, $R^3 = CN$, $R^4 = NHCOMe$
(13) $R^1 = Br$, $R^2 = H$, $R^3 = NO_2$, $R^4 = NHCOMe$
(14) $R^1 = Me$, $R^2 = H$, $R^3 = NO_2$, $R^4 = NHCOMe$
(15) $R^1 = Br$, $R^2 = H$, $R^3 = Me$, $R^4 = NHCOMe$
(16) $R^1 = R^2 = R^3 = H$, $R^4 = NHCOMe$
(17) $R^1 = R^3 = NO_2$, $R^2 = H$, $R^4 = NMeCOMe$
(18) $R^1 = NO_2$, $R^2 = H$, $R^3 = CN$, $R^4 = NMeCOMe$
(19) $R^1 = R^3 = NO_2$, $R^2 = R^4 = H$
(20) $R^1 = NO_2$, $R^3 = CN$, $R^2 = R^4 = H$
(21) $R^1 = Br$, $R^3 = NO_2$, $R^2 = R^4 = H$
(22) $R^1 = NO_2$, $R^2 = R^3 = R^4 = H$
(23) $R^1 = R^3 = R^4 = H$, $R^2 = NO_2$
(24) $R^1 = Br$, $R^3 = Me$, $R^2 = R^4 = H$
(25) $R^1 = R^2 = R^3 = R^4 = H$

o-Cyanodiarylazo compound	*Time* (h)	*Results*
(11)	24	complete conversion to (7)-1-nitrobenzene
(12)	24	no reaction
(13)	24	no reaction
(14)	24	no reaction
(15)	24	no reaction
(16)	24	no reaction
(17)	6	complete conversion to (9)
(18)	24	no reaction
(19)	—	conversion to (8) complete on reaching 90°C
(20)	3	complete conversion to (10)
(21)	24	no reaction
(22)	24	no reaction
(23)	24	no reaction
(24)	24	no reaction
(25)	24	no reaction



Scheme 1

presence of triethylamine (Table 3) is ascribed to the lower capacity of the cyano-group to aid unpaired electron delocalisation compared with that of the nitro-group.

The ability of copper compounds to promote the aerial oxidation of organic compounds has been recognised[11] for many years and reactions of this type are frequently carried out in the presence of organic bases. It has now been shown that the 3-aminoindazoles (7) and (8) are oxidised to the corresponding *o*-cyanodiarylazo-compounds (11) and (19) when a stream of air is passed through a solution of the former in nitrobenzene in the presence of a copper salt and a base. The reaction fails when the base is a primary, secondary or tertiary amine having an α-methylene or methyl-group but proceeds smoothly in the presence of co-ordinating tertiary bases, e.g. 2,6-lutidine. The mechanism of the oxidation is not clear[11] but it is apparent that the reverse reaction is dominant in the presence of those amines capable of promoting it.

The relatively facile conversion of the important bright blue dyestuff (11) into the brown aminoindazole (7) has considerable technical significance since, even at low concentrations, the latter has a very marked greening and dulling effect on the former.

3. EXPERIMENTAL

^{1}H nmr spectra were recorded on a Hitachi–Perkin–Elmer R-24A spectrometer at 60 MHz or a Varian HA-100 spectrometer at 100 MHz, using tetramethylsilane as internal standard, and mass spectra were recorded with an A.E.I. MS90 spectrometer. Thin layer chromatography was carried out on Eastman Chromagram Sheets 13181 (silica gel) using cyclohexane–chloroform (1 : 1), nitromethane–toluene (7 : 93), and ethylacetate–light petroleum (3 : 2) as eluants.

3.1. 3-*Amino*-2-(2-*acetylamino*-4-NN-*diethylaminophenyl*)-5,7-*dinitroindazole* (7)

(a) A stirred mixture of 3-acetylamino-4-(2-bromo-4,6-dinitrophenylazo-*NN*-diethylaniline) (4) (2·4 g), formaldoxime trimer (0·9 g), copper (I) iodide (1·0 g), triethylamine (0·85 g), and nitrobenzene (50 ml) was heated to 90°C for 2 h when tlc showed the reaction mixture to contain 3-acetylamino-4-(2-cyano-4,6-dinitrophenylazo)-*NN*-diethylaniline (11), small amounts of 3-acetylamino-4-(2,4-dinitrophenylazo)-*NN*-diethylaniline (5) and 3-acetylamino-4-{2-[3,5-dinitro-2-(2-acetylamino-4-*NN*-diethylaminophenylazo)phenyl]-4,6-dinitrophenylazo}-*NN*-diethylaniline (6) together with a brown product which remained on the baseline of the chromatogram. After a further 24 h the mixture, which now contained no 3-acetylamino-4-(2-cyano-4,6-dinitrophenylazo)-*NN*-diethylaniline (11), was cooled and filtered. The residue was extracted (thimble) with boiling ethanol and the extracts were filtered while still hot. On cooling the filtrate deposited 3-amino-2-(2-acetylamino-4-*NN*-diethylaminophenyl)-5,7-dinitroindazole-1 ethanol, which crystallised from ethanol as brown prisms. (Found: C, 55·4; H, 5·4; N, 21·0. M^+ 427. $C_{21}H_{27}N_7O_6$ requires C, 55·25; H, 5·75; N, 20·7%). $\delta(CF_3COOH)$ 1·4 (9H, overlapping triplets, CH_3CH_2N, CH_3CH_2O), 2·24 (3H, s, CH_3CO), 3·9 (4H, q, CH_3CH_2N), 4·45 (2H, q, CH_3CH_2O), 7·65–8·5 (3H, m, aromatic) and 9·42–9·7 (2H, d, 4,6H). Crystallisation from methanol gave 3-amino-2-(2-acetylamino-4-*NN*-diethylaminophenyl)-5,7-dinitroindazole-1 methanol as brown prisms. (Found: C, 52·6; H, 5·2; N, 21·4. M^+ 427. $C_{20}H_{25}N_7O_6$ requires C, 52·3; H, 5·5; N, 21·35%.) Crystallisation from DMSO gave 3-amino-2-(2-acetylamino - 4 - *NN* - diethylaminophenyl) - 5,7 - dinitroindazole - 1 DMSO as brown prisms. (Found: C, 50·3; H, 5·4; N, 19·6. M^+ 427. $C_{21}H_{27}N_7O_6S$

requires C, 49·9; H, 5·4; N, 19·4%.) δ(CF_3COOH) 1·4 (6H, t, CH_3CH_2), 2·26 (3H, s, CH_3CO), 2·97 (6H, s, CH_3SO), 3·9 (4H, q, CH_3CH_2) 7·65–8·5 (3H, m, aromatic), and 9·3–9·65 (2H, d, 4,6H).

(b) A stirred mixture of 3-acetylamino-4-(2-cyano-4,6-dinitrophenylazo)-*NN*-diethylaniline (11) (2·1 g), triethylamine (0·5 g), and nitrobenzene (50 ml) was heated at 90°C for 24 h when tlc showed effectively complete disappearance of the *o*-cyanodiarylazo-compound. The mixture was cooled to room temperature and filtered to obtain 3-amino-2-(2-acetylamino-4-*NN*-diethylaminophenyl)-5,7-dinitroindazole-1-nitrobenzene (1·75 g, 63·5%) which crystallised from nitrobenzene as brown prisms. (Found: C, 54·8; H, 4·8; N, 20·5, $C_{25}H_{26}N_8O_7$ requires C, 54·55; H, 4·75; N, 20·35%.) Crystallisation (thimble) from ethanol gave 3-amino-2-(2-acetylamino-4-*NN*-diethylaminophenyl)-5,7-dinitroindazole-1-ethanol as brown prisms. (Found: C, 55·1; H, 5·6: N, 20·7%.) The results of replacing the triethylamine used in this experiment by equimolecular amounts of various bases are summarised in Table 1.

(c) 3-Acetylamino-4-(2-cyano-4,6-dinitrophenylazo)-*NN*-diethylaniline (11) (0·5 g) was added to benzylamine (25 ml) with stirring at room temperature. The initially blue solution very rapidly became reddish-brown in colour and after 10 minutes light petroleum (400 ml) was added. Decantation of the solvent gave 3-amino-2-(2-acetylamino-4-*NN*-diethylaminophenyl)-5,7-dinitroindazole which, on crystallisation from ethanol, gave 3-amino-2-(2-acetylamino-4-*NN*-diethylaminophenyl)-5,7-dinitroindazole-1-ethanol as brown prisms, infrared spectrum identical with that of authentic material. The results of replacing the benzylamine used in this experiment by equal volumes of various bases are summarised in Table 2.

3.2. 3-*Amino*-2-(4-NN-*diethylaminophenyl*)-5,7-*dinitroindazole* (8)

A stirred mixture of 4-(2-cyano-4,6-dinitrophenylazo)-*NN*-diethylaniline (19) (4·2 g), triethylamine (1·7 g), and nitrobenzene (100 ml) was heated to 90°C when tlc showed complete disappearance of the *o*-cyanodiarylazo-compound. The mixture was cooled and methanol (300 ml) was added dropwise. After standing overnight the mixture was filtered to obtain 3-amino-2-(4-*NN*-diethylaminophenyl)-5,7-dinitroindazole (8) (3·05 g, 82·5%) which crystallised (thimble) from methanol as red–brown needles. (Found: C, 55·5; H, 4·9; N, 22·8. M^+ 370. $C_{17}H_{18}N_6O_4$ requires C, 55·1; H, 4·9; N, 22·7%.) δ(DMSO) 1·15 (6H, t, CH_3CH_2), 3·4 (4H, q, CH_3CH_2), 6·5–7·5 (4H, m, 1,2,4,5 aromatic) 8·65–9·3 (2H, d, 4,6H).

3.3. 3-*Amino*-2-(4-NN-*diethylaminophenyl*)-5-*nitro*-7-*cyanoindazole* (10)

When the 4-(2-cyano-4,6-dinitrophenylazo)-*NN*-diethylaniline in the preceding experiment was replaced by 4-(2,6-dicyano-4-nitrophenylazo)-*NN*-

diethylaniline (20), reaction to give 3-amino-2-(4-*NN*-diethylaminophenyl)-5-nitro-7-cyanoindazole (10) went to completion in 3 h. The *product* crystallised (thimble) from ethanol as red–brown prisms. (Found: C, 61·7; H, 4·8; N, 23·8. M^+ 350. $C_{18}H_{18}N_6O_2$ requires C, 61·7; H, 5·2; N, 24·0%.)

3.4. *3-Amino-2-(2-N-methylacetylamino-4-NN-diethylaminophenyl)-5,7-dinitroindazole* (9)

This *product* was obtained by a similar method and crystallised (thimble) from ethanol as red-brown needles. (Found: C, 54·3; H, 5·5; N, 22·3. M^+ 441. $C_{20}H_{23}N_7O_5$ requires C, 54·4; H, 5·25; N, 22·2%.) The results of similar experiments with a variety of *o*-cyanodiarylazo-compounds are summarised in Table 3.

3.5. *Aerial oxidation of 3-amino-2-(2-acetylamino-4-NN-diethylaminophenyl)-5,7-dinitroindazole* (7)

A stream of air was passed through a stirred mixture of 3-amino-2-(2-acetylamino-4-*NN*-diethylaminophenyl)-5,7-dinitroindazole (7) (2·15 g), copper (I) iodide (0·95 g), 2,6-lutidine (1·05 g), and nitrobenzene (50 ml) at 90°C for 20 h. The mixture was cooled, filtered and the filtrate was diluted with light petroleum (200 ml). Filtration gave 3-acetylamino-4-(2-cyano-4,6-dinitrophenylazo)-*NN*-diethylaniline (11) (1·8 g, 84%) which crystallised (thimble) from methanol as glistening green rods. (Found: C, 53·4; H, 4·3; N, 22·7. M^+ 425. Calc. for $C_{19}H_{19}N_7O_5$: C, 53·65; H, 4·45; N, 23·05%.) Infrared spectrum identical with that of authentic material. In the absence of either the copper (I) iodide or the 2,6-lutidine the aminoindazole remained unchanged.

3.6. *Aerial oxidation of 3-amino-2-(4-NN-diethylaminophenyl)-5,7-dinitroindazole* (8)

Under comparable conditions to those employed in the preceding experiment 3-amino-2-(4-*NN*-diethylaminophenyl)-5,7-dinitroindazole (5) gave 4-(2-cyano-5,7-dinitrophenylazo)-*NN*-diethylaniline (19) which crystallised (thimble) from methanol as black rods. (Found: C, 55·2; H, 4·1; N, 22·6. M^+ 368. Calc. for $C_{17}H_{16}N_6O_4$: C, 55·4; H, 4·5; N, 22·8%.) Infrared spectrum identical with that of authentic material.

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