[Chem. Pharm. Bull. 23(9)2025—2028(1975)]

UDC 547.833.04 : 547.835.1.057

Studies on the Syntheses of Heterocyclic Compounds. DCXXVII.[1] The Formation of 2,3,9,10-Tetramethoxybenz[*c*]acridine by Treatment of 6,7-Dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)-2-methylisoquinoline with Triethyl Phosphite

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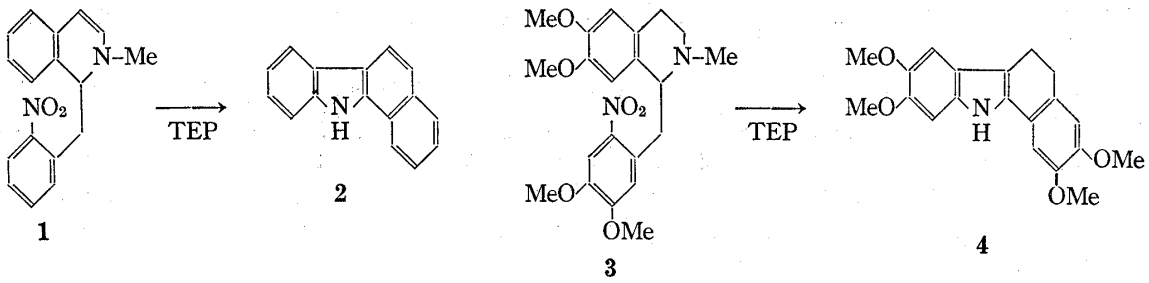
(Received January 20, 1975)

Reductive cyclization of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)-2-methylisoquinoline (**11**) with triethyl phosphite afforded 2,3,9,10-tetramethoxybenz[*c*]acridine (**12**), the structure of which was identical with the sample, which was synthesized in a different route, in spectral comparisons.

Reductive cyclization of aromatic nitro compounds by treatment with triethyl phosphite (TEP) has been hitherto investigated by many researchers[3] and its mechanism has been assumed to proceed through nitrene. Recently, reductive cyclization of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline (**1**) and 6′-nitrolaudanosine (**3**) with TEP has been reported to give benzo[*a*]carbazoles (**2**) and (**4**), respectively.[4] Herein we wish to report the result of the treatment of 6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)-2-methylisoquinoline (**11**) with TEP.



1 2 3 4

Chart 1

Schotten-Baumann reaction of the 4,5-dimethoxy-2-nitrophenylpropionic acid chloride (**7**), which was obtained by chlorination of the corresponding acid (**5**) with phosphorus pentachloride, with homoveratrylamine (**6**) afforded the amide (**8**) whose Bischler-Napieralski reaction gave 3,4-dihydroisoquinoline derivative (**9**). Methylation of **9** with methyl iodide, followed by reduction of the methiodide (**10**) with sodium borohydride, afforded the tetra-

1) Part DCXXVI: T. Kametani, S.-P. Huang, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 2010 (1975).
2) Location: *a*) *Aobayama, Sendai*; *b*) *Komagome, Bunkyo-ku, Tokyo.*
3) T. Kametani, K. Ogasawara, and T. Yamanaka, *J. Chem. Soc.* (*C*), **1968**, 1006; T. Kametani, K. Ogasawara, and T. Yamanaka, *J. Chem. Soc.* (*C*), **1969**, 138; T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Chem. Soc.* (*C*), **1968**, 385; T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Chem. Soc.* (*C*), **1969**, 1616; T. Kametani, T. Yamanaka, K. Ogasawara, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1970**, 380; J.I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc.*, **1962**, 361; J.I.G. Cadogan, M. Cameron-Wood, R.K. Mackie, and R.J. Searle, *J. Chem. Soc.* (*C*), **1965**, 4831; R.J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965); G. Smolinsky and B.I. Fener, *J. Org. Chem.*, **31**, 3882 (1966); R.J. Sundberg and T. Yamazaki, *J. Org. Chem.*, **32**, 290 (1967).
4) T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Org. Chem.*, **33**, 4446 (1968).

hydroisoquinoline derivative (**11**), whose nuclear magnetic resonance (NMR) spectrum (δ in $CDCl_3$) showed one N-methyl group at 2.41 as singlet, four O-methyl groups at 3.76, 3.78, 3.80 and 3.84 as each singlet and four aromatic protons at 6.44, 6.55, 7.21 and 7.41 as each singlet.

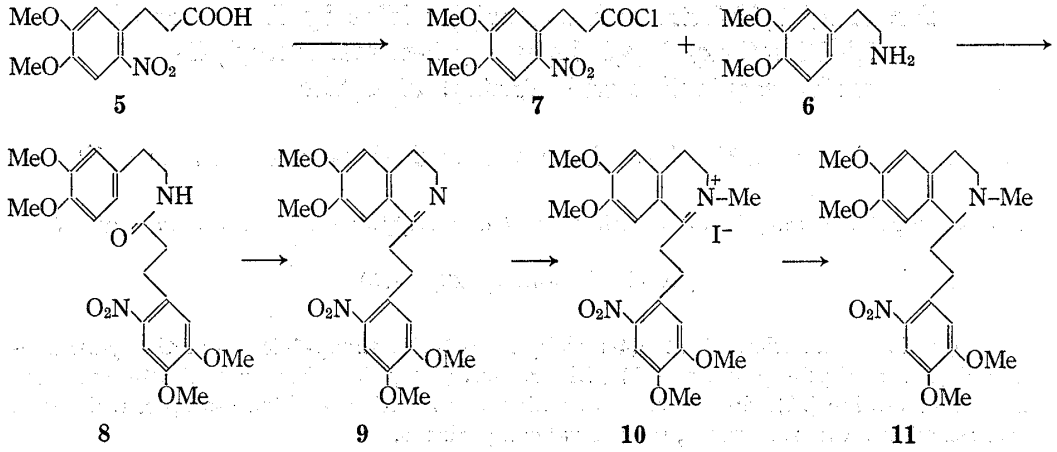


Chart 2

Heating the above tetrahydroisoquinoline (**11**) with TEP at 160—170° for 20 hr under reflux in a current of nitrogen afforded an unexpected 2,3,9,10-tetramethoxybenz[*c*]acridine (**12**) in 5% yield, whose high resolution mass spectrum showed the formula of $C_{21}H_{19}O_4N$. The NMR spectrum (δ in $CDCl_3$) showed four O-methyl resonances at 3.96, 4.00, 4.08 and 4.20 as each singlet and 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, the results of which supported the structure (**12**). The ultraviolet (UV), infrared (IR), NMR, and mass spectra and thin-layer chromatography (TLC) behavior of this compound (**12**) were identical with those of an authentic sample which was synthesized as follows.

Friedlaender reaction of 3,4-dihydro-6,7-dimethoxy-1-[2H]-naphthalenone (**13**) with 6-aminoveratraldehyde (**14**) gave 5,6-dihydrobenz[*c*]acridine (**15**), which was dehydrogenated by palladium-charcoal in refluxing decalin to afford our desired benz[*c*]acridine (**12**).

In the above reaction the TLC of the crude products was investigated, but it showed many spots, all of which could not be obtained in a pure state, and seemed to be a resinous material besides (**12**).

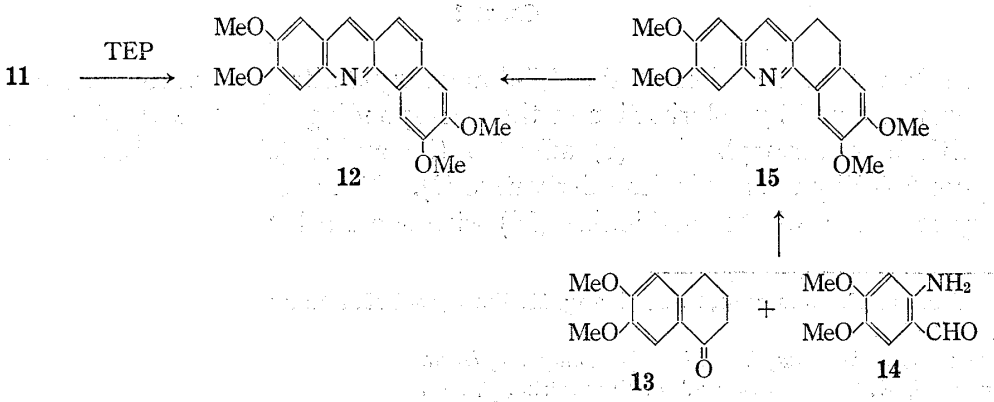


Chart 3

The formation mechanism of compound (**12**) would be presumed as follows. Firstly, Hofmann type degradation of (**11**) with triethyl phosphite would form the mono-ene (**16b**) through an intermediate (**16a**), the further transformation of which with TEP would give a nitrene (**16c**). Secondly an intramolecular addition of this nitrene would afford **16f** by way of **16d** and **16e**. Finally, dehydrogenation of **16f** would occur to give our final product (**12**).

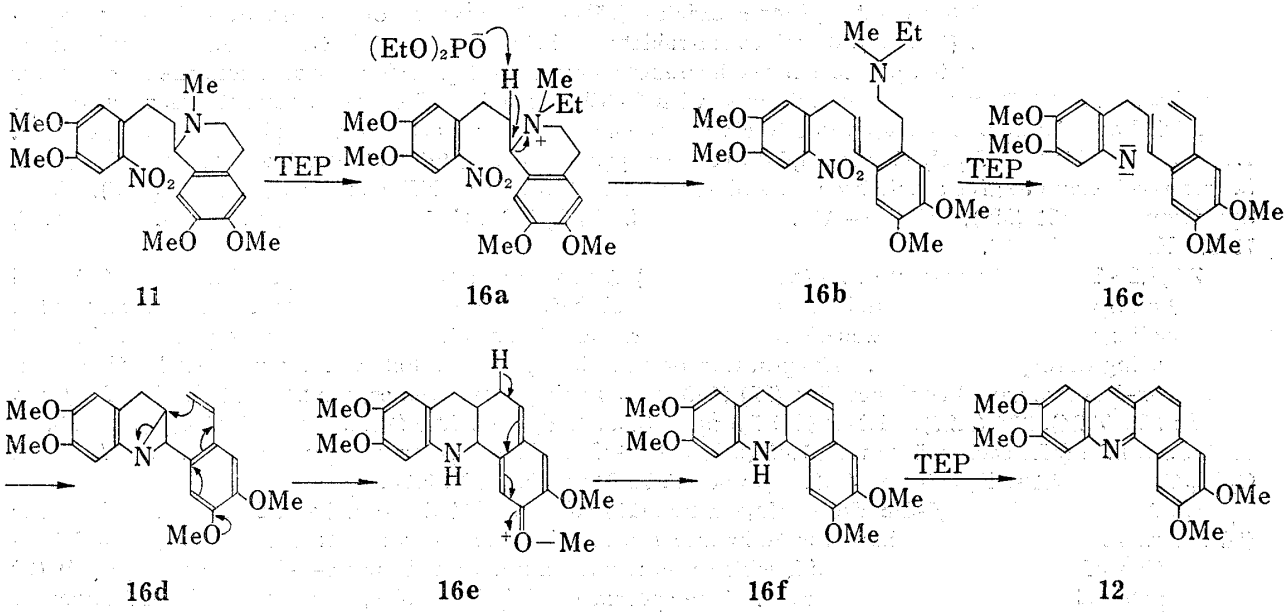


Chart 4

Experimental[5]

N-(3,4-Dimethoxyphenethyl)-3-(4,5-dimethoxy-2-nitrophenyl)propionamide (8)——To a stirred solution of 4,5-dimethoxy-2-nitrophenylpropionic acid (**5**) (5 g) in $CHCl_3$ (100 ml) PCl_5 (6 g) was added in portions at 0° for 20 min. After the addition, the stirring was continued for 30 min at room temperature and the resulting mixture was then refluxed for 30 min. After cooling, ice-water (200 g) was added to the reaction mixture which was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over $CaCl_2$ and evaporated. To a stirred mixture of homoveratrylamine (**6**) (3.6 g) and triethylamine (2.5 g) in $CHCl_3$ (30 ml) was added a solution of the above crude acid chloride in $CHCl_3$ (20 ml) under cooling with ice for 15 min, and the stirring was continued for 30 min at the same temperature and then for 3 hr at room temperature. The $CHCl_3$ layer was washed with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, dried over Na_2SO_4, and then evaporated. The residue was recrystallized from benzene–*n*–hexane to give a pale yellow powder (5 g), mp 126—127°. IR ($CHCl_3$) cm^{-1}: ν_{max} 3450 (NH), 1660 (C=O). *Anal.* Calcd. $C_{21}H_{26}O_7N_2$: C, 60.28; H, 6.26; N, 6.70. Found: C, 60.24; H, 6.28; N, 6.37.

3,4-Dihydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)isoquinoline (9) Hydrochloride——A mixture of the amide (**8**) (10 g), $POCl_3$ (10 g) and dry benzene (100 ml) was heated under reflux on a water bath for 3 hr. After cooling, the organic layer was evaporated to give an oil, which was washed with *n*–hexane (50 ml). The resulting syrup was recrystallized from EtOH to give pale yellow needles (8 g), mp 214—215° (decomp.). *Anal.* Calcd. $C_{21}H_{24}O_6N_2 \cdot HCl \cdot 1.5H_2O$: C, 54.37; H, 6.08; N, 6.04. Found: C, 54.56; H, 5.97; N, 6.33.

3,4-Dihydroisoquinoline Methiodide (10)——The 3,4-dihydroisoquinoline (**9**) hydrochloride (7.5 g) was taken up in $CHCl_3$ and the extract was basified with 10% NH_4OH. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated to give 3,4-dihydroisoquinoline (**9**) (7 g) as a brown oil. A mixture of (**9**) (7 g) and MeI (30 ml) was allowed to stand for 20 hr at room temperature and the excess of MeI was evaporated to give the methiodide (**10**) (8.5 g). Recrystallization from EtOH–ether afforded a pale yellow powder, mp 201—202° (decomp.). *Anal.* Calcd. $C_{22}H_{27}O_6N_2I$: C, 48.72; H, 5.02; N, 5.16. Found: C, 48.59; H, 5.10; N, 5.51.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)-2-methylisoquinoline (11)——To a solution of the methiodide (**10**) (8 g) in MeOH (100 ml) $NaBH_4$ (3 g) was added in small portions with stirring for 20 min at 0° and the stirring was continued for 2 hr at room temperature. MeOH was evaporated and the residue was decomposed with water. The separated oil was extracted with $CHCl_3$ and the extract was washed with water, dried over Na_2SO_4, and evaporated to give the tetrahydroisoquinoline (**11**) (6 g) as a syrup. NMR ($CDCl_3$) ppm: 2.41 (3H, s, NCH_3), 3.76, 3.78, 3.80, 3.84 (12H, each s, $4 \times OCH_3$), 6.44, 6.55, 7.21, 7.41 (4H, each s, $4 \times$ ArH). The hydrochloride of (**11**) was recrystallized from EtOH to give yellow needles, mp 169—171°. *Anal.* Calcd. $C_{22}H_{28}O_6N_2 \cdot HCl$; C, 58.34; H, 6.23; N, 6.18. Found: C, 58.18; H, 6.60; N, 6.56.

5) All melting points are uncorrected. IR spectra were taken with Hitachi EPI-G21 and Hitachi EPI-S_2, NMR spectra with JEOL 4H-100 and Varian S-60T, UV spectra with Hitachi EPS-032, and Mass spectra with Hitachi RMU-7L spectrometers.

5,6-Dihydro-2,3,9,10-tetramethoxybenz[*c*]acridine (15)——A mixture of 3,4-dihydro-6,7-dimethoxy-1-(2H)-naphthalenone (**13**) (100 mg), 6-aminoveratraldehyde (**14**) (100 mg), 10% NaOH (0.2 ml) and EtOH (2 ml) was stirred at room temperature for 96 hr under a current of N_2. After the reaction, the mixture was diluted with H_2O (100 ml) and then extracted with $CHCl_3$ (100 ml). The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give a brown oil, which was chromatographed on silica gel (10 g). Evaporation of the $CHCl_3$ eluate gave 5,6-dihydrobenz[*c*]acridine (**15**) (90 mg), which was recrystallized from benzene–*n*–hexane to give a pale brown powder, mp 192—193°. IR (KBr) cm^{-1}: ν_{max} 1600 (C=C). Mass Spectrum *m/e*: 351 (M^+), 336 (M^+-15). *Anal.* Calcd. $C_{21}H_{21}O_4N$: C, 71.78; H, 6.02; N, 3.99. Found: C, 72.07; H, 5.77; N, 3.56.

2,3,9,10-Tetramethoxybenz[*c*]acridine (12)——(a) A mixture of tetrahydroisoquinoline (**11**) (4 g) and triethyl phosphite (15 g) was heated under reflux in an oil bath at 160—170° for 20 hr under a current of N_2. After cooling the excess reagent was distilled off *in vacuo* and the residue was chromatographed on silica gel (150 g) using $CHCl_3$ as an eluent. Evaporation of the $CHCl_3$ eluate, followed by recrystallization from benzene–*n*–hexane, gave benz[*c*]acridine (**12**) (190 mg) as pale yellow needles, mp 218—219°. UV λ_{max}^{MeOH} nm (log ε): 309 (3.24), 282 (3.27). NMR ($CDCl_3$) ppm: 3.96, 4.00, 4.08, 4.20 (12H, each s, $4\times OC\underline{H}_3$), 6.99, 7.11, 7.54, 8.21, 8.79 (5H, each s, $5\times$ArH), 7.45 (2H, s, $2\times$ArH). Mass Spectrum *m/e*: 349 (M^+). *Anal.* Calcd. $C_{21}H_{19}O_4N$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.04; H, 5.47; N, 3.76.

(b) A mixture of the 5,6-dihydrobenz[*c*]acridine (**15**) (100 mg), Pd–C(100 mg) and decahydronaphthalene (50 ml) was refluxed in an oil bath for 10 hr and the reaction mixture was filtrated while warm and then evaporation of the filtrate gave a solid, which was recrystallized from benzene–*n*–hexane to give (**12**) (10 mg) as pale yellow needles, mp 218—219°. The spectra of UV, IR, NMR, and Mass and TLC bahavior were superimposable on those of the above benz[*c*]acridine (**12**).