Heterocyclic Mesomeric Betaines. Part 4.[1] Reductive Cyclization of Derivatives of 7-Methyl-2-(2'-nitrophenyl)imidazo[1,2-*a*]pyridine

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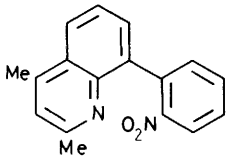
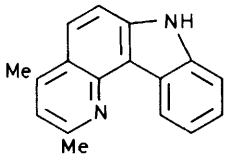
Reductive cyclization of derivatives of 7-methyl-2-(2'-nitrophenyl)imidazo[1,2-*a*]pyridine (**5**) with hot triethyl phosphite has been investigated and the following transformations were achieved: (**5**) ⟶ (**15**), (**6**) ⟶ (**16**), and (**7**) ⟶ (**11**). Compound (**11**) afforded a 2:1 adduct (**18**) when treated with dimethyl acetylenedicarboxylate.

Triethyl phosphite cyclization of the *o*-nitrophenyl compound (**1**) produced two compounds (**2**) and (**3**) whose formation has been postulated to involve two irreversible cyclizations of the corresponding intermediate nitrene (**4**). This study raised interesting mechanistic questions which have been considered in Part 2.[2] The possible involvement of 6π-electrocyclization of



(**1**)



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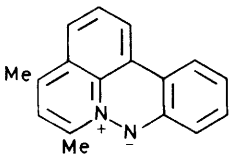
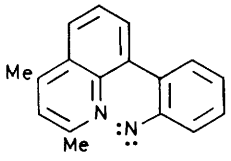


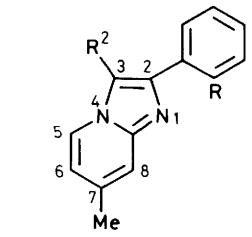
(**3**)



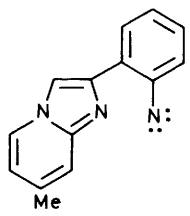
(**4**)

nitrenes as a route to type C heteropentalene mesomeric betaines has been recognized.[1-3] Treatment of derivatives of compound (**5**) with hot triethyl phosphite would be expected to yield the intermediate nitrene (**9**)[4] or its equivalent, and this nitrene (**9**) could then undergo either insertion into the C(3)-aryl C–H bond or electrophilic attack at the N-1 nitrogen lone pair. The formation of the type C heteropentalene mesomeric betaine (**13**) by the reductive cyclization of the corresponding 2'-nitrophenyl compound (**14**) with triethyl phosphite has been described[5] and we now report on the reductive cyclization of 7-methyl-2-(2'-nitrophenyl)imidazo[1,2-*a*]pyridine (**5**).

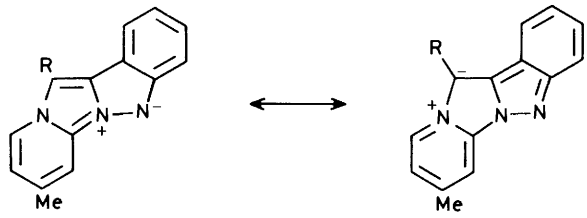
7-Methyl-2-(2'-nitrophenyl)imidazo[1,2-*a*]pyridine (**5**) was prepared by the condensation of 2-amino-4-methylpyridine with 2-nitrophenacyl bromide under basic conditions (57% yield) following the method for the preparation of 2-substituted imidazo[1,2-*a*]pyridine derivatives by reaction of 2-aminopyridines with α-halogeno ketones.[6] When compound (**5**) was treated with hot triethyl phosphite, only the C–H bond insertion product, 2-methyl-4a,5,10-triazaindeno[2,1-*a*]indene (**15**) (37% yield) was isolated. None of the azomethine imine (**10a**) was isolated. The i.r. spectrum (KBr) of the product (**15**) indicated the presence of an amine function ($\nu_{max.}$ 2 600—3 100) as did the ^{1}H n.m.r. spectrum {δ([$^2H_6$]DMSO) 11.48 (1 H, br s)}. The formation of the product (**15**) could well be due to a preference



(**5**) R^1 = NO_2, R^2 = H
(**6**) R^1 = NO_2, R^2 = CHO
(**7**) R^1 = NO_2, R^2 = CO_2Et
(**8**) R^1 = NH_2, R^2 = CO_2Et

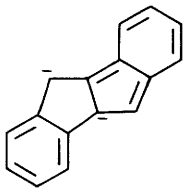


(**9**)

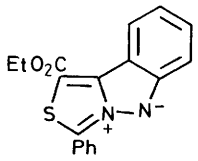


(**10a**) R = H
(**11a**) R = CO_2Et

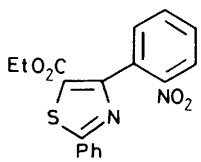
(**10b**) R = H
(**11b**) R = CO_2Et



(**12**)



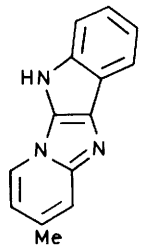
(**13**)



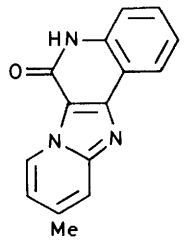
(**14**)

for C–N bond formation involving 6π-electrocyclization of the intermediate nitrene (**9**). In this respect, the transformation (**5**) ⟶ (**15**) matches some of the reactions discussed in Part 2.[2]

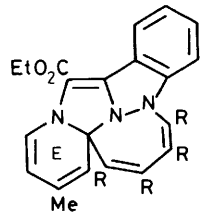
We then explored the possibility of promoting $\geqslant\overset{+}{N}-\overset{-}{N}-$ bond formation by blocking the C–H bond insertion process. Two blocking groups were chosen for study, the formyl and the ethoxycarbonyl groups. Vilsmeier-Haack formylation of compound (**5**) gave 3-formyl-7-methyl-2-(2'-nitrophenyl)-imidazo[1,2-*a*]pyridine (**6**) (80% yield). When compound (**6**) was treated with hot triethyl phosphite, 9-methyl-5,6b,11-



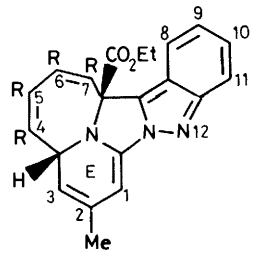
(15)



(16)

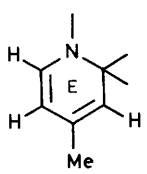


(17) R = CO_2Me



(18) R = CO_2Me

triazabenzo[*a*]fluoren-6(5*H*)-one (**16**) (27% yield) was the only product isolated. The structure of the lactam (**16**) was supported by analytical and spectral data {$\nu_{max.}$(KBr) 2 800—3 200 (NH), 1 665 (amide C=O); δ([$^2H_6$]DMSO) 11.80 (1 H, s, NH)} and was confirmed by the following synthesis. Catalytic hydrogenation of compound (**7**) (see below) gave the amine (**8**) (89% yield) which was thermally cyclized to give the lactam (**16**) (75% yield), identical with the product obtained previously. Two mechanisms for the formation of the lactam (**16**) can be visualized (Scheme). Mechanism (a) involves a ketene intermediate generated by an unusual 1,6-sigmatropic hydrogen shift. Mechanism (b) involves an intermediate oxaziridine formed by a sequence of 8π-electrocyclization followed by 6π-electrocyclization.* Formation of the lactam (**16**) is analogous to the intramolecular reaction between formyl substituents and adjacent vinyl azide substituents in derivatives of benzene [7] and thiophene.[8]



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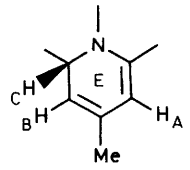
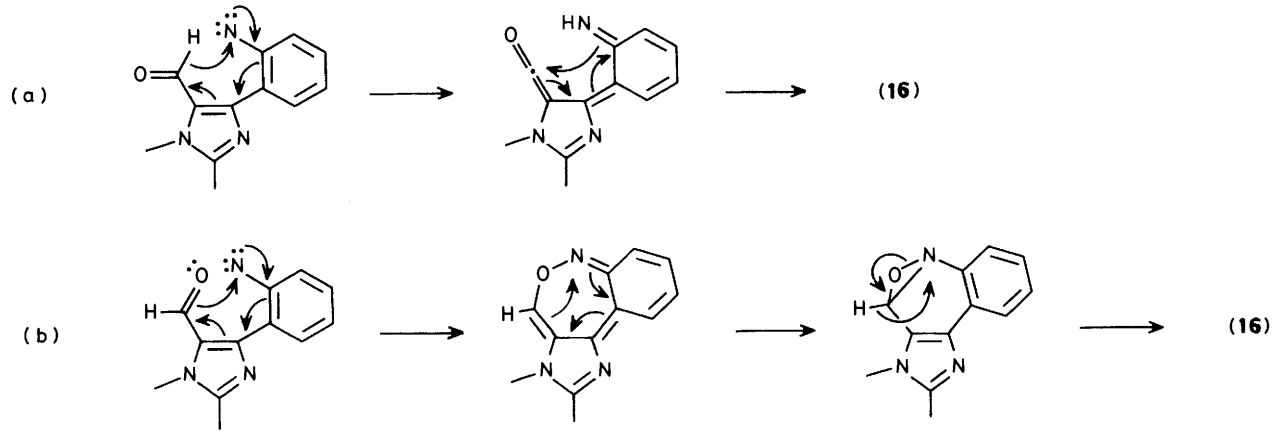


(20)

$J_{H,Me}$ 0.5 Hz), (1 H, δ 7.67, s), (3 H, δ 2.50, br s). These data are compatible only with the partial structure (**20**) and not with the partial structure (**19**). The singlet at δ 7.67 must be assigned to an allylic proton H_C (**20**). The coupling constant J_{BC} is zero and this corresponds with a torsion angle H_B–C–C–H_C of *ca.* 90°. The constitution of the 2:1 adduct (**18**) corresponds with that of the heterocyclic mesomeric betaine (**11b**).



Scheme. Two possible mechanisms for the formation of the lactam (**16**) from the intermediate nitrene

Condensation of ethyl 2-bromo-2′-nitrobenzoylacetate with 2-amino-4-methylpyridine under basic conditions afforded ethyl 7-methyl-2-(2′-nitrophenyl)imidazo[1,2-*a*]pyridine-3-carboxylate (**7**) (38% yield) which on treatment with hot triethyl phosphite yielded the required heterocyclic mesomeric betaine (**11**) (31% yield). The conjugated heterocyclic mesomeric betaine (**10b**) is a derivative of compound (**11**) which is isoconjugate with the even non-alternant hydrocarbon dianion (**12**).

The heterocyclic mesomeric betaine (**11**) and dimethyl acetylenedicarboxylate yielded a 2:1 adduct (11% yield). Two possible structures have been considered for this adduct: structure (**17**) is related to the canonical form (**11a**) and structure (**18**) is related to the canonical form (**11b**). A distinction between these two possible structures has been deduced from the ^1H n.m.r. spectrum of the 2:1 adduct: (1 H, δ 7.90, br dq, $J_{H,H}$ 1 Hz, $J_{H,Me}$ 0.5 Hz), (1 H, δ 7.55, br dq, $J_{H,H}$ 1 Hz,

Experimental

General experimental directions are given in Part 1.[9]

7-Methyl-2-(2′-nitrophenyl)imidazo[1,2-*a*]*pyridine* (**5**).—A mixture of 2-amino-4-methylpyridine (7.0 g), sodium hydrogen carbonate (20.0 g), and 2-nitrophenacyl bromide (12.0 g) in ethanol (100 ml) was heated under reflux (3 h). The hot mixture was then filtered and on cooling the filtrate gave a crystalline product. Recrystallization of this from ethanol gave the *title compound* (**5**) (7.1 g, 57%), buff needles, m.p. 146—148 °C (Found: C, 66.1; H, 4.6; N, 16.8%; $M^{+\bullet}$, 253. $C_{14}H_{11}N_3O_2$ requires C, 66.4; H, 4.4; N, 16.6%; *M*, 253); $\nu_{max.}$ 1 645, 1 520, and 1 370 cm^{-1}; δ 7.94 (2 H, m), 7.68 (2 H, m), 7.58 (1 H, dt, *J* 7 and

* We are grateful to the Referee who kindly suggested this mechanism.

1.5 Hz), 7.40 (1 H, dt, *J* 7 and 1.5 Hz), 7.31 (1 H, s, 3-H), 6.57 (1 H, dd, *J* 7 and 1.5 Hz), and 2.37 (3 H, s, CH_3).

2-*Methyl*-4a,5,10-*triazaindeno*[2,1-a]*indene* (**15**).—Compound (**5**) (0.20 g) and triethyl phosphite (2.0 ml) were heated (37 h) at 120 °C under an atmosphere of nitrogen. A yellow solid which had formed was collected and recrystallized from methanol to give the *title compound* (**15**) (62 mg, 37%) as pale yellow plates, m.p. 298 °C (decomp.) (Found: C, 75.9; H, 5.1; N, 18.8%; $M^{+\bullet}$, 221. $C_{14}H_{11}N_3$ requires C, 76.0; H, 5.0; N, 19.0%; *M*, 221); $\nu_{max.}$(KBr) 2 600—3 100, 1 310, and 1 265 cm^{-1}; δ([$^2H_6$]DMSO) 11.48 (1 H, br s, NH), 8.35 (1 H, dd, *J* 6.5 and 0.5 Hz, 4-H), 7.82 (1 H, ddd, *J* 8, 1, and 0.5 Hz), 7.57 (1 H, dt, *J* 8 and 1 Hz), 7.36 (1 H, m, 1-H), 7.22 (1 H, dt, *J* 8 and 1 Hz), 7.15 (1 H, dt, *J* 8 and 1 Hz), 6.78 (1 H, dd, *J* 6.5 and 1.5 Hz, 3-H), and 2.40 (3 H, d, *J* 1.5 Hz, CH_3).

3-*Formyl*-7-*methyl*-2-(2′-*nitrophenyl*)*imidazo*[1,2-a]*pyridine* (**6**).—Phosphoryl chloride (0.9 ml) was added dropwise with stirring to cooled (< 15 °C) dimethylformamide (4.0 ml) and compound (**5**) (2.0 g) was then added to the stirred mixture. After being allowed to warm to room temperature, the mixture was stirred for 1 h and then heated on a steam bath (3 h). The cooled mixture was diluted with water (30 ml) and the resulting solid collected. Recrystallization of this from ethanol gave the *title compound* (**6**) (1.77 g, 80%) as light tan rods, m.p. 185—188 °C (Found: C, 64.3; H, 4.1; N, 14.7%; $M^{+\bullet}$, 281. $C_{15}H_{11}N_3O_3$ requires C, 64.0; H, 4.0; N, 14.9%; *M*, 281); $\nu_{max.}$ 1 645 cm^{-1}; δ 9.74 (1 H, s, CHO), 9.46 (1 H, d, *J* 7 Hz), 7.62—7.68 (4 H, m), 7.55 (1 H, m), 7.03 (1 H, dd, *J* 7 and 2 Hz), and 2.53 (3 H, d, *J* 1 Hz, CH_3).

9-*Methyl*-5,6b,11-*triazabenzo*[a]*fluoren*-6(5H)-*one* (**16**).—*Method 1*. Compound (**6**) (100 mg) and triethyl phosphite (1.0 ml) were heated (88 h) at 120 °C under an atmosphere of nitrogen. The resulting solid was collected and recrystallization from methanol to give the *title compound* (**16**) (24 mg, 24%) as cream rhombs, m.p. > 300 °C (Found: C, 72.5; H, 4.6; N, 16.6%; $M^{+\bullet}$, 249. $C_{15}H_{11}N_3O$ requires C, 72.3; H, 4.5; N, 16.9%; *M*, 249); $\nu_{max.}$(KBr) 2 800—3 200br, 1 665, 1 435, and 1 170 cm^{-1}; δ([$^2H_6$]DMSO) 11.80 (1 H, s, NH), 9.22 (1 H, dd, *J* 7 and 1 Hz), 8.23 (1 H, dd, *J* 8 and 2 Hz), 7.69 (1 H, m, 10-H), 7.48—7.58 (2 H, m), 7.33 (1 H, ddd, *J* 7, 6, and 2 Hz), 7.11 (1 H, dd, *J* 7 and 2 Hz), and 2.48 (3 H, d, *J* 1 Hz, CH_3).

Method 2. Compound (**8**) (26 mg) in toluene (5 ml) was heated (24 h) at 100 °C. After cooling, the solid product was collected and recrystallized from methanol to give compound (**16**) (15 mg, 75%), identical with the above product.

Ethyl 7-*Methyl*-2-(2′-*nitrophenyl*)*imidazo*[1,2-a]*pyridine*-3-*carboxylate* (**7**).—A mixture of 2-amino-4-methylpyridine (2.2 g) and ethyl bromo-(2′-nitrobenzoyl)acetate [5] (2.2 g) in benzene (50 ml) under an atmosphere of nitrogen was heated under reflux in the dark (18 h). The cooled reaction mixture was evaporated and the residue fractionated by column chromatography (silica gel; ether) to give the *title compound* (**7**) (0.86 g, 38%) as yellow rods, m.p. 165—166 °C (from ethanol) (Found: C, 62.7; H, 4.7; N, 13.1%; $M^{+\bullet}$, 325. $C_{17}H_{15}N_3O_4$ requires C, 62.8; H, 4.7; N, 12.9%; *M*, 325); $\nu_{max.}$ 1 690, 1 525, 1 400, 1 380, 1 350, and 1 170 cm^{-1}; δ 9.22 (1 H, d, *J* 8 Hz), 8.11 (1 H, d, *J* 9 Hz), 7.5—7.7 (4 H, m), 6.90 (1 H, d, *J* 8 Hz), 4.14 (2 H, q, *J* 8 Hz, OCH_2CH_3), 2.47 (3 H, s, CH_3), and 1.03 (3 H, t, *J* 8 Hz, OCH_2CH_3).

Ethyl 2-(2′-*Aminophenyl*)-7-*methylimidazo*[1,2-a]*pyridine*-3-*carboxylate* (**8**).—Compound (**7**) (0.20 g) in 95% ethanol (50 ml) was hydrogenated overnight (2—3 atm) in the presence of a 10% palladium on carbon catalyst. The mixture was filtered and evaporated to give the *title compound* (**8**) (0.16 g, 89%) as colourless rhombs, m.p. 128—129 °C {Found: C, 68.9; H, 5.6; N, 14.0%; *m/z* 223 [(*M* + 1) − CO_2Et]. $C_{17}H_{17}N_3O_2$ requires C, 69.1; H, 5.8; N, 14.2%; *M*, 295}; $\nu_{max.}$ 3 440, 3 350, 1 680, 1 620, 1 400, 1 380, and 1 160 cm^{-1}; δ 9.25 (1 H, d, *J* 7 Hz), 7.42 (1 H, s, 8-H), 7.36 (1 H, dd, *J* 8 and 1 Hz), 7.15 (1 H, dt, *J* 8 and 1 Hz), 6.7—6.9 (3 H, m), 4.58 (2 H, br s, NH_2), 4.23 (2 H, q, *J* 8 Hz, OCH_2CH_3), 2.41 (3 H, s, CH_3), and 1.15 (3 H, t, *J* 8 Hz, OCH_2CH_3).

10-*Ethoxycarbonyl*-3-*methyl*-5H-4bλ^5,5,10a-*triazaindeno*-[2,1-a]*inden*-4b-*ium*-5-*ide* (**11**).—Compound (**7**) (0.50 g) and triethyl phosphite (5.0 ml) were heated (4.5 days) at 120 °C under an atmosphere of nitrogen and then set aside at room temperature for 2 days. The resulting solid product was collected and recrystallized from acetonitrile to give the *title compound* (**11**) (0.14 g, 31%) as orange needles, m.p. 185—187 °C (Found: C, 69.9; H, 5.1; N, 14.3%; $M^{+\bullet}$, 293. $C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.2; N, 14.3%; *M*, 293); $\nu_{max.}$ 1 665 cm^{-1}; δ 9.43 (1 H, br d), 8.08 (1 H, d, *J* 9 Hz), 7.81 (1 H, s, 4-H), 7.54 (1 H, d, *J* 8 Hz), 7.40 (1 H, m), 6.93 (2 H, m), 4.47 (2 H, q, *J* 8 Hz, OCH_2CH_3), 2.46 (3 H, s, CH_3), and 1.53 (3 H, t, *J* 8 Hz, OCH_2CH_3).

7a-*Ethyl* 4,5,6,7-*Tetramethyl* 3a,7a-*Dihydro*-2-*methyl*-12,12a,12c-*triazabenz*[cd]*indeno*[1,2-a]*azulene*-4,5,6,7,7a-*pentacarboxylate* (**18**).—A mixture of compound (**11**) (80 mg) and dimethyl acetylenedicarboxylate (0.2 ml) in toluene (3.0 ml) was heated (3 h) in an oil-bath at 120 °C under an atmosphere of nitrogen. Evaporation gave a residue which was fractionated by preparative thick layer chromatography (silica gel; ether–light petroleum, 2:1). The yellow band (R_F 0.3) was collected and re-fractionated (silica gel; ether). Recrystallization from ethanol gave the *adduct* (**18**) (17 mg, 11%) as yellow plates, m.p. 164—165 °C (Found: $M^{+\bullet}$, 577.1722. $C_{29}H_{27}N_3O_{10}$ requires *M*, 577.1696); $\nu_{max.}$ 1 765 and 1 735 cm^{-1}; δ 7.95 (1 H, dt, *J* 8.5 and 1 Hz), 7.90 (1 H, dq, *J* 1 and 0.5 Hz, 1-H or 3-H), 7.84 (1 H, dt, *J* 8.5 and 1 Hz), 7.67 (1 H, s, 3a-H), 7.55 (1 H, dq, *J* 1 and 0.5 Hz, 3-H or 1-H), 7.30—7.42 (2 H, m), 4.21 (2 H, m, OCH_2CH_3), 3.87 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.36 (3 H, s, OCH_3), 2.50 (3 H, br s, CH_3), and 1.11 (3 H, t, *J* 7 Hz, OCH_2CH_3).

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