

Dihydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-3,5,8,10(2*H*,5*aH*,10*aH*)-tetrone and  
Octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine

*J. Pengman Li and John H. Biel*

Research Laboratories, Aldrich Chemical Company, Inc.

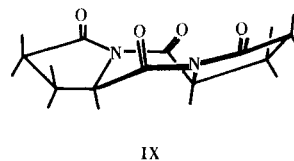
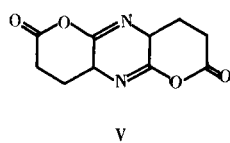
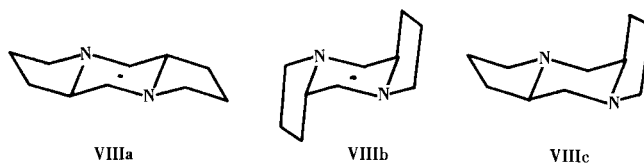
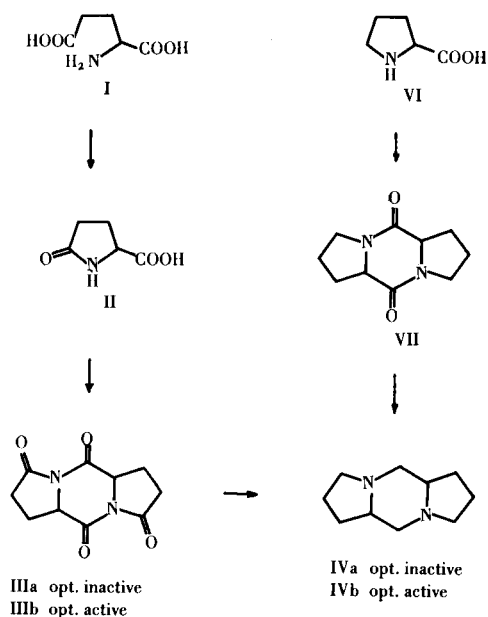
Recently Harnden (1) has confirmed the structure of the dehydration product of glutamic acid originally formulated by King and McMillan (2). We have also obtained evidence supporting this conclusion.

Repeating Koch and Kotlan's synthesis (3) of  $\alpha$ -imidoglutamic anhydride by heating L-glutamic acid (I) and various dicarboxylic anhydrides first in pyridine and then in acetic anhydride led to the isolation of a substance in moderate yields. This substance was optically inactive, insoluble in water and most of the common organic solvents, slightly soluble in hot acetic acid, and was readily

soluble in trifluoroacetic acid. It decomposed at 320-335° without melting. Elemental analysis established the empirical formula  $C_5H_5NO_2$ . On the basis of the infrared and pmr data and the fact that this compound was obtained in several reactions regardless of the dicarboxylic anhydride used, it was thought to be solely originated from I and to have structure IIIa, *i.e.*, dihydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-3,5,8,10(2*H*,5*aH*,10*aH*)-tetrone.

5-Oxopyrrolidine-2-carboxylic acid (II) was thought to be the intermediate. Thus, the L(-)-isomer of II was briefly heated to reflux with acetic anhydride. The product IIIb thus obtained differed from IIIa in its optical activity, its greater solubility in acetic acid, lower melting point, and in the infrared spectrum. However, both IIIa and IIIb showed identical pmr spectra. Although the conversion of II to III was described by King, *et al.* (2), and by Harnden (1), no optical information on their products was given.

Compound IIIa was reduced to the optically inactive octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine (IVa). Compound IVa was also characterized as the dipicrate. If III had the structure V, as proposed by El-Zanfally, *et al.* (4), a product having the same composition as IV could not possibly be obtained from the reduction



reaction. The first synthesis of IV was described by Segel (4). However, the substance which he obtained by reductive cyclization of butyl pyrrolidone had a much higher melting point (84.0-84.5°, from hexane) than our compounds.

In order to confirm the fused heterocyclic skeleton of IV, optically inactive octahydroprocoll (VII) (6-11) was prepared by condensing L(-)-prolin (VI) and then likewise reduced. The product was optically inactive and was identical in every respect with IVa obtained from IIIa. Its dipicrate was also identical with that originated from IIIa.

Reduction of the optically active IIIb afforded the optically active IVb. The infrared spectrum of IVb in dichloromethane solution was superimposable with that of IVa, whereas that in nujol mull showed considerable difference. The pmr spectrum was identical with that of IVa. When treated with a limited amount of picric acid, IVb gave the monopicate. When treated with an excess of picric acid, either IVb or its monopicate was converted to the dipicrate. This dipicrate was different from that of the optically inactive IVa in melting point and in the infrared spectrum (nujol mull).

The optical purity of IVb is not known. It may be purely the (+)-enantiomer or predominantly so. Structures VIIIa and VIIIb, which have a center of symmetry (assuming a chair conformation for the pyrazine ring and an envelope conformation for the pyrrolidine rings), may be excluded for IVb. Structure VIIIb may also be ruled out on the ground of the Bohlmann band exhibited by IVb. A structure like VIIIc (or its mirror image), which possesses no element of symmetry, appears to be responsible for the observed physical properties. The infrared (in solution) and pmr spectral data indicate that both IVa and IVb must have the same steric structure. Compound IVa is therefore a racemic modification of VIIIc.

The molecular shape of III is dramatically changed by the four oxo functions. The two planar imide linkages render the central ring in a flat boat conformation while the pyrrolidinone rings on the sides remain in an envelope conformation. Dreiding models show that the molecule is rather rigid and no conformational change by flipping can occur. Thus, the molecule possesses a C<sub>2</sub> axis and is optically active, as represented by structure IX. Accordingly, IIIb may be considered to be purely or predominantly the (-)-enantiomer, and IIIa, a racemic modification of IX.

#### EXPERIMENTAL

The following instruments were used for physical measurements and analysis: Calibrated Thomas-Hoover Unimelt, Beckman IR5A spectrophotometer, Varian A60-spectrometer, Schmidt-Haensch Model 15680 polarimeter. Tetramethylsilane was used as internal

standard in all pmr spectra. Microanalyses were conducted by the Aldrich Analytical Laboratories on an F and M Model 185 CHN Analyser and by Dr. A. Bernhardt, Max-Planck-Institute, Germany.

Dihydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-3,5,8,10-(2*H*,5*aH*,10*aH*)-tetrone.

Optically Inactive Form (IIIa). From L-Glutamic Acid.

A typical reaction in which IIIa was isolated is as follows. A mixture of L-glutamic acid (Aldrich, m.p. 199° dec.; 0.3 mole), glutaric anhydride (Aldrich, technical grade; 0.3 mole), and pyridine (120 ml.) was heated to reflux for 19 hours. The pyridine was removed *in vacuo*, and the syrupy residue refluxed with acetic anhydride (120 ml.) for 30 minutes. The shiny flakes thus separated were collected and rinsed with acetic acid and acetone, yield, 8.7 g.

A small amount of the substance was recrystallized from glacial acetic acid, washed with acetone, and dried *in vacuo*. The pure IIIa was pinkish, shiny flakes,  $[\alpha]_D^{20}$  0.0° (c 2.66, trifluoroacetic acid), decomposing at 320-335° without melting [lit. m.p. 340° (aq. EtOH) (1,2,5)]; infrared (nujol mull) 5.64 (s), 5.9 (m, sharp), 7.36, 7.57, 7.78, 7.98, 8.33, 8.68  $\mu$ ; pmr (trifluoroacetic acid),  $\tau$  4.93 (triplet, J=8Hz), 6.89-7.70 (multiplet, main peak at  $\tau$  7.22); relative area ratio 1:4.

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>: C, 54.05; H, 4.53; N, 12.61. Found: C, 54.24; H, 4.60; N, 12.55.

Optically Active Form (IIIb). From L(-)-5-Oxopyrrolidine-2-carboxylic Acid (II).

A mixture of II (Aldrich,  $[\alpha]_D^{17}$  -9.2° (c 13, H<sub>2</sub>O), 20 mmoles) and acetic anhydride (5 ml.) was heated to reflux for 30 minutes, and concentrated *in vacuo*. The product IIIb (1.15 g., 50% yield) thus collected was washed with acetone and recrystallized from glacial acetic acid. Pure IIIb, white shiny flakes, m.p. 310-320° dec., m.m.p. 305-320° dec. (with IIIa);  $[\alpha]_D^{20}$  -132±1° (c 3.04, trifluoroacetic acid); infrared (nujol mull), 5.65(s), 5.93 (m, sharp), 7.28, 7.48, 7.69, 7.93, 8.20, 8.58, 8.7  $\mu$ ; pmr (trifluoroacetic acid), superimposable with that of IIIa.

*Anal.* Found: C, 54.00; H, 4.57; N, 12.40.

Octahydroprocoll (VII).

A mixture of L(-)-prolin (Aldrich; 5.8 g., 50 mmoles) and ethylene glycol (15 ml.) was stirred and heated to gentle reflux for 2 hours. The brown mixture was cooled, mixed with water, and extracted with chloroform. Drying (sodium sulfate) and evaporating *in vacuo* the extract afforded the product (3.0 g., 61.6%), which was recrystallized from benzene-petroleum ether (30-60°). Pure VII, pale crystalline powder, m.p. 149-150° [lit. 143° (7), 149° (8), 156° (9), 180-181° (10), 183-184° (11)];  $[\alpha]_D^{19}$  0.0° (c 1.04, MeOH) [lit.  $[\alpha]_D^{20}$  -151.15° (7),  $[\alpha]_D^{19}$  -147.2° (8)]; infrared (chloroform), 6.03  $\mu$ ; (nujol), 6.05  $\mu$ ; pmr (chloroform)  $\tau$  5.79 (triplet, J=8Hz), 6.46 (triplet, J=6-7Hz), 7.49-8.25 (multiplet); relative area ratio 1:2:4.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 61.83; H, 7.26; N, 14.43. Found: C, 62.06; H, 7.33; N, 14.45.

Octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine.

Optically Inactive Form (IVa). From Compound IIIa.

To a stirred mixture of lithium aluminum hydride powder (3.0 g., 79 mmoles) in tetrahydrofuran (THF) (200 ml.) was added portionwise the solid compound IIIa (4.25 g., 19.1 mmoles). After refluxing for 44 hours, the excess lithium aluminum hydride was destroyed with saturated sodium sulfate solution. The resulting mixture was filtered through a bed of Celite and sodium sulfate.

Evaporation of the filtrate *in vacuo* afforded the product as a light yellow liquid (2.7 g., 84.8% yield). The material was purified by two successive Kugelrohr-distillations. The pure product, a colorless liquid, was collected at 50-55° (0.001 mm),  $n_D^{20}$  1.5050. The oil crystallized as needles upon standing, m.p. 29-35°.  $[\alpha]_D^{20}$  0.0° (c 3.04, MeOH); infrared (dichloromethane) 3.4, 3.46, 3.57, 6.83, 7.25, 7.33, 7.47, 7.6, 7.8, 8.3, 8.56, 8.68, 8.87, 8.95, 9.2, 9.55, 10.07, 10.32  $\mu$ ; infrared (chloroform), 3.45, 3.55, 3.98  $\mu$ . Pmr (carbon tetrachloride)  $\tau$  6.97-7.90 (broad envelope with a slightly split peak at  $\tau$  7.48), 7.90-8.62 (broad); relative area ratio 5:4.

*Anal.* Calcd. for  $C_{10}H_{18}N_2$ : C, 72.24; H, 10.91; N, 16.85. Found: C, 72.19; H, 10.76; N, 16.90.

Dipicrate, yellow crystals (from MeOH), m.p. 256-259°; infrared (nujol mull), 3.6-4.5 (m, broad), 6.2, 6.38, 6.46, 6.6, 6.85, 7.31, 7.47, 7.56, 7.9  $\mu$ .

*Anal.* Calcd. for  $C_{10}H_{18}N_2 \cdot 2C_6H_3N_3O_7$ : C, 42.31; H, 3.87; N, 17.94. Found: C, 42.52; H, 3.91; N, 18.08.

Optically Inactive Form (IVa). From Octahydroprocoll(VII).

A solution of VII (5.2 g., 26.7 mmoles) in THF (50 ml.) was added dropwise to a stirred mixture of lithium aluminum hydride (2.2 g., 55 mmoles) in THF (200 ml.). After refluxing for 44 hours workup as above afforded the product as a light-brown liquid (4.3 g., 97% yield). Kugelrohr-distillation gave the pure compound as white, prismatic needles, collected at 65-70° (0.006 mm), m.p. 28-33°, m.m.p. 28-33° (with IVa obtained from IIIa); infrared (dichloromethane, chloroform, nujol) and pmr (carbon tetrachloride) spectra were superimposable with those of IVa obtained from IIIa.

The dipicrate was prepared and purified as indicated above, m.p. 255-258° dec. The infrared spectrum (nujol) was superimposable with that of the dipicrate prepared from IVa originated from IIIa. Mixture melting point of the two samples showed no depression.

*Anal.* Found: C, 42.12; H, 3.95; N, 17.98.

Optically Active Form (IVb). From Compound IIIb.

The compound (-)-IIIb (22.2 g., 0.1 mole) was reduced in the same manner (lithium aluminum hydride, 7.6 g.; THF, 500 ml.) to give 6.5 g. (37% yield) of IVb. The material was purified by

sublimation at 0.001 mm. (air-bath, 55-65°). Pure IVb was obtained as white prisms, m.p. 48-55°, m.m.p. 29-50° (with IVa originated from IIIa);  $[\alpha]_D^{20}$  +2.3° (c 3.0, MeOH). Infrared (dichloromethane) and pmr (carbon tetrachloride) spectra were superimposable with those of the optically inactive IVa. However, the infrared spectrum in nujol mull was slightly different, mainly in band intensities.

*Anal.* Found: C, 72.01; H, 10.83; N, 16.73.

Monopicrate, yellow needles (from MeOH), m.p. 156-158°; infrared (nujol mull), 6.11, 6.18, 6.6, 6.8, 6.93, 7.32, 7.41, 7.55, 7.85  $\mu$ .

*Anal.* Calcd. for  $C_{10}H_{18}N_2 \cdot C_6H_3N_3O_7$ : C, 48.61; H, 5.35; N, 17.71. Found: C, 48.49; H, 5.30; N, 17.65.

Dipicrate, yellow crystalline powder, m.p. 245-248° dec., m.m.p. 245-248° dec. (with dipicrate of optically inactive IVa); infrared (nujol mull) *ca.* 3.7 (broad), 6.12, 6.18, 6.44, 7.31, 7.57, 7.85  $\mu$ .

*Anal.* Found: C, 42.33; H, 4.06; N, 17.70.

#### REFERENCES

- (1) M. R. Harnden, *J. Heterocyclic Chem.*, **5**, 307 (1968).
- (2) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **74**, 2859 (1952).
- (3) H. Koch and J. Kotlan, *Monatsh. Chem.*, **97**, 1648 (1966).
- (4) E. Segel, *J. Am. Chem. Soc.*, **74**, 851 (1952).
- (5) S. El-Zantally, M. Khalifa, and Y. M. Abou-Zeid, *Tetrahedron*, **22**, 2307 (1966).
- (6) E. Abderhalden, *Compt. Rend.*, **1**, 2697 (1926).
- (7) E. Abderhalden and H. Nienburg, *Fermentforschung*, **13**, 573 (1933).
- (8) J. Kapfhammer and A. Mathes, *Z. Physiol. Chem.*, **223**, 43 (1933).
- (9) A. Stoll, J. Rutschmann, and W. Schlientz, *Helv. Chem. Acta*, **33**, 375 (1950).
- (10) N. A. Poddubnaya and G. I. Lavrenova, *Vestnik Moskov. Univ., Ser. Mat., Mekh., Astron., Fiz., Khim.*, **13** (3) 1965 (1958); *Chem. Abstr.*, **53**, 11396b.
- (11) N. Putochin, *Chem. Ber.*, **59B**, 1987 (1926).

Received August 12, 1968

Milwaukee, Wisconsin 53210