NOVEL FORMATION OF THE BENZIMIDAZO[2,1-a]ISOQUINOLINE AND BENZ[c]ACRIDINE FROM THE 1,2,3,4-TETRAHYDRO-1-(2-NITROPHENETHYL)-ISOQUINOLINE WITH TRIETHYL PHOSPHITE

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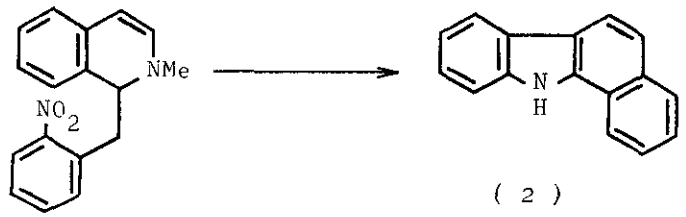
Reductive cyclisation of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)isoquinoline (10) and its 2-methyl derivative (11) with triethyl phosphite gave 5,6-dihydro-2,3,9,10-tetramethoxybenzimidazo[2,1-a]isoquinoline (13) and 2,3,9,10-tetramethoxybenz[c]acridine (18), respectively.

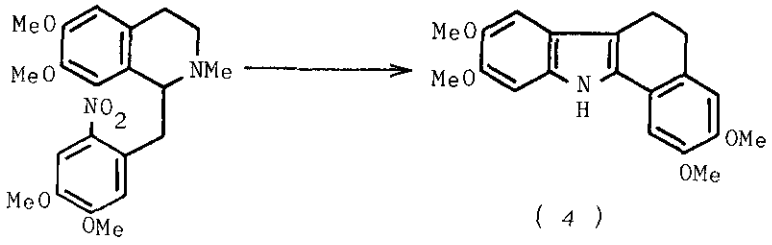
Many investigations have been published on the reductive cyclisation of aromatic nitro compounds with triethyl phosphite, and the mechanism of this type of reaction has been assumed to proceed through a nitrene.[1,2] Previously, we have reported the formation of the benzo[a]carbazoles (2 and 4) by reductive cyclisation of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline (1) and 6'-nitrolaudanosine (3)

respectively.[3] In order to extend and generalise this type of cyclisation, we investigated the reaction of the 1,2,3,4-tetrahydro-1-(2-nitrophenethyl)isoquinolines, and here wish to report these interesting results.

Chart 1



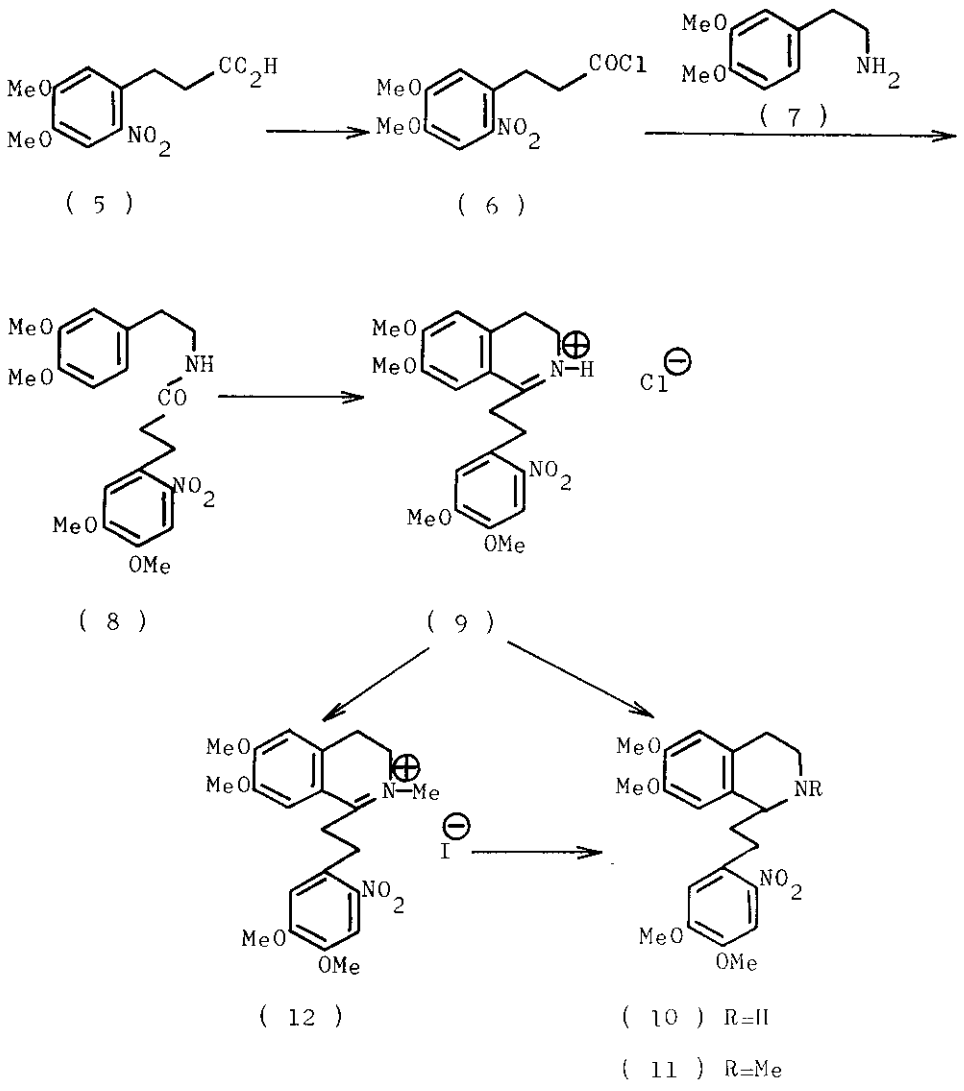
(1) (2)



(3) (4)

Condensation of 3,4-dimethoxyphenethylamine (7) with 4,5-dimethoxy-2-nitrophenylpropionic acid chloride (6), derived from the corresponding carboxylic acid (5) and phosphorous pentachloride, in the presence of triethylamine gave the amide (8) [m.p. 126 - 127°, $\nu_{max}(CHCl_3)$ 3450 (NH) and 1660 cm^{-1} (CO)], which was treated with phosphoryl chloride in boiling benzene to afford the 3,4-dihydroisoquinoline hydrochloride (9) [m.p. 214 - 215° (decomp.)]. Reduction of 9 with sodium borohydride gave the 1,2,3,4-tetrahydroisoquinoline (10) hydrochloride (m.p. 225 - 226°; ν_{max} $(CHCl_3)$ 1520 and

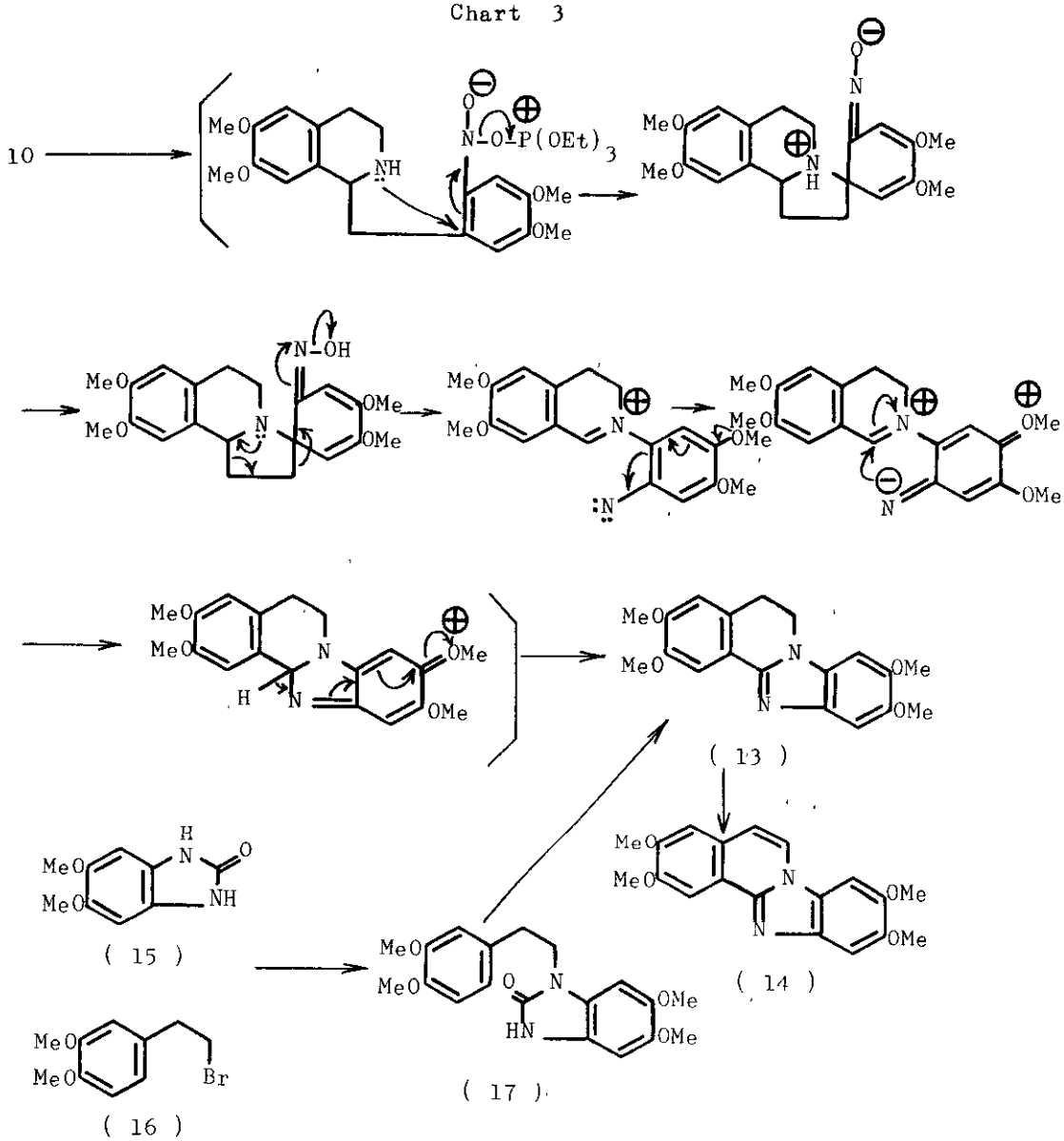
Chart 2


MeO
MeO
CO2H
NO2
(5)
COCl
(6)
NH2
(7)
NH
CO
OMe
(8)
N–H
Cl
(9)
N–Me
I
NR
(12)
(10) R=H
(11) R=Me

1330 cm^{-1} (NO_2); δ($CDCl_3$) 3.86, 3.88, 3.92, and 3.94 (each 3H, s, 4 x OMe) and 6.58, 6.68, 6.78, and 7.60 (each 1H, s, 4 x ArH). Methylation of the free base (9) with methyl iodide, followed by reduction of the resulting methiodide (12) [m.p. 201 - 202° (decomp.)] with sodium borohydride, afforded the 1,2,3,4-tetrahydro-2-methylisoquinoline (11) hydrochloride, m.p. 169 - 171°; δ(free base in $CDCl_3$) 2.41 (3H, s, NMe), 3.76, 3.78, 3.80, and 3.84 (each 3H, s, 4 x OMe), and 6.44, 6.58, 7.21, and 7.41 (each 1H, s, 4 x ArH).

Heating the 1,2,3,4-tetrahydroisoquinoline (10) with an excess of triethyl phosphite at 160 - 170° for 15 h in a current of nitrogen gave 5,6-dihydro-2,3,9,10-tetramethoxybenzimidazo[2,1-a]isoquinoline (13), m.p. 151 - 152°, in 12 % yield, whose structure was determined as follows: The high resolution mass spectrum [Calcd. m/e 340.1422 (M^+). Found: 340.1466 (M^+)] and microanalysis showed the molecular formula, $C_{19}H_{20}N_2O_4$, indicating elimination of two carbons from 10. The i.r. [ν_{max} (KBr) 1607 cm^{-1} (>C=N-)] and u.v. spectra [λ_{max} (MeOH) 335 and 350 nm (log ε 4.39 and 4.45)] suggested this product to have an Ar-N=C-Ar system. The n.m.r. spectrum (δ in $CDCl_3$) revealed an ethylene group between an aromatic ring and nitrogen at 3.10 and 4.14 (each 2H, t, $\underline{J}$ 8 Hz), and four isolated aromatic protons at 6.66, 6.70, 7.24, and 7.64 (each 1H, s) together with four methoxyl groups (3.88, 3.90, 3.92, and 3.96). Treatment of this product with 50 % palladium-on-carbon in boiling decalin for 50 h afforded the dehydrogenated product, $C_{19}H_{18}N_2O_2$ (14) [m.p. 130 - 131°; m/e 338 (M^+)], whose n.m.r. spectrum revealed two aromatic protons coupled each other at 6.56 and 7.68 as each doublet with

Chart 3



J 7 Hz in addition to four isolated aromatic protons (6.72, 6.96 7.20 and 7.56), but no methylene and methine protons. On the ground of these data, we assigned the structure 13 for this product, whose fact was proved by the following alternative synthesis.

3,4-Dimethoxyphenethyl bromide (16) was condensed with 5,6-dimethoxy-2(3H)-benzimidazolone (15) in the presence of potassium carbonate to give 5,6-dimethoxy-1-(3,4-dimethoxyphenethyl)-2(3H)-benzimidazolone (17), which was cyclised with phosphoryl chloride and phosphorous pentoxide to afford the benzimidazo[2,1-a]isoquinoline (13), identical with the above sample in mixed melting point test and i.r., u.v., n.m.r., and mass spectral comparisons.

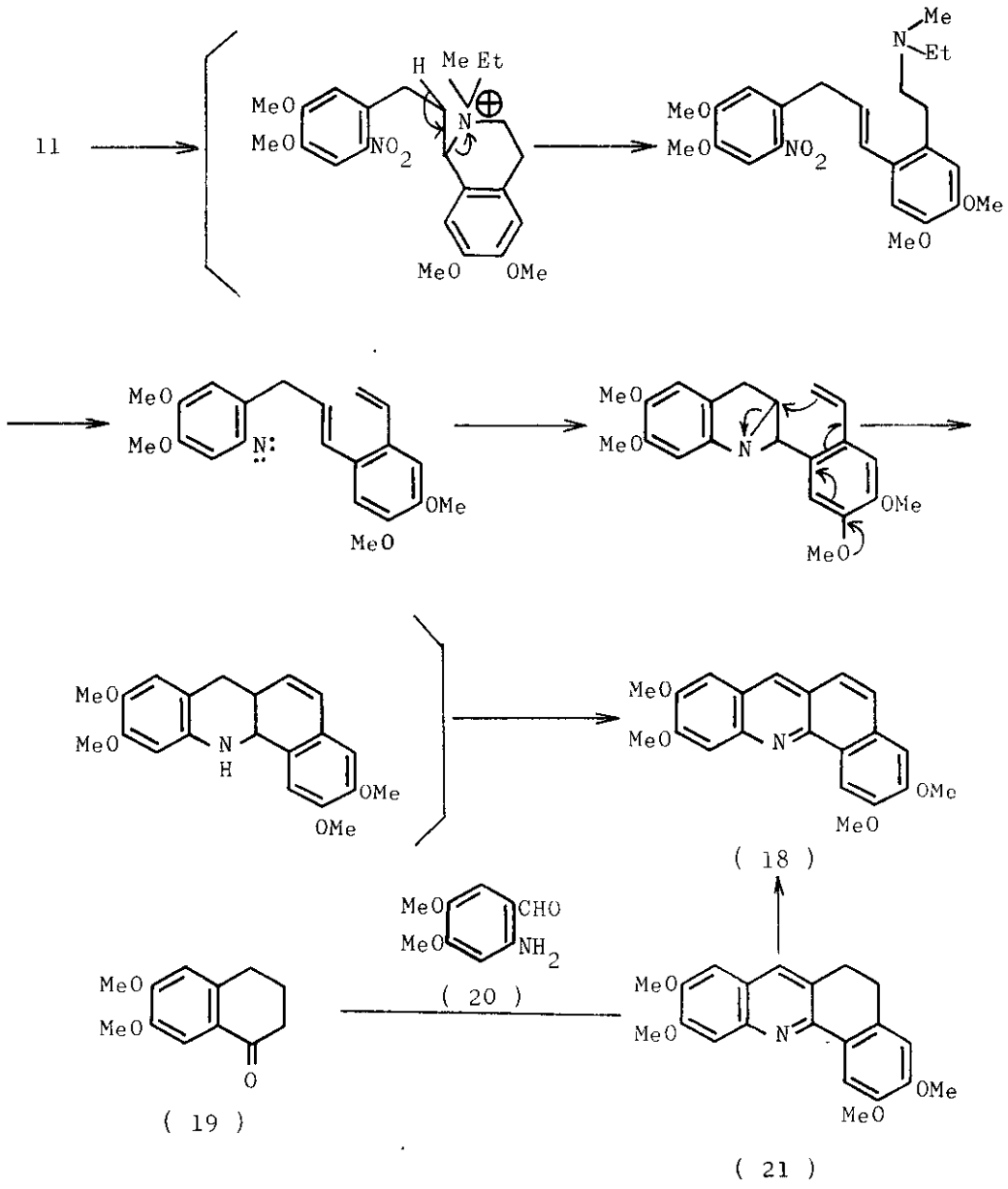
The formation mechanism of this product is outlined in Chart 3.

The same treatment of the 1,2,3,4-tetrahydro-2-methylisoquinoline (11) with triethyl phosphite afforded, in 50 % yield, 2,3,9,10-tetramethoxybenz[c]acridine (18) [m.p. 218 - 219°; λ_{max} (MeOH) 282 and 309 (log ε 3.27 and 3.24)], whose high resolution mass spectrum showed the formula of $C_{21}H_{19}NO_4$ [m/e 349 (M^+)]. The n.m.r. spectrum (δ in $CDCl_3$) showed aromatic protons at 6.99, 7.11, 7.54, 8.21, and 8.79 as each singlet and two aromatic protons at 7.45 as singlet in addition to four methoxyl groups at 3.96, 4.00, 4.08, and 4.20, but not N-methyl resonance, whose fact suggested the product to be structure (18). This structure was proven by comparison with an authentic sample which was prepared in the following marner.

Friedlaender reaction of 3,4-dihydro-6,7-dimethoxy-1(2H)-naphthalenone (19) with 6-aminoveratraldehyde (20) in the presence of 10 % sodium hydroxide in ethanol gave the 5,6-dihydrobenz[c]acridine (21) [m.p. 192 - 193°; m/e 351 (M^+)], which was dehydrogenated with palladium-on-carbon in boiling decalin to afford the benz[c]acridine (18). The u.v., i.r., n.m.r., and mass spectra of both products were identical in all aspects.

The mechanism of compound (18) is assumed as shown in Chart 4.

Chart 4


11
MeO
MeO
NO2
H
Me Et
N
MeO
OMe
Me
N
Et
OMe
MeO
N:
N
N
H
(18)
CHO
NH2
(20)
O
(19)
(21)

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REFERENCES

1 J. I. G. Cadogan, Quart. Rev., 1968, 22, 222; Synthesis, 1969, 11.

2 T. Kametani, F. F. Ebetino, T. Yamanaka, and K. Nyu, Heterocycles, 1974, 2, 209.

3 T. Kametani, T. Yamanaka, and K. Ogasawara, J. Org. Chem., 1968. 33, 4446.

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