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Syntheses of Some 1,2,3,4-Tetrahydropyrazino[1,2-a]benzimidazoles

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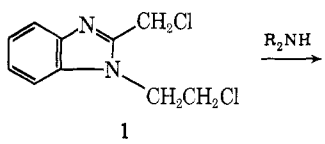
Received October 17, 1973

A general and convenient method for the synthesis of 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles has been developed. Evidence is presented for the existence of the 1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole system.

It was the purpose of this work to develop a general and convenient synthetic route to 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole and its derivatives. Saunders[1] prepared *N*-carbethoxy-1,2,3,4-tetrahydropyrazino-[1,2-a]benzimidazole in low yield by pyrolyzing 2-(4′-carbethoxypiperazine)phenyl azide. This method has been improved and extended by Garner, Garner, and Suschitzky.[2] Schmutz and Kunzle[3] prepared the ring system by treating 1-(β-chloroethyl)-2-chloromethylbenzimidazole with secondary amines. When one of the alkyl groups was



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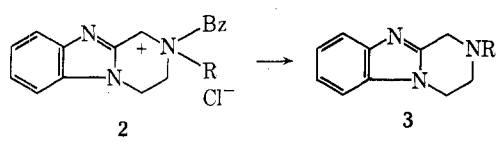

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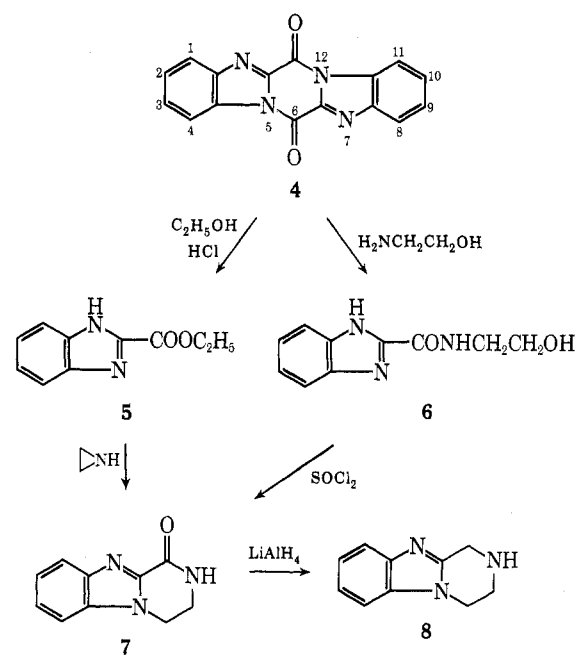
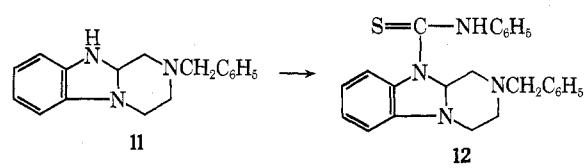
benzyl, hydrogenolysis gave the corresponding 2-alkyl derivative. A similar but more direct synthesis involved treating 1-(β-chloroethyl)-2-chloromethylbenzimidazole with primary amines. This leads directly to the 2-alkyl derivative.[4]

Freedman[5] explored a new synthetic pathway to this ring system which is shown in Scheme I. In this work,[5] difficulties were encountered in the conversion of **7** into **8**. This scheme, at this stage, was not very efficient. It appeared, however, to have one advantage, namely ease of procurement of starting materials. It was decided therefore to restudy the procedure, with special emphasis on the conversion of **7** into **8**. This has now been completed and we now have a convenient general method for the preparation of 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazoles in good yields.

The starting compound, dibenzimidazo[1,2-a,1′,2′-a]tetrahydropyrazine-6,13-dione (**4**), was prepared by a known method.[6] We found that the conversion of **6** into **7** proceeded in higher yield than the conversion of **5** into **7**. Initially the reduction of **7** with lithium aluminum hydride gave air-sensitive products from which only small amounts of 8 could be isolated. Suspecting the overreduction of **7**, we investigated the $LiAlH_4$ reduction of the more easily reducible 2-benzyl-1,2,3,4-tetrahydropyrazino-[1,2-a]benzimidazol-1-one (**10**). Compound **10** was prepared by the synthesis outlined in Scheme I, using 2-benzylaminoethanol in place of 2-aminoethanol. An analytical sample of the reduction product could not be obtained because of its instability. The product was shown to be 2-benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (**11**). The nmr and ir assignments agreed with this structure, and the product formed a stable thiourea derivative (**12**) in high yield when **10** was treated with phenyl isothiocyanate.

Scheme I





11 12

Dehydrogenation of 11 at room temperature over Pd on carbon gave 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (13) which was converted into 8 by debenzylation. Reexamination of the lithium aluminum hydride reduction of 7 showed that good yields of 8 were obtained when the crude reduction product was treated immediately with palladium on carbon. It would appear, from these observations, that the benzimidazole nucleus is reduced by lithium aluminum hydride to a benzimidazoline that is difficult to isolate in analytically pure form and that reverts to a benzimidazole in the presence of air (low conversion) or in the presence of palladium (high conversion).[7]

The following 2-substituted derivatives of 8 were prepared for biological testing purposes: 2-ethyl (14), 2-propyl (15), 2-cyanomethyl (16), 2-aminoethyl (17), and 2-(*p*-methoxybenzyl (18).

Experimental Section

All melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nuclear magnetic resonance spectra were determined with either a Varian Model HA-60EL or Model A-60A spectrometer. Infrared spectra were measured on a Perkin-Elmer Model 521 spectrophotometer. Ultraviolet spectra were obtained with a Cary Model 14 spectrophotometer.

***N*-(2-Hydroxyethyl)-2-benzimidazolecarboxamide (6).** To a cooled solution of 147.5 g (0.246 mol) of 2-aminoethanol in chloroform was added, with stirring, 50 g (0.1732 mol) of dibenzimidazo[1,2-*a*,1′,2′-*a*]tetrahydropyrazine-6,13-dione (4). The mixture was refluxed for 2 hr. The chloroform was removed *in vacuo* and the residual oil was poured into 400 ml of water. After cooling overnight, the solid was removed and recrystallized from ethanol, yield 80%, mp 219–220°.

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.49. Found: C, 58.55; H, 5.35; N, 20.53.

1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (7). A solution of 19.1 g (0.1 mol) of *N*-(2-hydroxyethyl)-2-benzimidazolecarboxamide (6), in 180 ml of dry dimethylformamide, was cooled to 0–5°. Thionyl chloride (12.6 g, 0.105 mol), in 80 ml of dry DMF, was added dropwise with stirring. A solid separated. The mixture was heated under reflux for 2 hr. The resulting solution was treated with decolorizing carbon and filtered hot. The DMF was removed *in vacuo* and the residual gummy solid was washed with 10% sodium hydroxide solution and then with cold water. The product was recrystallized from water: yield 65%; mp 292–294°; ir (KBr) 1680 cm^{-1}.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.15; H, 4.86; N, 22.44. Found: C, 64.24; H, 4.82; N, 22.35.

This compound (7) was obtained in lower yield by treating ethyl 2-benzimidazolecarboxylate (5) with ethylenimine. A solution of 4.4 g (0.023 mol) of (5), 1.3 ml (0.023 mol) of ethylenimine and 1 drop of ethanolic hydrogen chloride in 50 ml of ethanol was placed in a pressure flask and heated on a steam bath for 8 hr. After cooling, the solid was removed and recrystallized from water, yield 28%, mp 292–294°.

***N*-Benzyl-*N*-(2-hydroxyethyl)-2-benzimidazolecarboxamide (9).** Dibenzimidazo[1,2-*a*,1′,2′-*a*]tetrahydrapyrazine-6,13-dione (50 g) was added with stirring to a solution of 165 g (1.17 mol) of 2-benzylaminoethanol in 400 ml of benzene. A clear solution was obtained in about 1 hr. The benzene was removed *in vacuo* and the residual oil was solidified by washing with water. The solid was recrystallized from benzene: yield 55%; mp 143.5–145°; ir (KBr) 1620 cm^{-1}; nmr (DMSO) complex multiplet at δ 7.28–7.69 (9 H, aromatic protons), singlet at 5.70 (1 H, amino), singlet at 4.88 (2 H, benzylmethylene), multiplet at 3.97 (4 H, ethane protons), multiplet at 3.61 (1 H, hydroxyl proton). The absorptions at 5.70 and 3.61 disappeared on deuteration.

Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.28; H, 5.97; N, 14.34.

2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (10). Compound 10 was prepared by the method used for making compound 7, using *N*-benzyl-*N*-(2-hydroxyethyl)-2-benzimidazolecarboxamide as the starting material. The product was recrystallized from ethanol: yield 79%; mp 200–201°; ir (KBr) 1660 cm^{-1}; nmr (DMSO) multiplet at δ 7.30–7.79 (9 H, aromatic protons), singlet at 4.76 (2 H, benzyl methylene), multiplet at 3.96 (4 H, ethane protons).

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.66; H, 5.30; N, 15.32.

1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazole (8). Method A. Reduction of 1,2,3,4-Tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (7). To a cooled mixture of 2.42 g (0.08 mol) of lithium aluminum hydride in 100 ml of dry tetrahydrofuran was added, portionwise with stirring, 3.74 g (0.02 mol) of 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (7). The solution was heated under reflux for 68 hr and cooled to −78°. Water was added with stirring until all of the excess lithium aluminum hydride and its salts were destroyed. The solution was filtered directly into a mixture of 0.37 g of 10% palladium on carbon in 25 ml of ethanol, placed under nitrogen atmosphere, and stirred overnight. The solution was filtered free of catalyst, and excess dry hydrogen chloride gas was added. The resulting insoluble salt was collected by filtration, dissolved in water, and made basic (pH 9) with sodium bicarbonate. The water solution was continuously extracted with chloroform for 24 hr. The chloroform was dried ($MgSO_4$) and removed under reduced pressure to give 2.50 g (72.5%) of 8, mp 129–130°. Recrystallization from benzene afforded an analytical sample: mp 130–131.5°; yield 60%; ir showed no carbonyl absorption; nmr ($CHCl_3$) multiplet at δ 7.63 (1 H, for the 9 proton), multiplet at 7.20 (3 H, for the 6, 7, and 8 protons), singlet at 4.00 (2 H, methylene protons), triplet at 3.04 (2 H, J = 5.7 Hz, ethane protons), triplet at 3.64 (2 H, ethane protons), and a singlet at 2.32 (1 H, NH proton, disappeared on deuteration).

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.41; N, 24.25. Found: C, 69.26; H, 6.23; N, 24.11.

Method B. Two-Step Reduction of 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (10). Preparation of 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (13). To a mixture of 1.14 g (0.03 mol) of lithium aluminum hydride in 150 ml of dry ether was added 4.11 g (0.015 mol) of 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-1-one (10). The mixture was refluxed for 70 hr and cooled at 0°, and 5 ml of water was added dropwise, with stirring. The solid was removed and washed with cold ether. The filtrate, plus washings, was dried ($MgSO_4$). The ether was removed *in vacuo*. Ethanol (50 ml) and 0.4 g of 10% Pd on carbon was added to the residue. The mixture was stirred for 24 hr in a nitrogen atmosphere. The mixture was filtered and the filtrate was saturated with hydrogen chloride. The solution was concentrated to 20 ml, cooled, and filtered. The hydrochloride (mp 290–294°) was dissolved in water, and the solution was neutralized with sodium bicarbonate to yield the free base. The free base was recrystallized from cyclohexane: yield 76%; mp 124–124.75°; ir showed no carbonyl absorption; nmr ($CDCl_3$) multiplet at δ 7.70 (1 H, the 9 proton), complex multiplet at 7.28 (8 H, benzyl aromatic protons and 6, 7, and 8 protons), two triplets at 2.86 and 3.92 (2 H, represent the 3 and 4 methylene protons), singlet at 3.66 (2 H, benzyl methylene protons), singlet at 3.87 (2 H, one methylene protons).

Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.53; H, 6.51; N, 15.96. Found: C, 77.45; H, 6.49; N, 16.10.

Debenzylation of 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (13) to 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole (8). Dry hydrogen chloride was passed into a solution of 1.38 g (0.005 mol) of 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole in 30 ml of ethanol to form the hydrochloride. Palladium (10%) on carbon (0.07 g) was added and the solution was hydrogenated for 7 hr at 50° and 50 psi. The product precipitated from the solution. It was removed and dissolved in water, and the solution was neutralized with sodium bicarbonate. The solution was continuously extracted with chloroform for 10 hr. The extract was dried ($MgSO_4$) and the chloroform removed *in vacuo*. The residue was recrystallized from benzene, yield 97%, mp 130–131.5°. The ir and nmr spectra were identical with the spectra of an authentic sample.

A better overall yield of 1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole was obtained by method B when it was made a one-step method. An example of this method follows. A mixture of 4.56 g (0.12 mol) of lithium aluminum hydride and 16.58 g (0.06 mol) of 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazole in 400 ml of dry tetrahydrofuran was refluxed for 60 hr. The mixture was cooled to 0° and 15 ml of water was added dropwise with stirring. The insoluble solutions were removed and washed with cold ether. The ether solutions were dried ($MgSO_4$) at −15° and the ether then removed under reduced pressure. To the resulting oil was added 1.66 g of 10% Pd on carbon and 175 ml of ethanol, and the mixture was stirred for 12 hr in a nitrogen atmosphere. The catalyst was removed and hydrogen chloride was passed into the filtrate to form the hydrochloride. Palladium (1.66 g of 10%

Pd/C) was added and the mixture was hydrogenated at 55° and 58 psi for 7 hr. The product and catalyst were removed by filtration and the product was removed from the precipitate by extraction with water. The aqueous extract was neutralized with sodium bicarbonate and the solution was then continuously extracted with chloroform for 24 hr. The chloroform solution was dried ($MgSO_4$) and the chloroform was then removed *in vacuo*. The solid, so obtained, was recrystallized from benzene, yield 88%, mp 130.5–131.5°. It was identical in all respects with the previous samples.

Evidence for the Formation of 2-Benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (11). 2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazol-1-one (**10**) (4.11 g, 0.015 mole) was added to a stirred mixture of 1.14 g (0.03 mole) of lithium aluminum hydride in 150 ml of dry ether. The mixture was refluxed for 60 hr. After cooling to 0°, 5 ml of water was added dropwise with stirring. The insoluble salts were removed and the filtrate was dried ($MgSO_4$) at −15°. The ether was removed *in vacuo*. Scratching the walls of the flask caused the oil to crystallize. Because of its sensitivity to air, the product was collected under nitrogen. It was washed with a small amount of cold ether and sucked dry in a nitrogen atmosphere. It was sealed in a vial, under nitrogen, and stored at −15°, yield 62%, mp 82–88°. Because of its instability a good analytical sample could not be obtained. The ir spectrum (CCl_4) showed a band at 3390 cm^{-1} (N–H) and bands at 1600 and 1485 for aromatic C=C skeletal in-plane vibrations but no band was observed for a C=N group. The nmr ($CDCl_3$) showed a singlet at δ 7.29 (5 H, C_6H_5), multiplet at 6.54 (4 H, C_6H_4), quartet at 4.79 (1 H, 10a, X part of ABX with $J_{ax} + J_{bx} = 6$ Hz), multiplet at 3.50 (3 H, NH and 1 CH_2), singlet at 3.49 (2 H, $CH_2C_6H_5$), multiplet at 2.73 (2 H, 4 CH_2) and a multiplet at 2.18 (2 H, 3 CH_2).[8]

Phenylthiourea Derivative of 2-Benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (12). To a solution of 0.14 g (0.001 mol) of phenyl isothiocyanate in dry toluene (under nitrogen) was added 0.27 g (0.001 mol) of crude 2-benzyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]benzimidazole (**11**) and the solution allowed to stand overnight. The solid, which separated, was recyrstallized from petroleum ether, yield 79%, mp 137° dec.

Anal. Calcd for $C_{24}H_{24}N_4S$: C, 71.97; H, 6.04; N, 13.99; S, 8.00. Found: C, 71.84; H, 6.04; N, 13.86; S, 8.14.

Alkylation Products of 1,2,3,4-Tetrahydropyrazino[1,2-a]-benzimidazole, 2-Ethyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (14). A solution of 0.43 g (0.0025 mol) of 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (**8**), 0.27 g (0.0025 mol) of ethyl bromide, and 0.25 g (0.0025 mol) of triethylamine in 25 ml of acetone was refluxed for 138 hr. The volatile materials were removed *in vacuo*. The triethylamine hydrobromide was removed from the residue by extraction with water and the remaining solid was recrystallized from cyclohexane, yield 36%, mp 107–108°.

Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61: H, 7.51; N, 20.88. Found: C, 71.77; H, 7.42; N, 21.02.

2-Propyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (15). This compound was prepared similarly to **14** using *n*-propyl bromide. It was recrystallized from hexane, yield, 26%, mp 75.5–77°.

Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.67; H, 7.83; N, 19.66.

2-Cyanomethyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (16). The alkylating agent was chloroacetonitrile in this case and the solution was refluxed for 48 hr. The product was recrystallized from acetone, yield 70%, mp 176–176.5°.

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.06; H, 5.77; N, 26.58.

2-(2-Aminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole Trihydrochloride (17). 2-Cyanomethyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (0.53 g, 0.0025 mol) in 10 ml of dry tetrahydrofuran was added slowly to a stirred suspension of 0.284 g (0.0075 mol) of lithium aluminum hydride in 40 ml of THF. The mixture was refluxed for 72 hr. The mixture was cooled to −78° and 2 ml of water in 20 ml of THF was added dropwise with stirring. The cold mixture was then filtered into a mixture of 0.1 g of 10% Pd/C in 25 ml of ethanol. After stirring for 20 min, the catalyst was removed by filtration and the solvent was removed *in vacuo*. Ten milliliters of 20% ethanolic hydrogen chloride was added to the residual oil to convert it into the trihydrochloride. The salt was recrystallized from ethanol–concentrated hydrochloric acid, yield 40%, mp 256° dec.

Anal. Calcd for $C_{12}H_{19}Cl_3N_4$: C, 44.16; H, 5.88; Cl, 32.66; N, 17.20. Found: C, 43.91; H, 6.08; Cl, 32.44; N, 16.99.

2-Benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (13). Benzyl chloride was the alkylating agent and the solution was refluxed for 31 hr. The product was recrystallized from cyclohexane, yield 66%, mp 124–124.75°. The product was identical in all respects with the one previously prepared from 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazol-1-one.

2-(p-Methoxybenzyl)-1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole (18). *p*-Methoxybenzyl chloride was the alkylating agent and the solution was refluxed for 18 hr. The compound was recrystallized from cyclohexane, yield 57%, mp 150–150.25°.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.96; H, 6.46; N, 14.16.

Registry No.—**4**, 14483-72-8; **5**, 1865-09-4; **6**, 14484-06-1; **7**, 51052-05-2; **8**, 4744-53-0; **9**, 51052-06-3; **10**, 51052-07-4; **11**, 51052-08-5; **12**, 51052-09-6; **13**, 51052-10-9; **13** HCl, 51052-11-0, **14**, 51052-12-1; **15**, 15052-13-2; **16**, 51052-14-3; **17**, 51052-15-4; **18**, 51108-09-9; 2-aminoethanol, 141-43-5; ethylenimine, 151-56-4; 2-benzylaminoethanol, 104-63-2.

References and Notes

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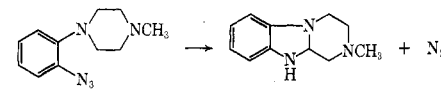
(7) Just as the present work was completed, R. Garner, G. V. Garner, and H. Suschitzky (ref 2) reported the preparation of hexahydropyrazino[1,2-a]benzimidazoles by the decomposition of azides as shown by the following example.



They also prepared hexahydropyrido[1,2-a]benzimidazole by the $LiAlH_4$ reduction of the corresponding benzimidazole.
(8) A four-line pattern centered at δ 3.23 was observed which may be the A part of the ABX pattern of the 1 CH_2 and 10a H; if so, J_{AB} = 11 Hz.