58-8; **9** (R = Cl), 35053-59-9; **9** (R = H), 35053-60-2; **10**, 35053-61-3; **11**, 35053-62-4; **12**, 35053-63-5; **13**, 35053-64-6.

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Alkaline Sodium Dithionite and Catalytic Reduction of Di-, Tri-, and Tetraalkoxycarbonylpyrazines. The Synthesis of 1,2-Dihydropyrazines

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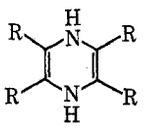
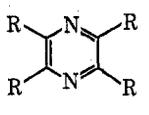
Catalytic reduction of di-, tri- and tetraalkoxycarbonylpyrazines afford 1,2-, not 1,4-dihydropyrazines, as the major products. 2,3,5,6-Tetraethoxycarbonylpyrazine (**2b**) and 3,5-dimethoxycarbonylpyrazine (**9**) yield only the 1,2-dihydropyrazines **3b** and **10**, respectively. 2,3,5,6-Tetramethoxycarbonylpyrazine (**2a**) gave tetramethoxycarbonyl-1,2-dihydropyrazine (**3a**) together with the tetra- and hexahydro products **4** and **5**, respectively. 2,3,5-Trimethoxycarbonylpyrazine (**6**) afforded the 1,2-dihydropyrazine **7** and the tetrahydropyrazine **8**. The 3,5-dimethoxycarbonylpyrazine **9** afforded the 1,2-dihydropyrazine **10**, whereas the 2,5-dimethoxycarbonylpyrazine **11** gave the tetrahydropyrazine **12**. The unstable tetrahydropyrazines **8** and **12** were identified by spectral data. Alkaline sodium dithionite reduction of tetra- and trialkoxycarbonylpyrazines **3a**, **3b**, and **6** yielded their 1,2-dihydropyrazines as the only product. Attempted reduction of disubstituted pyrazines led to hydrolysis of the esters.

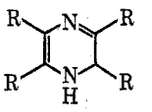
According to quantum mechanical calculations, systems with $4n$ π electrons ought to have antiaromatic character, *i.e.*, be destabilized by resonance.[1] This prediction has been extensively examined for the simplest system having $4n$ π electrons where $n = 1$.[1b] The 1,4-dihydropyrazine ring system **1a**, a cyclic conjugated system with $4n$ π electrons ($n = 2$), is generally thought to be a known structure.[2] However, recent results have cast doubt on the structures of many previously reported 1,4-dihydropyrazines.[3] We have reexamined the reduction of alkoxycarbonylpyrazines reported to yield 1,4-dihydropyrazines and find the original structural assignments to be in error. We now wish to report a convenient method for the synthesis of 1,2-dihydropyrazines.



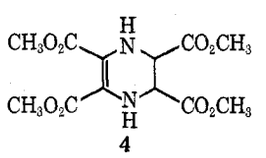
1a, R = H
b, R = $CO_2C_2H_5$



2a, R = CO_2CH_3
b, R = $CO_2C_2H_5$



3a, R = CO_2CH_3
b, R = $CO_2C_2H_5$



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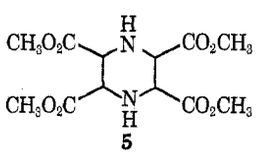

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Mager and Berends[4,5] reported that alkaline sodium dithionite and catalytic reduction under vigorous conditions of 2,3,5,6-tetraethoxycarbonylpyrazine (**2b**) yielded the 1,4-dihydropyrazine **1b**. In contrast, we find that catalytic reduction occurs readily at room temperature to yield the same yellow product as was isolated previously.[4,5] The nmr spectrum of this product showed two doublets, δ 5.50 (1 H, J = 5.0 Hz) and 6.85 (1 H, J = 5.0 Hz), together with two very complex multiplets due to the different environments of the four ethyl ester groups. This spectrum is clearly inconsistent with **1b**. Deuteration caused the peak at δ 6.85 to disappear and that at δ 5.50 to collapse to a singlet. The ir spectrum confirmed the presence of a secondary amine. Therefore, the yellow product is assigned the 1,2-dihydropyrazine structure **3b**.

To simplify the nmr spectrum, the tetramethoxycarbonylpyrazine **2a** was reduced under identical conditions. In contrast to the single product formed in the ethyl case, the tetramethyl ester was reduced further to yield a mixture of the di-, tetra-, and hexahydro derivatives. In the nmr spectrum of the 1,2-dihydropyrazine **3a** the C-2 hydrogen, initially a singlet at δ 5.55, changed to a multiplet upon hydration.

The nmr spectrum of the second product showed two absorption peaks at δ 3.74 and 3.78 for the four methyl esters. Peaks at δ 4.28 were assigned to the hydrogens on the carbon next to nitrogen and the ester, and a broad absorption at 4.30 was due to the NH proton, which disappeared upon deuteration. This data is consistent with the 1,2,3,4-tetrahydropyrazine structure **4**, for the second product.

The third product showed a singlet at δ 3.69 for the four methyl esters, a singlet at δ 3.87 (4 H) for the hydrogens on the carbon next to nitrogen and the ester, and a broad 2 H multiplet at δ 2.82 due to the NH. There was no absorption maximum in the uv above 210 nm, confirming the structure of the compound as 2,3,5,6-tetramethoxycarbonylpiperazine (**5**).

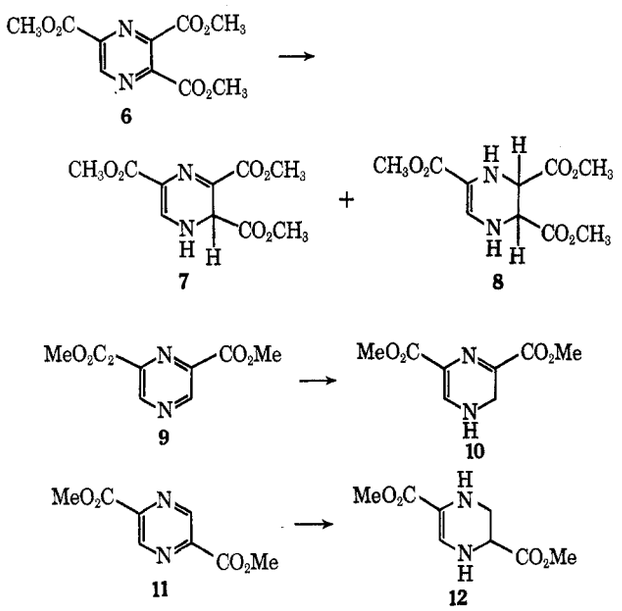
Disproportionation, previously observed for 1,2-dihydropyridine,[6] did not occur in the case of the 1,2-dihydropyrazine **3a**.

To test the generality of this reaction, catalytic reduction of tri- and dimethoxycarbonyl-substituted pyrazines was investigated.

Catalytic reduction of 2,3,5-trimethoxycarbonylpy-

(1) For leading references see (a) J. F. Labarre and F. Crasnier, *Fortschr. Chem. Forsch.*, **24**, 33 (1971); (b) R. Breslow, *Angew. Chem.*, **7**, 565 (1968).
(2) Y. T. Pratt and R. C. Elderfield, *Heterocycl. Compounds*, **6**, 414 (1957).
(3) S. J. Chen and F. W. Fowler, *J. Org. Chem.*, **35**, 3987 (1970).
(4) H. I. X. Mager and W. Berends, *Recl. Trav. Chim., Pays-Bas*, **79**, 282 (1960).
(5) H. I. X. Mager and W. Berends, *ibid.*, **76**, 28 (1957).
(6) U. Eisner, *Chem. Commun.*, 1348 (1969).

razine (6) occurred with the uptake of 1.3 mol of hydrogen and yielded a mixture of reduction products. Upon standing, 2,3,5-trimethoxycarbonyl-1,2-dihydropyrazine (7) crystallized out of the mixture. Deuteration of the NH proton in 7 caused both the C-2 and C-6 protons in the nmr spectrum to collapse to singlets.



The nmr spectrum of the yellow gum immediately after reduction was different from either that of the starting material or 1,2-dihydro product. A singlet at δ 4.32 integrating for two hydrogens and a doublet at δ 6.84 (J = 4.0 Hz) due to an olefinic hydrogen indicates that reduction has occurred at the C-2 and C-3 positions. Furthermore, the ultraviolet spectrum, λ_{max} (MeOH) 295 nm (ϵ 7700), is different from either that of 6 or 7. Mass spectra, both by electron impact ionization and chemical ionization, indicate addition of 2 mol of hydrogen, and therefore the unstable product is the tetrahydropyrazine 8. Attempts to obtain 8 crystalline were unsuccessful due to its ready oxidation to 6 and 7.

Catalytic reduction of 3,5-dimethoxycarbonylpyrazine (9) yielded the corresponding 1,2-dihydropyrazine 10. 2,5-Dimethoxycarbonylpyrazine 11 yielded the tetrahydropyrazine 12 in low yield. The nmr spectrum of 12 showed an ABX pattern due to the C-2 and C-3 protons. This coupling pattern was confirmed by irradiation at δ 4.01, causing the AB part of the ABX to collapse to a typical AB quartet. Attempts to purify and isolate 12 resulted in oxidation and formation of the aromatic starting material.

From the above results it appears that catalytic hydrogenation using palladium on charcoal results in initial formation of a 1,2-dihydropyrazine. It is interesting to note that reduction of the tetraethyl ester stops after 1 mol of hydrogen has been taken up, whereas for the methyl ester both the tetra- and hexahydropyrazines are isolated. This is probably due to the smaller size of the methyl group, allowing the pyrazine molecule to get closer to the catalyst surface. Recently, catalytic reduction of pyridine has also been shown to occur to give 1,2-dihydropyridines.[6]

Mager and Berends[4] also examined the alkaline sodium dithionite reduction of the tetraethoxycarbonylpyrazine 2b. They obtained the same yellow product as from the catalytic reduction which they reported[4] to be the 1,4-dihydropyrazine 1b but now is shown to be the 1,2-dihydropyrazine 3b. Alkaline sodium dithionite reduction of the tetra- and trimethoxycarbonylpyrazines 2a and 6 also afforded the corresponding 1,2-dihydropyrazines 3a and 7, respectively, as the only products. Dithionite reduction of the disubstituted esters led to hydrolysis of the esters, with very little reduction of the ring.

Therefore, sodium dithionite offers a convenient method for the reduction of pyrazines and synthesis of 1,2-dihydropyrazines in good yield (60–70%). This result is in contrast to the extensively examined dithionite reduction of the pyridine nucleus, which has been shown to occur 1,4.[7]

To our knowledge this is the first reported method for the synthesis of 1,2-dihydropyrazines by reduction from the corresponding pyrazine. Previous reduction methods have resulted in the formation of saturated piperazines.[2] The 1,2-dihydropyrazines 3a, 3b, 7, and 10 are stable, since they are not antiaromatic as the corresponding 1,4-dihydropyrazines would be predicted to be.[1] Furthermore, it should be noted that the reduction products become much more sensitive to oxidation as the number of electron-withdrawing substituents is reduced.

Experimental Section[8]

2,3,5,6-Tetraethoxycarbonylpyrazine (2b).—2,3,5,6-Pyrazinetetracarboxylic acid was obtained as colorless needles, mp 230° (lit.[5] mp 205°), using the method of Mager and Berends.[5] Esterification of the tetraacid yielded the tetraethyl ester 2b, mp 103–104° (lit.[5] mp 104°), uv max (MeOH) 277–279 nm (ϵ 8500).

2,3,5,6-Tetramethoxycarbonylpyrazine (2a).—A solution of 2.23 g of 2,3,5,6-pyrazinetetracarboxylic acid in 70 ml of methanol saturated with HCl was refluxed for 16 hr. The solvent was evaporated and the residue was filtered through alumina (neutral activity 1) in ethyl acetate. Recrystallization from methanol afforded 2,3,5,6-tetramethoxycarbonylpyrazine (2a) as colorless needles: mp 181–182°; uv max (MeOH) 278 nm (ϵ 11,060); ir (Nujol) 1740 and 1730 cm^{-1} (ester C=O).

Anal. Calcd for $C_{12}H_{12}N_2O_8$: C, 46.16; H, 3.87; N, 8.97. Found: C, 46.36; H, 3.84; N, 8.93.

General Procedure for 5% Palladium on Charcoal Reduction of Alkoxycarbonylpyrazines.—To 100 mg of alkoxycarbonylpyrazine dissolved in 25 ml of 95% ethanol was added with stirring 25 mg of 5% palladium on charcoal, under hydrogen at atmospheric pressure and room temperature. The reaction was allowed to continue until hydrogen absorption ceased, usually about 70 min. The catalyst was filtered off, and the filtrate was concentrated.

2,3,5,6-Tetraethoxycarbonyl-1,2-dihydropyrazine (3b).—Catalytic hydrogenation of 2,3,5,6-tetraethoxycarbonylpyrazine proceeded with the absorption of 10.0 ml (1.67 molar equiv) of hydrogen to yield 78 mg (77%) of 2,3,5,6-tetraethoxycarbonyl-1,2-dihydropyrazine (3b) as yellow needles: mp 128–129° (lit.[2] mp 127–127.5°); uv max (MeOH) 278 nm (ϵ 9280), 374 (6280); ir (Nujol) 4200 (NH), 1755, 1735, 1680 cm^{-1} (ester C=O); nmr ($CDCl_3$)δ 1.3 (m, 12, 4 CH_3CH_2), 4.25 (m, 8, CH_2CH_3), 5.50 (d, 1, J = 5.0 Hz, NCHCO$_2$Me), 6.85 (d, 1, J = 5.0 Hz, NH).

(7) For leading references see J. F. Biellmann and H. J. Callot, *Bull. Soc. Chim. Fr.*, 1299 (1969).

(8) Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined in methanol with a Cary 14 recording spectrometer. Nmr spectra were obtained with Varian A-60A and XL100 spectrometers. The mass spectra were measured on an AE1 MS-9 mass spectrometer at an ionizing energy of 70 eV. Microanalyses were performed by Micro-Analysis Inc., Wilmington, Del.

Anal. Calcd for $C_{16}H_{22}N_2O_8$: C, 51.89; H, 5.95; N, 7.56. Found: C, 51.67; H, 6.02; N, 7.36.

2,3,5,6-Tetraethoxycarbonyl-1,2-dihydropyrazine (3a).—Catalytic hydrogenation of 2,3,5,6-tetraethoxycarbonylpyrazine proceeded with the absorption of 17.9 ml (2.5 molar equiv) of hydrogen. Recrystallization of the residue from methanol afforded 51 mg of **2,3,5,6-tetraethoxycarbonyl-1,2,3,4-tetrahydropyrazine (4)** as pale yellow prisms: mp 165–166°; uv max 277 nm (ε 10, 130), 372 (4290); ir (Nujol) 3380, 3350, (NH), 1735, 1730, 1670 (ester C=O), and 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 3.74 (6, s, 2 CO_2Me) 3.78 (6, s, 2 CO_2Me) 4.28 (2, s, $NCHCO_2Me$), and 4.30 (2, m, NH).

Anal. Calcd for $C_{12}H_{16}N_2O_8$: C, 45.57; H, 5.10; N, 8.86. Found C, 45.75; H, 5.06; N, 8.72.

A further crop (21 mg) of the tetrahydropyrazine, mp 160–164°, was obtained from the filtrate. Upon standing, the above filtrate afforded 64 mg of **2,3,5,6-tetramethoxycarbonylpiperazine (5)**, which upon recrystallization from methanol yielded colorless needles: mp 162–163°; uv (MeOH) no absorption maximum; ir (Nujol) 3380, 3250 (NH), 1755 and 1725 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 3.69 (12, s, 4 CO_2Me), 3.87 (4, s, $NCHCO_2Me$), 2.82 (2, m, NH).

Anal. Calcd for $C_{12}H_{18}N_2O_8$: C, 45.28; H, 5.70 N, 8.80. Found: C, 45.51; H, 5.51; N, 8.85.

The mother liquors were all combined, reduced in volume, and cooled to −10°. Deep yellow crystals (1.01 g) of **2,3,5,6-tetramethoxycarbonyl-1,2-dihydropyrazine (3a)**, mp 144–145°, were obtained: uv max (MeOH) 276 nm (ε 8800), 371 (6160); ir (Nujol) 3200 (NH), 1755, 1730, 1685 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 3.68 (3, s, CO_2Me), 3.79 (3, s, CO_2Me), 3.87 (3, s, CO_2Me), 3.90 (3, s, CO_2Me), 5.55 (1, s, $NCHCO_2Me$).

Anal. Calcd for $C_{12}H_{14}N_2O_8$: C, 45.87; H, 4.49 N, 8.91. Found: C, 45.61; H, 4.53; N, 8.93.

Treatment of **3a** in methanol with Pd/C yielded only starting material.

Catalytic Reduction of 2,3,5-Trimethoxycarbonylpyrazine (6).—Catalytic reduction of **6** proceeded with the absorption of 11.8 ml (1.34 molar equiv) of hydrogen. The yellow residue would not crystallize: uv max (MeOH) 289 nm (ε 7700); ir (liquid film) 3360 (NH), 1740, 1670 (ester C=O), 1648 cm^{-1} (C=C); nmr δ 3.72 (3, s, CO_2Me), 3.98 (3, s, CO_2Me), 4.30 (2, s, $NCHCO_2Me$), 4.70 (1, m, NH), 6.84 (1, d, C=CHN, J = 4.2 Hz). Deuteration caused the peak at δ 4.70 to disappear and the peak at δ 6.84 to become a singlet.

The oil was taken up in methanol and upon standing crystallized as yellow prisms, mp 182–184°, of **2,3,5-trimethoxycarbonyl-1,2-dihydropyrazine (7)**: uv max (EtOH) 270 nm (ε 14,400), 369 (5800); ir (Nujol) 3200 (NH), 1735 and 1695 cm^{-1} (C=O, ester); nmr ($CDCl_3$) δ 3.75 (3, s, CO_2Me), 3.87 (3, s, CO_2Me), 3.98 (3, s, CO_2Me), 5.49 (1, d, $NCHCO_2Me$, J = 4.0 Hz), 7.64 (1, d, C=CHN, J = 6.0 Hz), 6.54 (m, 1, NH).

Anal. Calcd for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93. Found: C, 46.64; H, 4.86; N, 10.75.

Catalytic Reduction of 3,5-Dimethoxycarbonylpyrazine (9).—Catalytic reduction of **9** (500 mg) proceeded with the absorption of 64 ml (1.12 molar equiv) of H_2. The residue was crystallized from methanol to yield **3,5-dimethoxycarbonyl-1,2-dihydropyrazine (9)** (320 mg) as orange needles: mp 202–204° (evacuated capillary); uv max (MeOH) 275 nm (ε 15,000), 386 (5400); ir (Nujol) 3280 (NH), 1705 (CO_2Me), 1675 (CO_2Me), 1615 cm^{-1} (C=C); nmr (DMSO-d_6) δ 3.62 (3, s, CO_2Me), 3.72 (3, s, CO_2Me), 3.95 (2, s, NCH_2), 7.48 (1, s, C=HN), 8.20 (m, 1, NH); mass spectrum *m/e* (rel intensity) 198.0634 (46), 197 (14), 167 (22), 166 (24), 165 (10), 159 (9), 140 (13), 139 (49), 138 (100), 137 (25).

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.26; H, 5.04; N, 14.52.

Catalytic Reduction of 2,5-Dimethoxycarbonylpyrazine (11).—Catalytic reduction of **11** (200 mg) proceeded with the absorption of 23.0 ml (1.01 molar equiv) of H_2. The residue was very unstable and was readily oxidized by the oxygen of the air, back to the starting aromatic ester. The residue had the following nmr ($CDCl_3$): δ 3.12 (1, q, J_{AB} = 11.4, J_{AX} = 6.0 Hz), 3.47 (1, q, J_{AB} = 11.4, J_{BX} = 3.5 Hz), 4.01 (1, q, J_{AX} = 11.2, J_{BX} = 3.5 Hz), 3.67 (3, s, CO_2Me), 3.74 (3, s, CO_2Me), 6.91 (1, d, J = 2.5 Hz), attributable to 2,5-dimethoxycarbonyl-1,2,3,4-tetrahydropyrazine (**12**).

Alkaline Sodium Dithionite Reduction of 2,3,5,6-Tetraethoxycarbonylpyrazine (2b).—The method of Mager and Berends[4] was used. Reduction of **2b** yielded the 1,2-dihydropyrazine **3b** (67%), mp 128–129° (lit.[4] mp 129.5–131°), identical (ir, uv, nmr, melting point, mixture melting point) with the 1,2-dihydropyrazine obtained by catalytic reduction of **2b**.

Alkaline Sodium Dithionite Reduction of 2,3,5,6-Tetramethoxycarbonylpyrazine (2a).—Using the above method, reduction of **2a** yielded 2,3,5,6-tetramethoxycarbonyl-1,2-dihydropyrazine (**2b**), mp 146–148°, in 82% yield, identical with the product obtained by catalytic reduction of **2a**.

Alkaline Sodium Dithionite Reduction of 2,3,5-Trimethoxycarbonylpyrazine (6).—Using the above method, 2,3,5-trimethoxycarbonyl-1,2-dihydropyrazine (**7**), mp 182–184°, was obtained as yellow needles in 68% yield.

Alkaline Sodium Dithionite Reduction of 2,3-, 2,5-, and 3,5-Dimethoxycarbonylpyrazines.—Using the above method resulted in hydrolysis of the ester functions.

Registry No.—**2a**, 35042-21-8; **3a**, 35042-22-9; **4**, 35042-23-0; **5**, 35042-24-1; **7**, 35042-25-2; **9**, 35042-26-3; **12**, 35042-27-4.

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