

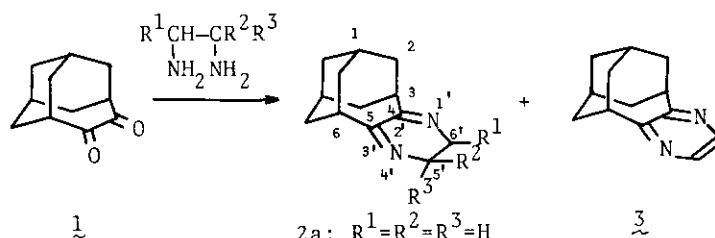
SYNTHESIS OF HOMOADAMANTANO[4,5-d]IMIDAZOLES VIA PHOTOCHEMICAL
RING TRANSFORMATIONS

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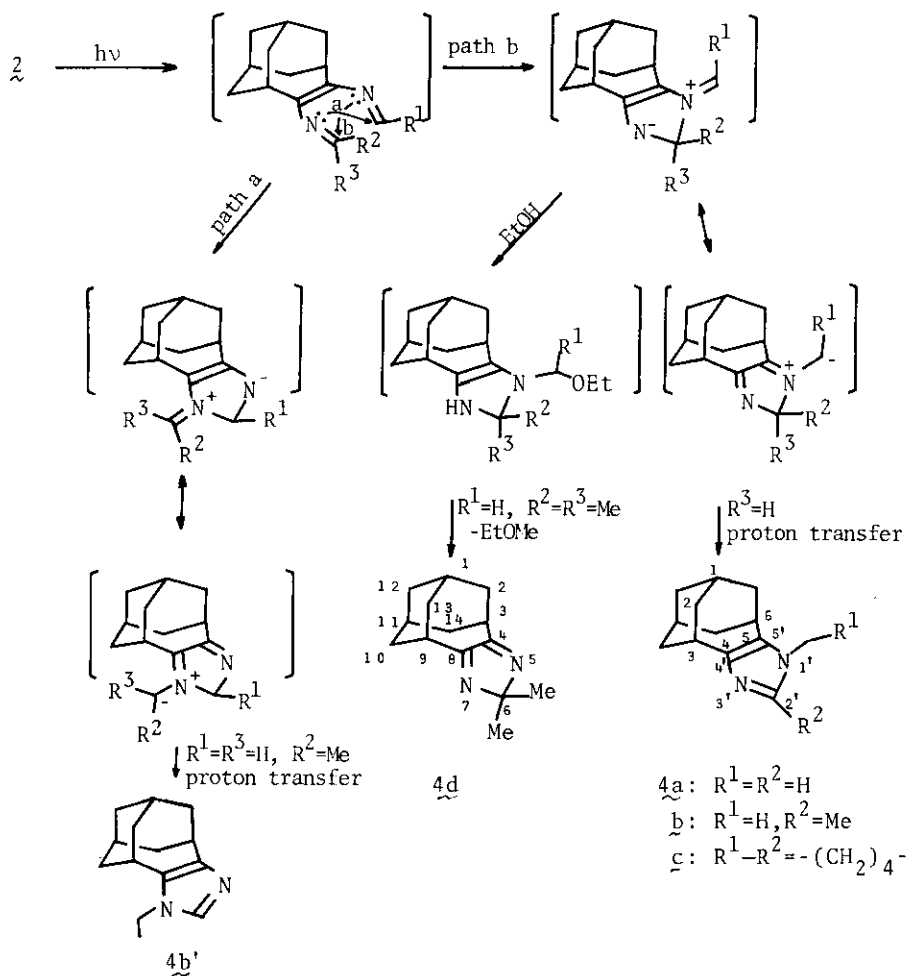
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Abstract-The irradiation of homoadamantano[4,5-b]-5',6'-dihydro-
pyrazines afforded homoadamantano[4,5-d]imidazoles via photo-
chemical ring cleavage followed by cyclization and proton
transfer.

The photochemical ring transformation is known as a useful route for synthesis of certain heterocycles.¹ We describe here a facile synthesis of homoadamantano[4,5-d]imidazoles via photochemical ring transformation of homoadamantano[4,5-b]-5',6'-dihydropyrazines which are readily obtainable from homoadamantane-4,5-dione.² The dione 1 was treated with ethylenediamine in ethanol to afford a dihydropyrazine derivative 2a in 95% yield after usual work up and distillation. Similarly, the reaction of 1 with 1,2-diaminopropane, 1,2-diaminocyclohexane, and 1,2-diamino-2-methylpropane under the conditions summarized in Table 1 afforded the corresponding dihydropyrazine derivatives 2b-d in high yields. However, the reaction of 1 with methyl 2,3-diaminopropionate gave homoadamantano[4,5-b]pyrazine (3) after heteroaromatization via loss of methyl formate. The structures of these products were supported by spectral and analytical data (Table 1). The irradiation of an ethanolic solution of 2a with a high-pressure mercury lamp through a Pyrex filter under argon for 3.75 h afforded an isomeric product 4a in a 50% yield after usual work up and preparative T.L.C. The structure of 4a was determined as 1'-methylhomoadamantano[4,5-d]imidazole based on spectral and analytical data (Table 2). The appearance of characteristic ¹H N.M.R. signals at δ 6.97 (s, 1H, 2'-H) and 3.47 (s, 3H, N-CH₃) supported the given structure.³ The similar irradiation of the unsymmetrically substituted dihydropyrazine 2b afforded a 7:1 mixture of 1',2'-dimethyl- (4b) and 1'-ethyl-imidazole (4b') in 79% yield based on ¹H N.M.R. analysis. The major product 4b revealed characteristic



- $\underline{2a}$: $R^1=R^2=R^3=H$
 \underline{b} : $R^1=R^3=H, R^2=Me$
 \underline{c} : $R^1-R^2=-(CH_2)_4-, R^3=H$
 \underline{d} : $R^1=H, R^2=R^3=Me$



signals at δ 3.50 (s, 3H, N-CH₃) and 2.30 (s, 3H, 2'-CH₃), while the minor product 4b' had signals at δ 7.03 (s, 1H, 2'-H), 3.84 (q, 2H, N-CH₂CH₃), and 1.33 (t, 3H, N-CH₂CH₃), supporting the formation of 4b and 4b'. The pure 4b was readily obtained as colorless crystals after recrystallization of the mixture from *n*-hexane but purification of 4b' was not successful by preparative T.L.C. (Merck, Kieselgel 60 F-254, 5%MeOH-CH₂Cl₂; aluminium oxide F-254, type E, CH₂Cl₂). The irradiation of the symmetrical dihydropyrazine 2c gave 1',2'-pentamethylenehomoadamantano[4,5-d]imidazole (4c) in 72% yield. However, irradiation of the unsymmetrical 5',5'-dimethyl-5',6'-dihydropyrazine 2d afforded exclusively an isoimidazole, 6,6-dimethyl-5,7-diazatetracyclo[7.3.1.1^{3,11}.0^{4,8}]tetradeca-4,7-diene (4d) in 66% yield. Any trace amount of 1'-isopropylhomoadamantano[4,5-d]imidazole could not be detectable, indicating a regioselective cyclization (path b) of the initially produced 2,5-diaza-1,3,5-hexatriene moiety via photochemical 6e electrocyclic ring opening of 2d. These results are different from the fact that the photolysis of 2,3-dihydro-2,2,3,3-tetramethyl-5,6-diphenylpyrazine (5) affords 2,2-dimethyl-4,5-diphenyl-3-imidazoline (6) (60%) and 2,2-dimethyl-4,5-diphenylisoimidazole (7) (9%) as reported by Beak and Miesel.⁴ The photolysis of 2,3-diphenyl-5,6-pentamethylene-5,6-dihydropyrazine (8) in ethanol is reported by these authors to afford an EtOH-adduct 10 as the major product (62%) and the simple 1,2-pentamethylene-4,5-diphenylimidazole (9) only as the minor product (9%).⁴ We obtained cleanly only the imidazoles 4a-c and the isoimidazole 4d and none of the corresponding EtOH-adducts in the photolysis of the dihydropyrazines 2a-d. However, the observed selective cyclization via an attack of N lone pair on a more substituted imino C of the diazahexatriene moiety, i.e., path b for the unsymmetrical 2b and 2d was in accord with the observation by Beak and Miesel.⁴

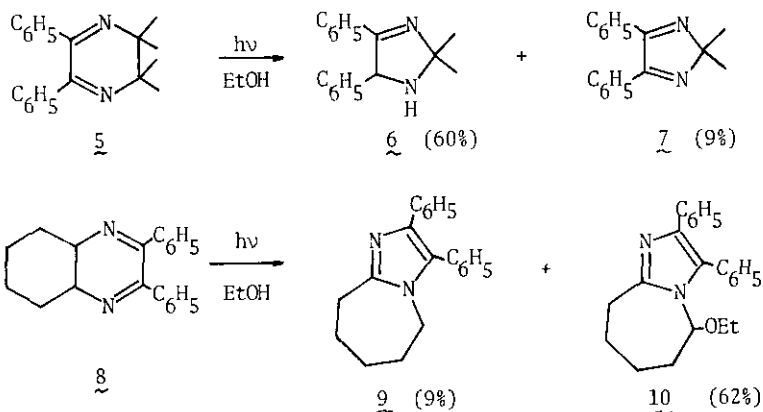


Table 1 The Reactions of 1 with 1,2-Diamines and Physical and Analytical Data of the Products^a

| diamine (mol. ratio to <u>1</u>) | solvent temp. °C time, h | product (yield, %) bp (°C/mmHg) or mp (°C) | IR (cm ⁻¹) ^b | ¹ H NMR (δ) ^c | molecular formula | analysis (%) | | |
|--|--------------------------------|--|--|--|--|--------------|------|-------|
| | | | | | | calcd./found | C | H N |
| ethylene- diamine (1.00) | EtOH refl. 0.5 | <u>2a</u> (95) 95-100/0.5 | 2915, 2845, 1585, 1450 1315 | 3.21(s, 4H), 2.9-2.5(m, 2H), 2.3-1.4(m, 12H) ^d | C ₁₃ H ₁₈ N ₂ | 77.18 | 8.97 | 13.85 |
| | | | | | | 77.17 | 9.06 | 13.77 |
| | | | | | | | | |
| 1,2-diamino- propane (1.05) | EtOH 25 3.7 | <u>2b</u> (90) oil | 2970, 2910, 2845, 1585, 1445, 1315, 1075 | 3.9-2.5(m, 5H), 2.50-1.45(m, 12H), 1.27(d, J=6.0Hz, 3H) | C ₁₄ H ₂₀ N ₂ | 77.73 | 9.32 | 12.95 |
| | | | | | | 77.66 | 9.42 | 12.92 |
| | | | | | | | | |
| 1,2-diamino- cyclohexane (1.01) | EtOH 25 48 | <u>2c</u> (98) oil | 2925, 2850, 1585, 1445, 1320, 1090, 1010, 940 | 3.5-2.6(m, 6H), 2.4-1.0(m, 18H) | C ₁₇ H ₂₄ N ₂ | 79.64 | 9.44 | 10.93 |
| | | | | | | 79.75 | 9.46 | 10.79 |
| | | | | | | | | |
| 1,2-diamino- 2-methyl- propane (1.00) | MeOH 25 4.0 | <u>2d</u> (91) mp 48-50 | 2950, 2900, 2845, 1580, 1455, 1435, 1355, 1320, 1310, 1090, 980, 970, 900 | 3.19(s, 2H), 2.70(br s, 2H), 2.4-1.3(m, 12H), 1.02(s, 6H) | C ₁₅ H ₂₂ N ₂ | 78.21 | 9.63 | 12.16 |
| | | | | | | 78.25 | 9.65 | 12.10 |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| methyl 2,3- diamino- propionate ^e (1.20) | MeOH 25 72 | <u>3</u> (46) mp 82-85 | 3040, 2910, 2840, 1435, 1405, 1385, 1080, 935, 840 | 8.04(s, 2H), 3.15(br s, 2H), 2.5-1.5(m, 12H) ^d | C ₁₃ H ₁₆ N ₂ | 77.96 | 8.05 | 13.99 |
| | | | | | | 77.98 | 8.00 | 14.02 |
| | | | | | | | | |
| | | | | | | | | |

^a All the reactions were carried out in the presence of molecular sieves 4A or 3A (1/16-inch beads) under argon. Crude product was purified by distillation or by chromatography (Woelm-N alumina, CH₂Cl₂). ^b Solid compounds were scanned as KBr disks and oils were scanned as neat films.

^c Chemical shifts are given in δ values (ppm) downfield from TMS as an internal standard (s: singlet, d: doublet, m: multiplet). The solvent was CDCl₃ unless otherwise cited. ^d In CCl₄.

^e dl-2,3-Diaminopropionic acid monohydrochloride was treated in methanol with HCl gas for 1 day to afford crude methyl ester dihydrochloride (IR_{CO} 1735 cm⁻¹) which was used in the presence of triethylamine (2.0 equivalents).

Table 2 Photochemical Ring Transformations of Homoadamantano[4,5-b]-5',6'-dihydropyrazines 2a-d^a

| dihydro- pyrazine | irradiation time, h (concentration, M) | Product (yield, %) mp (°C) (recrystallized from) | IR (cm ⁻¹) ^b | ¹ H NMR (δ) ^c | molecular formula | analysis (%) | | |
|----------------------|--|---|--|---|--|----------------|--------------|----------------|
| | | | | | | calcd./found | C | H N |
| <u>2a</u> | 3.75 (0.00049) | <u>4a</u> (50) 169-172 (n-hexane) | 2910, 2840, 1500, 1440, 1250, 1235, 1215, 1090, 805 | 6.97 (s, 1H), 3.47 (s, 3H), 3.0-2.6 (m, 2H), 2.4-1.5 (m, 12H) | C ₁₃ H ₁₈ N ₂ | 77.18 77.17 | 8.97 9.00 | 13.85 13.63 |
| <u>2b</u> | 7.00 (0.00189) | <u>4b</u> (40) (69) ^d 169-172 (n-hexane) <u>4b'</u> (10) ^{d,e} | 2920, 2880, 2850, 1440, 1395, 1235, 1090 | 3.50 (s, 3H), 2.30 (s, 3H), 3.0-2.5 (m, 2H), 2.4-1.5 (m, 12H) 7.03 (s, 1H), 3.84 (q, J=7.0 Hz, 2H), 1.33 (t, J= 7.0 Hz, 3H) ^f | C ₁₄ H ₂₀ N ₂ | 77.73 77.52 | 9.32 9.48 | 12.95 13.00 |
| <u>2c</u> | 6.00 (0.00110) | <u>4c</u> (72) 164-166 (n-hexane) | 2915, 2845, 1475, 1440, 1420, 1090 | 3.9-3.5 (m, 2H), 3.0-2.5 (m, 4H), 2.4-1.2 (m, 18H) | C ₁₇ H ₂₄ N ₂ | 79.64 79.60 | 9.44 9.52 | 10.93 10.89 |
| <u>2d</u> | 4.00 (0.00043) | <u>4d</u> (66) 67-70 (CH ₂ Cl ₂ - n-hexane) | 2980, 2930, 2840, 1585, 1575, 1460, 1440, 1340, 1185, 1175, 1075, 890 | 3.05 (m, 2H), 2.4-1.4 (m, 12H), 1.30 (s, 6H) | C ₁₄ H ₂₀ N ₂ | 77.73 77.78 | 9.32 9.31 | 12.95 12.90 |

^a The irradiation was carried out in EtOH under argon at room temperature with a 100-W high-pressure mercury lamp through a Pyrex filter. Crude product was purified by chromatography (Merck, alumina 60 PF₂₅₄, type E, CH₂Cl₂-MeOH 100/1 v/v). ^b As KBr disks. ^c See Table 1, note c.

^d Based on ¹H NMR analysis of (4b + 4b') mixture. ^e 4b' could not be isolated from 4b.

^f Other signals were superimposed on the signals of 4b.

EXPERIMENTAL

General Procedure for Preparation of Homoadamantano[4,5-b]-5',6'-dihydropyrazines (2a-d).---

Homoadamantane-4,5-dione (1) was treated with an appropriate 1,2-diamine in ethanol or methanol under the conditions shown in Table 1. After removal of the solvent under reduced pressure, the residue was distilled or chromatographed on a neutral alumina (Woelm N, Akt. 1, CH_2Cl_2) column to afford the dihydropyrazines 2a-d in 90-98% yields. For physical and analytical data of 2a-d, see Table 1.

Homoadamantano[4,5-b]pyrazine (3).---A solution of di- α,β -diaminopropionic acid (500 mg, 3.56 mmol) in anhydrous methanol (100 ml) was saturated with dry hydrogen chloride gas and allowed to stand at room temperature for 1 day. Removal of the solvent under reduced pressure gave the corresponding methyl ester hydrochlorides, IR(neat) 1735, 1595, 1545, 1505, 1220, and 1205 cm^{-1} , which was dissolved in methanol (20 ml). To this solution was added the dione 1 (527 mg, 2.96 mmol), triethylamine (720 mg, 7.12 mmol), and molecular sieves (3 Å) (0.5 g), and the mixture was stirred at room temperature for 3 days. The molecular sieves were removed by filtration and the filtrate was evaporated to dryness under reduced pressure to afford crude product which was purified on an alumina (Woelm N, Akt. 1, CH_2Cl_2) column to give the pyrazine 3 as crystals (from CH_2Cl_2 -*n*-hexane) (270 mg, 46%). For physical and analytical data of 3, see Table 1.

General Procedure for Photochemical Ring Transformations of 2a-d.---An ethanol solution of the dihydropyrazines (2a-d) was irradiated under argon at room temperature with a 100-W high-pressure mercury lamp through a Pyrex filter under the conditions shown in Table 2. Removal of the solvent under reduced pressure gave a crude product which was purified on a preparative T.L.C. (Merck aluminium oxide 60 PF-254, CH_2Cl_2 -0.1-2.0%MeOH) to afford the imidazole derivatives 4a-d. For physical and analytical data of 4a-d, see Table 2.

REFERENCES

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