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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN BRIDGEHEAD POSITIONS

20.* SYNTHESIS OF NAPHTHO[2,3-b]-1,4-DIAZABICYCLO[2.2.2]OCTENE

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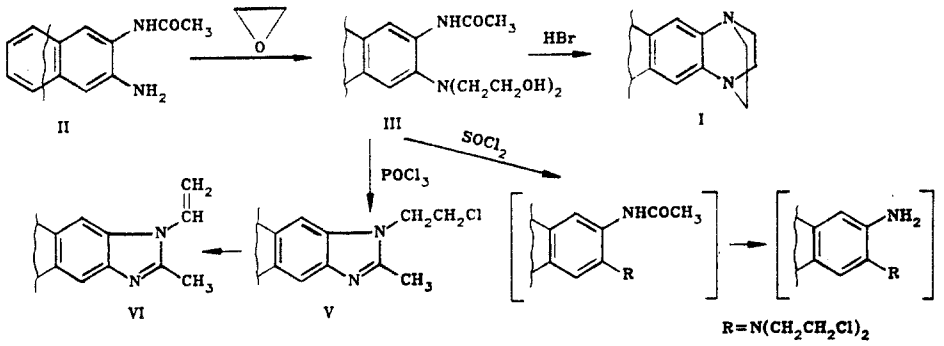
UDC 547.864:543.422

Reaction of 2-acetamido-3-bis(2-hydroxyethyl)aminonaphthalene with phosphorus oxychloride leads to the formation of 2-methyl-1-(2-chloroethyl)naphtho[2,3-d]imidazole, while reaction with hydrobromic acid gives naphtho[2,3-b]-1,4-diazabicyclo[2.2.2]octane in 13% yield. The yield of the latter can be increased to 45% by exchange of the hydroxyl groups in the starting material by chlorine and by deacetylation.

Continuing our studies of 1,4-diazabicyclic systems containing annelated aromatic rings, we have carried out the synthesis of naphtho[2,3-b]-1,4-diazabicyclo[2.2.2]octene (I) according to a scheme developed previously [2] for the synthesis of benzo[b]-1,4-diazabicyclo[2.2.2]octene:



Upon monoacetylation of 2,3-diaminonaphthalene we observed the formation of a multicomponent mixture, the composition of which was altered after recrystallization. Using TLC analysis we were able to select conditions for achieving a max-

*For Communication 19, see [1].

Institute of Bioorganic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 97-100, January, 1991. Original article submitted June 27, 1989.

 0009-3122/91/2701-0080$12.50

imum concentration of the component which gave a qualitative reaction for the presence of a primary aromatic amino group. The resulting product was then used without further purification in a reaction with excess ethylene. This resulted in the formation of a complex reaction mixture, from which 2-acetamido-3-bis(2-hydroxyethyl)aminonaphthalene (III) was isolated in ~50% yield. A hydrolysis step and subsequent double cyclization under conditions worked out earlier for the synthesis of benzo[b]-1,4-diazabicyclo[2.2.2]octene [2] again gave a multicomponent reaction mixture, from which compound I was isolated in 13% yield. The spectral and analytical characteristics and data for the heterocyclic system in I corresponded to those of its benzene analog [3]. The PMR spectrum of base I in the 2.8-3.3 ppm region contains a symmetrical multiplet for the CH_2 group protons oriented exo and endo to the naphthalene fragment; there is also a singlet at 7.63 ppm which is assigned to the 1- and 4-protons in the substituted naphthalene ring, while two multiplets at 7.43-7.48 and 7.82-7.87 ppm can be attributed to the protons in the 6',7'- and 5',8'-positions, respectively. The mass spectrum, as is usual for structures containing a 1,4-diazabicyclo[2.2.2]octane fragment, contains, in addition to the molecular ion peak, a daughter fragment peak at [M–28], which corresponds to cleavage of an ethylene fragment; there are also present a series of ions with mass values reflecting a decrease by one methylene fragment unit apiece. The UV spectra of this material recorded in acidic and basic media are practically indistinguishable, which corroborates the absence of conjugation between the nitrogen atoms and the aromatic system. The process resulting in the formation of compound I upon refluxing the bis(hydroxyethyl) derivative III in concentrated hydrobromic acid is apparently very complex; based on our previous observations [4], this process probably involves hydrolysis of the amide group, substitution of hydroxyl groups by bromide, cyclization to give a substituted naphthopiperazine, and finally cyclization resulting in the formation of the 1,4-diazabicyclo[2.2.2]octane fragment. Analysis of the reaction mixture over time using HPLC has further shown that the starting material III is consumed relatively slowly under the reaction conditions and that the final product I is formed in significant concentrations only after 2 h, along with substantial amounts of unidentified intermediates and side products. After 4 h at reflux the composition of the reaction mixture is stabilized, containing, in addition to the desired product I, eight other components. According to the literature [4], under the reaction conditions compound I should exist in equilibrium with N-(bromoethyl)-naphthol[2,3-b]piperazine (IV); this equilibrium appears to be strongly shifted, however, in favor of compound I (based on preliminary estimates, I:IV > 4:1).

Due to the observed complexity and difficulties in this reaction sequence, we have attempted to reduce the number of uncontrolled steps in the cyclization of compound III to the heterocyclic system I. We anticipated exchanging the hydroxyl groups by halogens, for instance, and lifting the acetyl protecting group from the amino group. However, upon treatment with phosphorus oxychloride under conditions expected to exchange the hydroxyl groups by chlorine, we obtained in 85% yield a compound which, after analysis of its spectral and analytical data, was assigned the structure 2-methyl-1-(2-chloroethyl)naphthol[2,3-d]imidazole (V). Thus, upon reflux of compound III in phosphorus oxychloride, cyclization and dealkylation reactions of the cyclic product also take place, in addition to hydroxyl exchange by chlorine.

The structure of compound V received additional confirmation from the formation of 2-methyl-1-vinyl-1-methylnaphtho[2,3-d]imidazole (VI) upon treatment of compound V with strong base.

Reaction of compound III with thionyl chloride under mild conditions, followed by hydrolysis of the amide functional group, gave a reaction mixture in which the principal component, according to TLC analysis, was a compound containing a primary aromatic amino group; we were unable, however, to isolate this material in analytically pure form. Based on its chromatographic behavior and data this compound is relatively unstable, giving a series of components upon attempted recrystallization. For this reason the reaction mixture was subjected, without additional purification, to double cyclization by refluxing it in hydrobromic acid. HPLC analysis of samples of the reaction mixture withdrawn during the reaction process indicated that the starting material was rapidly consumed (10-15 min). After ~2 h heating time a maximum concentration of compound I was observed and the composition of the reaction stabilized (with three main components). Workup of the reaction mixture and chromatographic purification gave 45% of compound I, i.e., adding extra steps to the process seemed to facilitate the double cyclization stage.

In addition to the approach described above for the double cyclization process we have also tested reaction conditions similar to those used previously in the synthesis of dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene [5]. This was done by taking the reaction mixture obtained after treatment of compound III with thionyl chloride and subsequent amide group hydrolysis, heating it in sulfolane in the presence of $NaBH_4$ with BF_3 additive. Chromatography of the reaction mixture resulted in the isolation of the heterocyclic system I in 25% yield. We conclude, therefore, that both concentrated hydrobromic acid and sodium borohydride in sulfolane represent quite general conditions for the cyclization of aromatic β-haloethylamines with a neighboring amino group.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrophotometer using KBr pellets, UV spectra on a Specord UV-Vis spectrophotometer. PMR spectra were recorded on Bruker HX-90 and Bruker WP-200SY spectrometers versus HMDS. Mass spectra were measured on a Finnigan MAT 8200 spectrometer. HPLC analyses of reaction mixtures were performed under reverse phase conditions using Nucleasil SC-18 support, with a 2-mm-diameter and 50-mm-long microcolumn, on a Milichrom chromatograph; gradient elution with methanol–0.1 M aqueous Na_2HPO_4 was used. Preparative chromatography was carried out using thin-layer silica gel on 35 × 40 cm plates with chloroform–methanol (10:1) eluting system. TLC analysis was performed using Silufol UV-254 plates with chloroform–methanol (10:1, system A), or on HPTLC-Alufolien Kieselgel 60 F 254 plates with chloroform–acetone eluent (10:3, system B). The components were visualized under UV light and with a solution of p-dimethylaminobenzaldehyde (DAB) [6].

The results of C, H, N, and Cl elemental analysis agreed with calculations.

Acetylation of 2,3-Diaminonaphthalene. A solution of 20 g (12.6 mmoles) 2,3-diaminonaphthalene in 80 ml absolute ethanol and 200 ml absolute ethyl acetate was stirred vigorously and cooled to 0°C. The resulting suspension was treated over the course of 4 h with a solution of 15 ml (15.8 mmoles) acetic anhydride in 40 ml absolute ethyl acetate, added dropwise, while maintaining the temperature at 0-1°C. The reaction mixture was then stored overnight at 0-5°C. The resulting precipitate was removed by filtration and washed with cold (0°C) ethyl acetate and ether. Yield 20 g of a weakly colored product, mp 167-174°C; chromatography using system B showed, in addition to the principal component with R_f 0.32, two spots with R_f 0.44 and 0.55, which did not give a colored reaction with DAB. This product was used without further purification in the subsequent synthesis procedure.

Multiple reprecipitation of the product from DMF with ethyl ether gave 2,3-bisaectamidonaphthalene, mp 261-263°C, R_f 0.44; according to the literature [7], mp 262°C.

2-Acetamido-3-(2-hydroxyethyl)aminonaphthalene (III, $C_{16}H_{20}N_2O_3$). To a cooled (8°C) suspension of 15 g of this acetylated product II, described above, in 350 ml acetic acid was added 130 ml of ethylene oxide; the flask was stoppered and stored at 20°C for 24 h, and filtered; the filtrate was then evaporated under vacuum. The residue was washed with saturated K_2CO_3 solution to a basic reaction point, and extracted with chloroform. The extract was evaporated and the resulting oily product washed with 5 × 25 ml water. The wash water was extracted with chloroform and the extract combined with the washed product. The resulting solution was dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved upon heating in 25 ml toluene. After being cooled, the solution yielded compound III, which was removed by filtration (10 g, 55% calculated based on 2,3-diaminonaphthalene), mp 123-127°C (from toluene), R_f 0.17 (system A). IR spectrum: 1080 (C–O–), 1680 (C=O), 2840, 2920 (CH_2), 2880, 2960 (CH_3), 3070 (CH_{arom}), 3260 (OH), 3440 cm^{-1} (NH). PMR spectrum (in $CDCl_3$): 8.80 (1H, s, NH), 7.83-7.26 (6H, m, H_{arom}), 3.62 (4H, t, CH_2–O), 3.77-3.47 (2H, s, OH), 3.13 (4H, t, CH_2–N), 2.12 ppm (3H, s, CH_3).

2-Methyl-1-(2-chloroethyl)naphtho[2,3-d]imidazole (V, $C_{14}H_{13}ClN_2$). A solution of 0.25 g compound III in 5 ml $POCl_3$ was refluxed for 2 h, evaporated under vacuum, and the residue was treated with 10 ml alcohol and evaporated again. The resulting oil was washed with ethyl ether (3 × 5 ml), and dissolved in 0.5 ml isopropyl alcohol. Addition of ether resulted in the precipitation of 0.28 g compound V·HCl, mp 170-190°C (decomp.). The product was dissolved in 5 ml water with 5% $NaHCO_3$ and the pH adjusted to 8. The crystalline deposit was removed by filtration to give 0.18 g (85%) of compound V, mp 143-144°C, R_f 0.46 (system A). IR spectrum: 840 (C–Cl), 960, 1010, 1410, 1460, 1630 (imidazole ring), 2960, 2980 (aliphat. C–H), 3060 cm^{-1} (arom. C–H). PMR spectrum (in $CDCl_3$): 8.14 (1H, s, 9-H), 7.95-7.80 (2H, m, 5-H, 8-H), 7.60 (1H, s, 4-H), 7.45-7.30 (2H, m, 6-H, 7-H), 4.46 (2H, t, $-CH_2Cl$), 3.84 (2H, t, NCH_2), 2.65 ppm (3H, s, CH_3). Found: M 244:246 (3.1:1.0). Calculated: M 244:246 (3.1:1.0).

1-Vinyl-2-methylnaphtho[2,3-d]imidazole (VI, $C_{14}H_{12}N_2$). A solution of 0.1 g compound V·HCl in 2 ml 0.2 N sodium methoxide in methanol solution was evaporated to dryness. The residue was heated at 150°C under vacuum (1-2 mm Hg) in a sublimation apparatus, and gave 0.03 g (41%) compound VI, mp 128-130°C, R_f 0.5 (system A). IR spectrum: 960, 1020, 1410, 1620 (imidazole ring), 1640 (–C=CH_2), 3060 (H_{arom}), 3140 cm^{-1} (=CH_2). PMR spectrum (in $CDCl_3$): 8.08 (1H, s, 9-H), 8.09-7.71 (2H, m, arom. 5-H, 8-H), 7.82 (1H, s, arom. 4-H), 7.50-7.21 (2H, m, arom. 6-H, 7-H), 7.08-6.81 (1H, dd, =CH) 5.52 (1H, d, trans-H, =CH_2, J = 16.0 Hz), 5.13 (1H, d, cis-H, =CH_2, J = 9.0 Hz), 2.56 ppm (3H, s, CH_3). Found: M 208. Calculated: M 208.

Naphtho[2,3-b]1,4-diazabicyclo[2.2.2]octene (I, $C_{14}H_{14}N_2$). A. A solution of 1 g (3.47 mmoles) compound III, 0.1 g $SnCl_2$ in 20 ml 48% HBr was refluxed for 4 h, filtered, and evaporated under vacuum. To the residue was added 2 ml n-propanol, and the solution was heated, cooled, and filtered to remove a crystalline product, which was then

treated with ~10 ml saturated aqueous K_2CO_3 solution. The resulting mixture was extracted with chloroform (5 × 10 ml). The extract was dried over sodium sulfate and evaporated to dryness. The residue was sublimed under vacuum at 140°C (1-2 mm Hg) to give 0.1 g (13%) compound I, mp 201-202°C (from hexane), R_f 0.4 (system A). IR spectrum: 1040, 1150 (C–N), 2870, 2930, 2950 (–CH_2), 3010, 3060 cm^{-1} (arom. C–H). UV spectrum (in alcohol), λ_{max}, nm (log ε): 224 (5.01), 274 (3.49). PMR spectrum (in $CDCl_3$): 7.87-7.82 (2H, n, 5-H, 8-H), 7.63 (2H, s, 1-H, 4-H), 7.48-7.43 (2H, m, 6-H, 7-H), 3.31-2.83 ppm (8H, sym. m, CH_2). Found: M 210. Calculated: M 210.

B. To a solution of 0.5 g (1.73 mmoles) compound III in 20 ml absolute chloroform was added 0.5 ml (5 mmoles) thionyl chloride, and the mixture was heated at 45-50°C for 45 min, then evaporated under vacuum; to the residue was added 4 ml 2 N HCl in absolute ethanol. The resulting solution was then refluxed for 1 h, evaporated to dryness, and the residue dissolved in ~10 ml toluene and evaporated again. The oily product was dissolved in 48% HBr and refluxed for 3 h; the mixture was evaporated to dryness and treated with a mixture of 8 ml 20% Na_2CO_3 solution and 8 ml 20% $Na_2S_2O_3$ solution, then extracted with chloroform (5 × 15 ml). The extract was dried over sodium sulfate, evaporated to dryness, and the residue subjected to preparative chromatography on thin layer silica gel. The band at R_f 0.4 ± 0.1 (UV control) was removed. Compound I was eluted from the sorbent with a mixture of chloroform–methanol (10:3), and the solution evaporated; the residue was sublimed under vacuum at 140°C (1-2 mm Hg) to yield 0.165 g (45%) compound I, mp 201-202°C. Its IR, PMR, and mass spectra were completely superimposable with the spectra of compound I prepared according to A.

C. Hydroxyl group exchange and removal of the acetyl protecting group for 0.5 g (1.73 mmoles) of compound III were carried out as described above in B. To a solution of the resulting oily product in 10 ml sulfolane was added in portions 0.25 g $NaBH_4$; after gas evolution had ceased, the mixture was heated at 120°C for 1 h. Boron trifluoride etherate (10 drops) was added and the mixture was heated for 3 h at 150°C. After cooling the reaction mixture it was diluted twofold with a mixture of ether–dioxane (1:1), filtered, and the filtrate evaporated under vacuum. To the residue was added 20 ml methanol; the solution was allowed to stand until gas evolution was complete, and the resulting solution was then passed through a column (1.5 × 25 cm) filled with a cation exchange resin KRS-2p (H^+ form). The column was washed with 200 ml ethanol and the product eluted with 2 N NH_3 in ethanol. The eluate was evaporated to dryness and chromatographed as described in B, to yield 0.097 g (27%) of compound I, mp 200-201°C.

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