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REDUCTIVE CYCLIZATION OF AROMATIC NITRO COMPOUNDS TO BENZIMIDAZOLES WITH TITANOUS CHLORIDE

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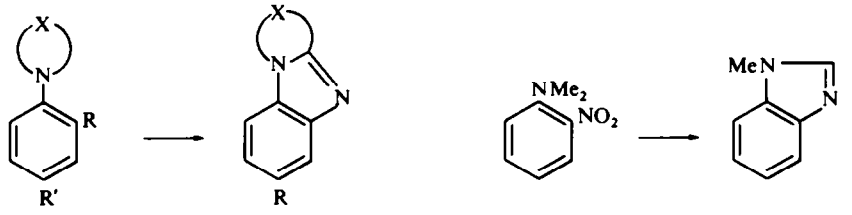
Abstract—N-2-Nitrophenyl-, -naphthyl-, -pyridyl-, and -quinolyl- heterocycles have been reductively cyclized to the corresponding benzimidazoles of type II and X–XVI in excellent yield with $TiCl_3$. A reaction mechanism for this convenient synthesis is postulated.

WE have recently reported on the scope and mechanism of the uncatalysed thermal cyclization of various N-2-nitroaryl heterocycles, N-substituted 2-nitroanilines, and 2-nitrophenyl ethers[1] as well as of oxidative cyclizations of N-2-aminoaryl heterocycles[2] to give the appropriate benzimidazoles. We now wish to describe a convenient method involving reductive cyclization of N-2-nitroaryl heterocycles with titanous chloride, again yielding benzimidazoles.

A few examples of nitro compounds undergoing cyclization to benzimidazoles by reducing agents are scattered in the literature. For instance, Spiegel and Kaufmann noted[3] that 2,4-dinitrophenyl piperidine (I; R = R′ = NO_2, X = $[CH_2]_5$) gave the tetrahydropyridobenzimidazole (II; R = NO_2, X = $[CH_2]_4$) in very small yield together with the expected aminocompound (I; R = NH_2, R′ = NO_2, X = $[CH_2]_5$). Cyclization was thought to be due to the intermediacy of the 2-nitrosocompound (I; R = NO, R′ = NO_2, X = $[CH_2]_5$) which ring-closed onto the α-methylene group of the piperidine. All attempts by these workers to improve the yields were abortive. Analogous results describing the conversion of dimethylamino-2-nitrobenzene (III) into the benzimidazole (IV) with tin and hydrochloric acid or with sulphur dioxide were reported by Pinnow[4] and by Lauer[5] respectively.

As part of our general benzimidazole studies we decided to investigate the scope and mechanism of such reductive cyclizations by using the easily standardized titanous chloride as a reducing agent. We chose N-2-nitrophenylhydroazepine (I; R = NO_2, R′ = H, X = $[CH_2]_6$) for the initial experiments because the ring-size of the heterocyclic moiety is sterically favourable for cyclization according to models (Stuart-Briegleb) and previous experience.[2,6] The reduction under nitrogen was carried out by adding titanous chloride to a hydrochloric acid solution of the nitro compound at 80°. When two equivalents of the reducing agent had been consumed the benzimidazole (II; R = H, X = $[CH_2]_5$) separated as hydrochloride in quantitative yield. The scope of this reaction was explored by varying the heteroparaffinic as well as the aromatic moiety and results are given in Table 2.

Piperidino compounds gave usually lower yields than their 5- or 7-membered ring analogues, possibly for steric reasons. When the heteroparaffinic moiety was either

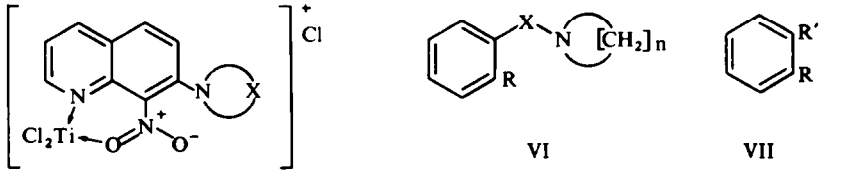


I II III IV

morpholine or N-methylpiperazine (e.g. I; $X = CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2$ or $CH_2 \cdot CH_2 \cdot NMe \cdot CH_2 \cdot CH_2$) cyclization did not occur and only the appropriate amine corresponding in amount to the reducing agent used was obtained. The lower yield of pyridinoimidazoles (cf. Table 2; XVI) was partly due to the products being very water soluble. Nevertheless, this route is superior to the azide method by which we have prepared these compounds previously[6] in 10–15% yield only. In the naphthalene series reduction had to be carried out below 45° because at a higher temperature the nitrocompounds underwent a rearrangement which we are investigating at present.

The quinolines (XII–XV) as well as the pyridines (XVI) required 3 mole equivalents of $TiCl_3$ for cyclization. Undoubtedly 1 mole of reagent was used up in complex formation involving the 'aromatic' nitrogen in addition to the 2 moles needed for cyclization. The formation of 1:1 adducts with tertiary nitrogen is well known for aliphatic[7] and aromatic[8] compounds. With 8-nitroquinolines the endpoint was not detectable and the reaction required excess of reagent yet giving much lower yields (cf. Table 2; XV). Formation of a stable complex (e.g. V) involving the nitro group is possibly responsible for interfering with the normal mechanism of cyclization. Complexes of the reagent with nitro compounds[9] as well as chelates with 8-substituted quinolines[10] have, in fact, been observed.

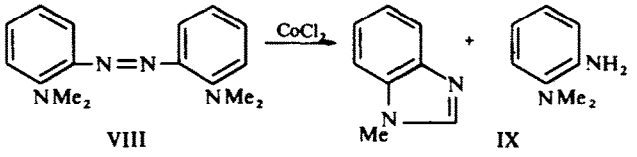
The importance of the role and position of the "tertiary nitrogen" in these reactions was clearly illustrated by the failure of other nitro compounds (e.g. VI; $R = NO_2$, $X = CH_2$, $n = 4$–5 or VII; $R = NO_2$, $R' = OMe$, Ac, $C_6H_{11}NH$, Ph, and $PhNH \cdot CH_2$) to cyclize under the reaction conditions. The corresponding 2-amino compounds (VI and VII, $R = NH_2$) were the only new materials detected. If the function of the reducing agent were simply to produce a nitroso compound for cyclization to occur as originally suggested[3] then some of the above nitro compounds (VI and VII) would be expected to ring-close. Moreover, Caro's acid ($H_2S_2O_8$) which is a specific reagent for converting a primary amine into a nitroso compound[11]



V VI VII

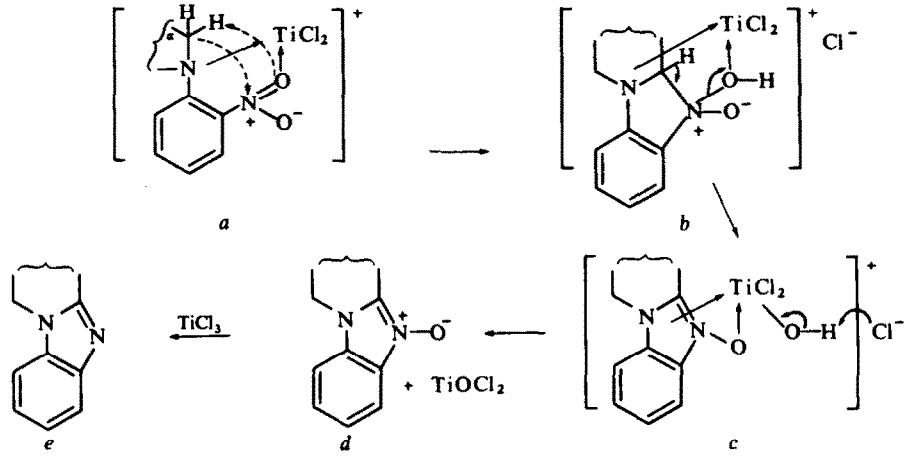
failed to cyclize the amine (I; $R = NH_2$, $R' = NO_2$, $X = [CH_2]_5$) to the corresponding benzimidazole. In fact it appears from our previous work that nitroso compounds (e.g. I; R = NO) will be cyclized to benzimidazoles (II) under oxidizing

rather than reducing conditions involving an N-oxide as intermediate[2]. Titanous chloride and similar reagents appear to have a dual function in this reaction, namely as a reducer as well as chelating agent which aligns the reactive centres. A similar example of the effect co-ordination can have on the reactivity of organic compounds was described only recently[12] when cobalt chloride was observed to cause cyclization of the t-amino compound (VIII) to the benzimidazole (IX) with elimination of a



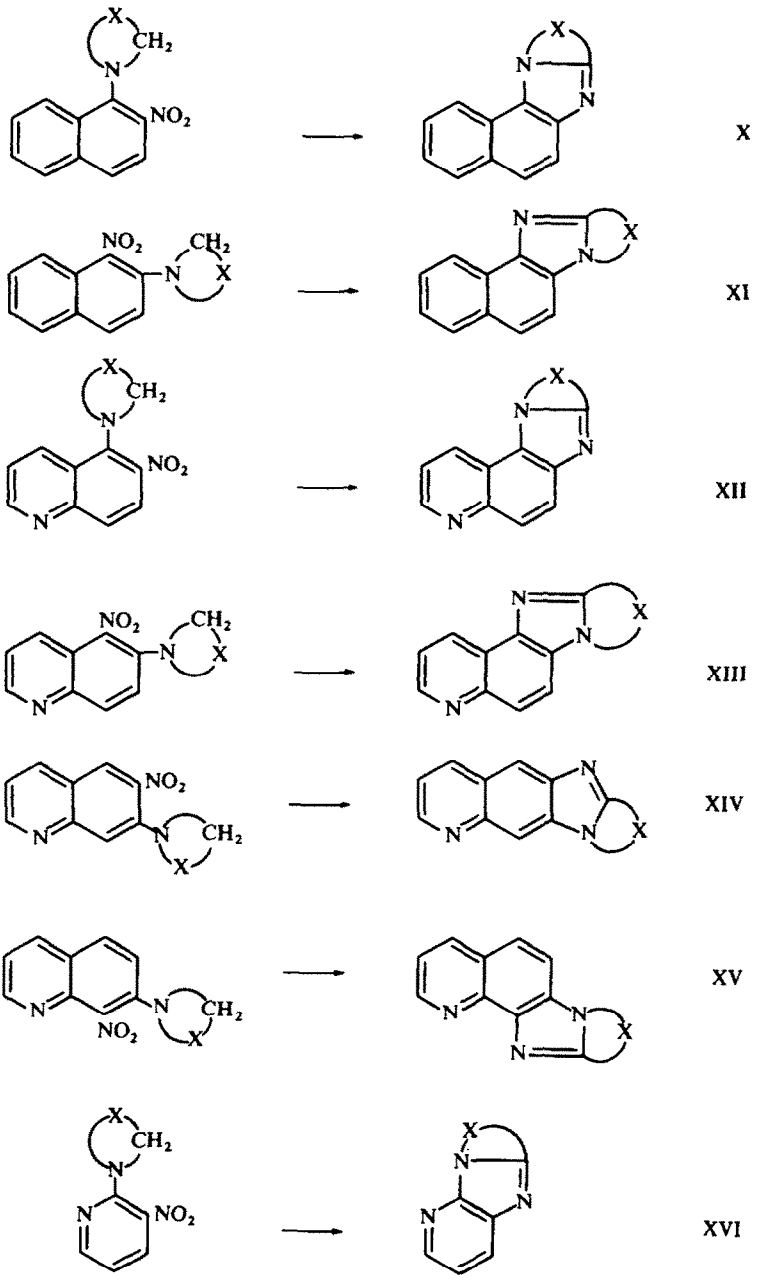
VIII IX

diamine. On the basis of the above arguments we proposed the mechanism as set out ($a \rightarrow e$) to account for the reductive cyclization of the nitro compounds with $TiCl_3$. Complex formation with the reagent (a) is followed by proton transfer and



ring-closure (b) on to the activated and favourably positioned α-methylene group. Benzimidazole-N-oxide (d) is produced via the π-complexed intermediate* (c)—which is formed by overlap of the metal atom with the π-orbitals of the benzimidazole nitrogen and O atoms—with elimination of $TiOCl_2$ which accounts for 1 mole of reagent. The deoxygenation of the N-oxide ($d \rightarrow e$) which was shown in a blank experiment to require 1 mole of $TiCl_3$ completes the reaction with overall consumption of 2 moles of the reducing agent. The failure of the morpholino- and N-methylpiperazino-derivatives to cyclize (cf. above) is probably due to titanous chloride being prevented from forming the complex (a) because of preferential chelation with the other hetero-atom (O or N) in the ring.

* We thank the referee for this suggestion.



EXPERIMENTAL

Preparation of nitro compounds. The compounds of type I (R = R′ = NO_2 and R = NO_2, R′ = H) the nitropyridines (XVI; X = $[CH_2]_{3-4}$) and the nitronaphthalenes (X; XI; X = $[CH_2]_{2-4}$) were prepared as described.[6,13] *The N-(o-nitrobenzyl) heterocycles* (VI, X = CH_2; n = 4 or 5) were made from

2-nitrobenzyl bromide (1 mole) dissolved in benzene and piperidine or pyrrolidine (2·1 moles) added dropwise in the cold. The precipitated base hydrobromide was filtered off and the filtrate extracted with dilute HCl. On neutralizing the acid extract with Na_2CO_3 the nitro compounds separated as oils and were purified by distillation *in vacuo*. The pyrrolidino compound had b.p. 160°/1 mm,and the piperidino compound m.p. 38° corresponding to lit. values.[14,15]

The 5-chloro-6-nitro-[21] and 7-chloro-6-nitro-,[21] 7-chloro-8-nitro-[22] and 6-chloro-5-nitroquinolines[23] were made by literature methods as indicated. Condensation with the required bases was as above and usually quantitative and properties of the products are listed in Table 1.

TABLE 1. N-NITROQUINOLYL HETEROCYCLES MADE FROM CHLORONITROQUINOLINES AND N-HETEROPARAFFINIC BASES

Quinoline substituent	Found (%)				Required (%)	
	M.p.	C	H	Formula	C	H
6-NO_2—5-C_4H_8N—	102°	64·5	5·4	$C_{13}H_{13}N_3O_2$	64·2	5·4
6-NO_2—5-$C_5H_{10}N$—	102	65·4	5·7	$C_{14}H_{15}N_3O_2$	65·0	5·9
6-NO_2—5-$C_6H_{12}N$—	106	66·7	6·3	$C_{15}H_{17}N_3O_2$	66·4	6·3
5-NO_2—6-C_4H_8N	183	63·8	5·5	$C_{13}H_{13}N_3O_2$	64·2	5·4
5-NO_2—6-$C_5H_{10}N$	62	65·4	5·9	$C_{14}H_{15}N_3O_2$	65·0	5·9
6-NO_2—7-C_4H_8N	115	64·0	5·7	$C_{13}H_{13}N_3O_2$	64·2	5·4
6-NO_2—7-$C_5H_{10}N$	83	65·4	5·5	$C_{14}H_{15}N_3O_2$	65·0	5·9
6-NO_2—7-$C_6H_{12}N$	80	66·6	6·2	$C_{15}H_{17}N_3O_2$	66·4	6·3
8-NO_2—7-C_4H_8N	169	63·9	5·3	$C_{13}H_{13}N_3O_2$	64·2	5·4
8-NO_2—7-$C_5H_{10}N$	105	65·4	5·4	$C_{14}H_{15}N_3O_2$	65·0	5·9
8-NO_2—7-$C_6H_{12}N$	72	66·5	6·3	$C_{15}H_{17}N_3O_2$	66·4	6·3

All other nitro compounds used were commercially available.

Reudctive cyclization. In a typical example the nitro compound (2 g) was dissolved in conc HCl (60 ml) and the stirred soln (magnetic stirrer) kept at 80° under N_2 after it had been de-aerated (15 min) by passing a stream of N_2 through the mixture. $TiCl_3$ standardized against *m*-nitroaniline[16] was added slowly over 1 hr to the hot reaction mixture until the purple colour of the reagent persisted which required approximately 2 moles. The reaction mixture was cooled and the imidazole hydrochloride filtered off. If the salt did not separate the reaction mixture was made alkaline (NH_4OH) and extracted with $CHCl_3$. For the pyridines extraction was continuous for 24 hr.

In the case of the quinolines and pyridines 3 moles $TiCl_3$ were used because of complex formation. Results are given in Table 2.

The nitronaphthalenes were heated to 45° only.

When N-(2,4-dinitrophenyl)piperidine (2 g) was treated as above and the product was chromatographed on alumina with benzene the following compounds were eluted in the order given: (i) starting material (33%), (ii) N-(2-amino-4-nitrophenyl piperidine (10%, m.p. 96° lit. m.p. 96°[17], (iii) 7-nitro-1,2,3,4-tetrahydro [1.2-*a*] benzimidazole (II; R = NO_2, *n* = 4), (55%, m.p. 220–222° lit. m.p. 219°[17]), and (iv) N-(4-amino-2-nitrophenyl) piperidine (2%, m.p. 114° lit. m.p. 116°[17]).

Miscellaneous reductions. Nitro-morpholino- and -N-methylpiperazino compounds gave only the corresponding amino compounds when treated with $TiCl_3$ under various conditions. The benzylnitro compounds (VI; R = NO_2, X = CH_2, *n* = 4 or 5) and the nitro compounds (VII, R = NO_2 R′ = OMe. Ac, $C_6H_{11}N$—, Ph and Ph NH·CH_2) produced aminocompounds only.

Benzimidazole-N-oxide required 1 mole $TiCl_3$ for conversion into the parent compound under the general reaction conditions.

Oxidation with Caro's acid. Treatment of 2-amino-4-nitrophenylpiperidine with Caro's acid in the usual way[11] produced an intractable mixture of compounds. A similar result was obtained from 2-amino-phenylpiperidine.

TABLE 2. IMIDAZOLES (II, X–XVI) OBTAINED BY REDUCTION OF THE APPROPRIATE NITRO COMPOUNDS (I, X–XVI) WITH TITANOUS CHLORIDE IN CONCENTRATED HCl AT 80°

Imidazole	X	R	M.p.	Yield (%)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
II	$[CH_2]_3$	CF_3	148°	quant.	58·2	3·8	$C_{11}H_9F_3N_2$	58·4	4·0
	$[CH_2]_4$	Me	126[19]	quant.	—	—	—	—	—
	$[CH_2]_3$	H	115[20]	quant.	—	—	—	—	—
	$[CH_2]_5$	H	124[20]	quant.	—	—	—	—	—
X	$[CH_2]_3$	H	147	quant.	80·3	5·9	$C_{14}H_{12}N_2$	80·7	5·8
	$[CH_2]_4$	H	128	74	81·1	6·7	$C_{15}H_{14}N_2$	81·1	6·4
	$[CH_2]_5$	H	155	quant.	81·2	6·9	$C_{16}H_{16}N_2$	81·3	6·8
XI	$[CH_2]_3$	H	160	quant.	80·7	6·0	$C_{14}H_{12}N_2$	80·7	5·8
	$[CH_2]_4$	H	162[21]	72	—	—	—	—	—
XII	$[CH_2]_3$	H	213	quant.	74·4	5·4	$C_{13}H_{11}N_3$	74·6	5·3
	$[CH_2]_4$	H	190	82	75·5	6·0	$C_{14}H_{13}N_3$	75·3	5·9
	$[CH_2]_5$	H	161	quant.	75·8	6·5	$C_{15}H_{15}N_3$	76·0	6·4
XIII	$[CH_2]_3$	H	184	quant.	68·9	6·0	$C_{13}H_{13}N_3O$*	68·7	5·8
	$[CH_2]_4$	H	125	80	70·1	6·4	$C_{14}H_{15}N_3O$*	69·7	6·3
XIV	$[CH_2]_3$	H	210	quant.	74·3	5·1	$C_{13}H_{11}N_3$	74·6	5·3
	$[CH_2]_4$	H	250	quant.	75·1	6·0	$C_{14}H_{13}N_3$	75·3	5·9
	$[CH_2]_5$	H	228	quant.	75·8	6·5	$C_{15}H_{15}N_3$	76·0	6·4
XV	$[CH_2]_3$	H	238	28	74·4	5·6	$C_{13}H_{11}N_3$	74·6	5·3
	$[CH_2]_4$	H	232	20	75·0	6·1	$C_{14}H_{13}N_3$	75·3	5·9
	$[CH_2]_5$	H	257	35	75·8	6·4	$C_{15}H_{15}N_3$	76·0	6·4
XVI	$[CH_2]_4$	H	100[6]	52	—	—	$C_{10}H_{11}N_3$	—	—
	$[CH_2]_5$	H	93[6]	66	—	—	$C_{11}H_{13}N_3$	—	—

* Monohydrate.

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