

Et<sub>2</sub>O (3:2 v/v): total yield 53%. The later crops each had mp 77–78°. A sample recrystallized twice from C<sub>6</sub>H<sub>6</sub>–cyclohexane had mp 79–80°. *Anal.* (C<sub>15</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>) C, H, N.

**Diethyl Acetamido[4-(2-oxo-3-oxazolidinyl)butyl]malonate (2b).** Alkylation of the Na derivative of 1 with 3-(4-chlorobutyl)-2-oxazolidinone<sup>13</sup> was carried out on a 0.614-mol scale as described for the preparation of 2a. The Norit treatment and filtration (silica gel mat) of an EtOAc solution of the crude residue (from removal of the DMAC) were performed twice. Following the removal of EtOAc, the orange oil was redissolved in EtOAc, and addition of ligroine (bp 30–60°) caused partial separation of crude 2b (85.2 g), mp 71–77°, which was recrystallized from C<sub>6</sub>H<sub>6</sub>–cyclohexane to give pure 2b (69.6 g), mp 80–81°. The residue from evaporation of the EtOAc–ligroine filtrate was chromatographed on a silica gel column, and elution with EtOAc led to additional crops of crude product, which were recrystallized from C<sub>6</sub>H<sub>6</sub>–cyclohexane to give pure 2b (29.2 g): mp 81–83°; total yield 45%. An analytical sample (from C<sub>6</sub>H<sub>6</sub>–cyclohexane) had mp 81–82°. *Anal.* (C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>) C, H, N.

**Diethyl Acetamido[3-(2-bromoethylamino)propyl]malonate Hydrobromide (3a).** A solution of 2a (25.0 g) in freshly prepared 30% dry HBr in AcOH solution (125 ml) was stirred at 25–30° for 43 hr. Addition of Et<sub>2</sub>O (500 ml) precipitated 3a as a viscous gum, which was washed with three 500-ml portions of Et<sub>2</sub>O by decantation. The remaining gum was extracted with portions of boiling EtOAc (4 l. total), and evaporation of the clarified EtOAc solution gave a crystalline residue. Recrystallization from MeCN–Et<sub>2</sub>O gave pure 3a, mp 111–113°, in 63% yield (22.6 g). *Anal.* (C<sub>14</sub>H<sub>25</sub>BrN<sub>2</sub>O<sub>5</sub>·HBr) C, H, N.

**Diethyl Acetamido[4-(2-bromoethylamino)butyl]malonate Hydrobromide (3b).** A solution of 2b (99.1 g) in 30% dry HBr in AcOH solution (500 ml) was stirred at 25–30° for 72 hr and then added in a thin stream to stirred Et<sub>2</sub>O (2.5 l.). The clear supernatant was removed by decantation from the gummy precipitate, which was stirred with three more 2.5-l. portions of Et<sub>2</sub>O. The still-gummy residue was dissolved in boiling EtOAc (900 ml), and a small crop (5.1 g) of 3b separated from the cooled solution. The filtrate was evaporated, and the gummy residue was dissolved in EtOAc–EtOH solution (9:1, 750 ml). Evaporation of this solution gave a solid residue, which was combined with the small first crop and recrystallized from MeCN–Et<sub>2</sub>O to give pure 3b, mp 147–149°, in 65% yield (85.4 g). *Anal.* (C<sub>15</sub>H<sub>27</sub>BrN<sub>2</sub>O<sub>5</sub>·HBr) C, H, Br, N.

**S-2-[4-Acetamido-4,4-bis(ethoxycarbonyl)butylamino]ethyl Hydrogen Thiosulfate (5a).** A mixture of 20.00 mmol each of Ti<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10.418 g) and 3a (9.244 g) in H<sub>2</sub>O (35 ml) was stirred at 25–30° for 64 hr, filtered from TiBr, and evaporated to dryness (bath at 25–30°, final pressure <1 mm). The residual syrup was stirred with EtOH (250 ml); the solution was clarified by filtration and evaporated to dryness. The glassy residue was again dissolved in EtOH (300 ml), and the Norit-treated and filtered (Celite) solution was evaporated as above to give 5a as an amorphous, deliquescent, solidified foam, which was pulverized under Et<sub>2</sub>O, collected under N<sub>2</sub>, and dried *in vacuo* (25–30°, P<sub>2</sub>O<sub>5</sub>): yield 77% (6.40 g); *ir* (KBr) 3400 (NH), 2980, 2830 (aliphatic CH), 1730 (ester C=O), 1660 (amide I), 1500 (amide II), 1190, 1015, 620 cm<sup>-1</sup> (SSO<sub>3</sub><sup>-</sup>); *pmr* (DMSO-*d*<sub>6</sub>-TMS)  $\delta$  1.15, 1.90, 0.8–2.2 (t, s, m, 13, CH<sub>3</sub>CH<sub>2</sub>, COCH<sub>3</sub>, CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>S), 2.6–3.5 (m, 6, CH<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>S), 4.12 (q, 4, CH<sub>3</sub>CH<sub>2</sub>), 8.2 (s, 1, CONH), 8.0–8.6 (2, br s, NH<sub>2</sub><sup>+</sup>). *Anal.* (C<sub>14</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>) C, H, N, S. A 30.3-mmol run gave 5a in 87% yield (12.5 g); *ir* spectrum identical with that of analytical sample.

**S-2-[5-Acetamido-5,5-bis(ethoxycarbonyl)pentylamino]ethyl Hydrogen Thiosulfate (5b).** Treatment of 3b (28.57 g, 60.00 mmol) with an equimolar amount of Ti<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (31.25 g) in H<sub>2</sub>O (100 ml) and subsequent work-up like that described for 5a gave deliquescent 5b as an amorphous glass in 96% yield (24.7 g): *ir* (KBr) 3380 (NH), 2980, 2870 (aliphatic CH), 1740 (ester C=O), 1665 (amide I), 1515 (amide II), 1190, 1020, 625 cm<sup>-1</sup> (SSO<sub>3</sub><sup>-</sup>); *pmr* (D<sub>2</sub>O–DSS)  $\delta$  1.23, 2.05, 0.9–2.4 (t, s, m, 15, CH<sub>3</sub>CH<sub>2</sub>, COCH<sub>3</sub>, CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>S), 3.1 (br t, 2, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.2–3.7 (m, 4, NCH<sub>2</sub>CH<sub>2</sub>S), 4.27 (q, 4, CH<sub>3</sub>CH<sub>2</sub>). *Anal.* (C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>) C, H, N, S.

**N<sup>6</sup>-(2-Mercaptoethyl)lysine Dihydrochloride (6a).** A solution of 5a (10.983 g, 26.50 mmol) in 6 N HCl (200 ml) was refluxed under N<sub>2</sub> for 4.5 hr, cooled to ~80°, treated with a solution of Ba(OAc)<sub>2</sub> (6.769 g, 26.50 mmol) in H<sub>2</sub>O (50 ml), kept at ~80° for 30 min, cooled in an ice bath, and stored in a refrigerator overnight. The mixture was filtered from BaSO<sub>4</sub>, and the filtrate was evaporated to near dryness. The remaining syrup was dissolved in H<sub>2</sub>O (50 ml), and the solution was treated with Norit,

filtered (Celite), and evaporated to ~20 ml. The colorless solution was freeze-dried to give deliquescent 6a as a frothy glass, which was dried further *in vacuo* (25–30°, P<sub>2</sub>O<sub>5</sub>), broken up under Et<sub>2</sub>O, collected under N<sub>2</sub>, and redried as before: yield 97% (6.80 g); *ir* (KBr) 3300–2100 (NH<sub>3</sub><sup>+</sup>), 1960 (amino acid hydrochloride), 1740 (C=O), 1580 (NH<sub>3</sub><sup>+</sup> deformation), 1200 cm<sup>-1</sup> (CO<sub>2</sub>H deformation); *pmr* (DMSO-*d*<sub>6</sub>-TMS)  $\delta$  1.5–2.3 (br m, 4, CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.5–3.6 (br m, 6, CH<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>SH), 3.9 (br m, 1, CHNH), 9 (v br s, ~7, NH<sub>3</sub><sup>+</sup>, NH<sub>2</sub><sup>+</sup>, OH, SH; not observed separately because of exchanging). *Anal.* (C<sub>7</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S·2HCl·0.6H<sub>2</sub>O) C, H, Cl, N, S; SH (by iodometric titration).

**N<sup>6</sup>-(2-Mercaptoethyl)lysine Dihydrochloride (6b).** Hydrolysis of 5b (13.1 g) and subsequent treatment of the solution with Ba(OAc)<sub>2</sub> was carried out as described for the conversion of 5a to 6a. The filtered solution was evaporated under reduced pressure to dryness with filtrations at half-volume (to remove a small amount of crystalline BaCl<sub>2</sub>) and at ~50 ml (to remove a trace of other insoluble material). The clear glassy residue was kept *in vacuo* over P<sub>2</sub>O<sub>5</sub> for 66 hr, pulverized under Et<sub>2</sub>O, collected under N<sub>2</sub>, and dried *in vacuo* (25–30°, P<sub>2</sub>O<sub>5</sub>) to give deliquescent 6b in 70% yield (6.1 g); *ir* (KBr) 3300–2100 (NH<sub>3</sub><sup>+</sup>), 1980 (amino acid hydrochloride), 1735 (C=O), 1580 (NH<sub>3</sub><sup>+</sup> deformation), 1200 cm<sup>-1</sup> (CO<sub>2</sub>H deformation); *pmr* (D<sub>2</sub>O–DSS)  $\delta$  1.2–2.3 (m, 6, CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.7–3.6 (m, 6, CH<sub>2</sub>CH<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>S), 4.10 (t, 1, NCHCH<sub>2</sub>). *Anal.* (C<sub>8</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S·2HCl·0.3H<sub>2</sub>O) C, H, Cl, N; SH: calcd, 11.62; found, 11.18 (by iodometric titration).

**Acknowledgment.** This investigation was supported by the U. S. Army Medical Research and Development Command through Contract No. DADA 17-69-C-9033. The authors are indebted to D. W. C. Coburn, Jr., and Mrs. Martha Thorpe for interpretation of spectral data.

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† Cf. ref 14 for the interpretation of amino acid spectra.

## Synthesis of *dl*-3-(Hydroxymethyl)tyrosine

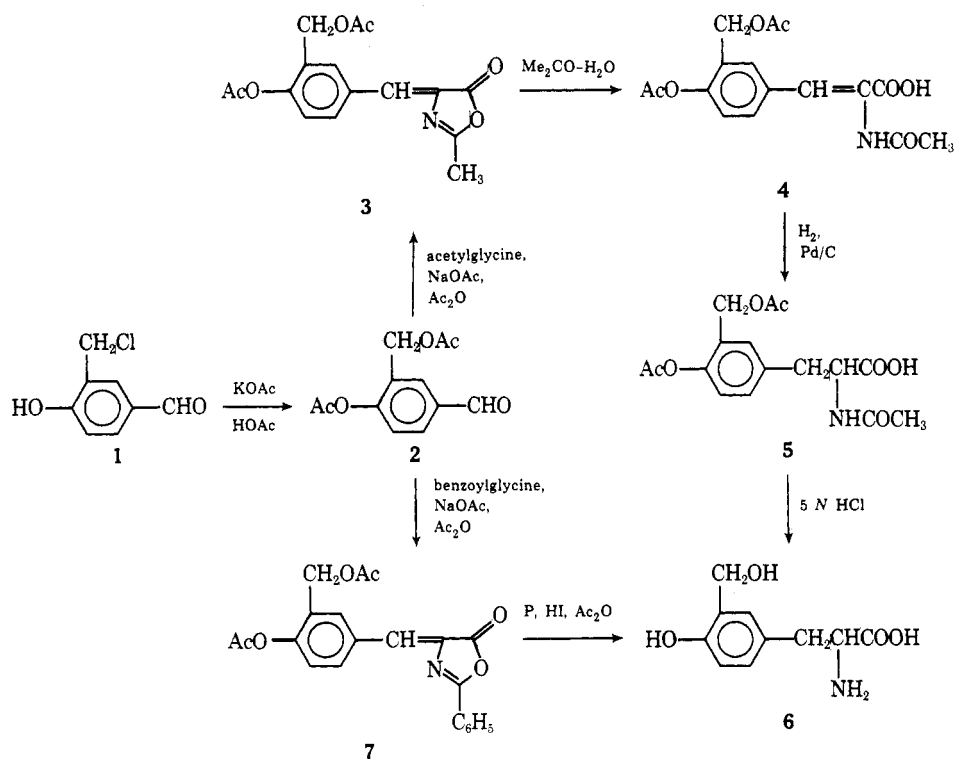
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Received August 11, 1972

Dopa has been widely used in the treatment of Parkinson's disease. The efficacy of *l*-Dopa has been attributed to the penetration of *l*-Dopa and its metabolic conversion into dopamine in the extrapyramidal brain centers.<sup>1,2</sup>

Scheme I



Since dopamine cannot penetrate into the brain tissue, potentiation of *l*-Dopa therapy has been achieved by peripheral decarboxylase inhibitors preventing formation of dopamine before *l*-Dopa penetration can occur.<sup>3</sup>

Inactivation of dopamine in brain tissue occurs through metabolic breakdown by monoamine oxidase (MAO) or catechol *O*-methyltransferase (COMT) enzymes. As a result, potentiation of the central action of *l*-Dopa has been obtained by MAO and COMT inhibitors.<sup>4,5</sup>

Recent reports<sup>6</sup> indicate that replacement of the meta phenolic group of the catechol by related functions stable to COMT does not destroy  $\beta$ -adrenergic-stimulating activity displayed by selected catecholamines. Therefore, it occurred to us that 3-(hydroxymethyl)tyrosine, where a hydroxymethyl function stable to COMT replaces the meta phenolic group of Dopa, may possess greater and longer lasting anti-Parkinsonian activity than *l*-Dopa.<sup>†</sup>

**Synthesis.** The synthetic scheme used for the preparation of *dl*-3-(hydroxymethyl)tyrosine (6) is outlined in Scheme I. Acetolysis of the chloromethyl aldehyde 1 to the acetoxymethylaldehyde 2 was followed by azlactone formation<sup>8</sup> to produce compound 3. Hydrolysis<sup>9</sup> of the azlactone 3 to the unsaturated carboxylic acid 4 was followed by hydrogenation to *dl*-3-(hydroxymethyl)tyrosine triacetate (5). Finally, hydrolysis of the triacetate 5 produced *dl*-3-(hydroxymethyl)tyrosine (6).

In another approach compound 7 obtained by azlactone formation from the aldehyde 2 could be converted by reductive cleavage<sup>10</sup> into *dl*-3-(hydroxymethyl)tyrosine (6).

**Biochemical and Pharmacological Activities.** The antitremorine effects were determined in male albino mice of the Charles River strain weighing 20–30 g each. Two doses of the test compounds were administered intraperitoneally to groups of ten mice 0.5 hr before intraperitoneal injection of tremorine (20 mg/kg). The fraction showing

lethality and prevention of tremors, as well as other effects on the CNS, is shown in Table I.

Compound 6 is not a substrate for Dopa decarboxylase as determined by the method of Sourkes<sup>11</sup> using Worthington (lot no. 25A) *l*-Dopa decarboxylase enzyme. Compound 6 was also tested for tyrosine hydroxylase inhibitory activity.

*In vivo* tyrosine hydroxylase inhibitors are known to produce sedation and can, therefore, be screened by observation. The injection of 1 mmol/kg of 6 into the tail vein of mice produced no sedation, no ptosis, and no piloerection. No significant effects could be observed when 3 mmol/kg was injected; these results, therefore, suggest that 6 produces no alteration of amine function through tyrosine hydroxylase inhibition.

*In vitro* testing of tyrosine hydroxylase<sup>12</sup> was made with bovine tyrosine hydroxylase and screened in triplicate at 10<sup>-3</sup>, 10<sup>-4</sup>, and 10<sup>-5</sup>M, using the method of Nagatsu.<sup>13</sup> After the appropriate quench and blank corrections were applied, the results shown in Table II were obtained.

As a conclusion, 6 does not act *in vivo* or *in vitro* as an inhibitor of tyrosine hydroxylase. The lack of gross effects at 3 mmol/kg in mice further suggests no significant interference with overall catecholamine biosynthesis or storage.

These results indicate that compound 6 is not likely to be useful in the treatment of Parkinson's disease. The same conclusion was reached by Atkinson, *et al.*,<sup>7</sup> for *l*-3-(hydroxymethyl)tyrosine.

## Experimental Section

Microanalyses were within  $\pm 0.3\%$  of the theoretical values as performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were obtained on a Fisher-Johns hot stage and are corrected. Ir spectra were recorded on a Perkin-Elmer 337 grating ir spectrophotometer. Nmr spectra were run on Varian A-60A and HA-100 spectrometers in (CD<sub>3</sub>)<sub>2</sub>SO with Me<sub>4</sub>Si as internal reference. Uv spectra were recorded on a Bausch & Lomb spectronic 505 spectrophotometer. Mass spectra were determined on a Hitachi RMU-6D double-focusing spectrometer at 70 eV. Type QIF

<sup>†</sup> After our original manuscript was submitted for publication, the preparation of *l*-3-(hydroxymethyl)tyrosine was reported by an independent synthesis.<sup>7</sup>

Table I

Compd	Dosage, mg/kg ip	Fraction showing prevention of tremors	Fraction showing lethality	Other effects
3	500	0/10	10/10	CNS depression
	1000	0/10	10/10	Writhing movements
7	500	9/10	3/10	
	1000	10/10	3/10	
6	500	0/10	3/10	
	1000	3/10	6/10	
dl-Dopa	500	0/10	5/10	
	1000	9/10	6/10	
l-Dopa	250	3/10	1/10	
	500	10/10	5/10	

Table II

	<i>M</i>	% control <sup>a</sup>	% inhibn <sup>a</sup>
l-Monoiodotyrosine	10 <sup>-5</sup>	42	58
6	10 <sup>-5</sup>	95	5
6	10 <sup>-4</sup>	97	3
6	10 <sup>-3</sup>	102	

<sup>a</sup>Means of triplicate.

silica gel plates from Quantum Industries were used for tlc development. Ir, nmr, uv, mass spectra, and tlc were all appropriate.

**4-Hydroxy-3-hydroxymethylbenzaldehyde Diacetate (2).** A mixture of 1<sup>4</sup> (1.7 g, 0.01 mol), KOAc (2 g, 0.2 mol), and AcOH (15 cc) was stirred at 60° for 5 hr and then at 25° for 16 hr. The solvent was evaporated to yield a solid, to which 100 g of ice-H<sub>2</sub>O was added. The product was extracted into Et<sub>2</sub>O, and the solvent was evaporated to yield crystals. Recrystallization from Et<sub>2</sub>O provided 2 (1.1 g, 57% yield), mp 99–100°. Compound 2 gave a positive 2,4-DNP and negative FeCl<sub>3</sub> test. *Anal.* (C<sub>12</sub>H<sub>12</sub>O<sub>5</sub>) C, H.

**4-[4'-Hydroxy-3'-(hydroxymethyl)benzylidene]-2-methyl-2-oxazolin-5-one Diacetate (3).** A mixture of 2 (23.6 g, 0.1 mol), acetyl glycine (11.7 g, 0.1 mol), NaOAc (8.23 g, 0.1 mol), and Ac<sub>2</sub>O (80 ml) was stirred at 110° for 1 hr and then poured into 500 g of ice-H<sub>2</sub>O. The obtained solid was filtered and crystallized from EtOAc-Et<sub>2</sub>O to give 3 (26 g, 81%), mp 116–118°. *Anal.* (C<sub>16</sub>H<sub>15</sub>NO<sub>6</sub>) C, H, N.

**4-[4'-Hydroxy-3'-(hydroxymethyl)benzylidene]-2-phenyl-2-oxazolin-5-one Diacetate (7).** Compound 7 was prepared from 2 in the same way as described for the synthesis of compound 3, except the reaction time at 110° was extended for 6 hr. Obtained was 7 (28.1 g, 74%), mp 156–157°. *Anal.* (C<sub>21</sub>H<sub>17</sub>NO<sub>6</sub>) C, H, N.

**2-Acetamido(3-acetoxymethyl-4-acetoxy)cinnamic Acid (4).** Compound 3 (12.2 g, 0.04 mol) in 75% aqueous Me<sub>2</sub>CO (400 ml) was heated at reflux until a clear solution was obtained (approximately 6 hr). The solvent was evaporated to give a solid. Crystallization from THF-Et<sub>2</sub>O gave 4 (10.4 g, 78%); mp 183–185°; tlc (Me<sub>2</sub>CO-MeOH, 1:1) *R*<sub>f</sub> 0.78. *Anal.* (C<sub>16</sub>H<sub>17</sub>NO<sub>7</sub>) C, H, N.

**dl-3-(Hydroxymethyl)tyrosine Triacetate (5).** A solution of 4 (3.4 g, 0.01 mol) in 75% aqueous MeOH (80 ml) was hydrogenated at 25° over 10% Pd/C (350 mg) at an initial H<sub>2</sub> pressure of 50 lb/in.<sup>2</sup>. When hydrogenation was complete the catalyst was filtered, the solvent was evaporated, and the residue was crystallized from Me<sub>2</sub>CO to give 5 (3.04 g, 91%); mp 157–158°; tlc (C<sub>6</sub>H<sub>6</sub>-EtOAc-MeOH, 7:3:3) *R*<sub>f</sub> 0.50. *Anal.* (C<sub>16</sub>H<sub>19</sub>NO<sub>7</sub>) C, H, N.

**dl-3-(Hydroxymethyl)tyrosine (6).** **Procedure A.** A mixture of 5 (3.4 g, 0.01 mol) and 5 N HCl (100 ml) was stirred at reflux until a clear solution was obtained (approximately 5 hr). The solution was concentrated (to 20 ml) under reduced pressure, treated with activated charcoal, filtered, and kept at 0° for 2 days. The precipitated crystals were filtered and washed with EtOH and then with Me<sub>2</sub>CO to yield the HCl salt of 6 (1.71 g, 71%), mp >300°. *Anal.* (C<sub>10</sub>H<sub>14</sub>NO<sub>4</sub>Cl) C, H, N, Cl.

The HCl salt was dissolved in H<sub>2</sub>O (30 ml), dilute NH<sub>4</sub>OH was added to pH 5.5, and the solution was concentrated. The precipitated crystals were filtered and washed with H<sub>2</sub>O to give 6 (1.34 g, 64%); mp 290–294° dec; tlc (96% EtOH-34% NH<sub>4</sub>OH, 7:3) *R*<sub>f</sub> 0.85; tlc (*n*-BuOH-H<sub>2</sub>O-HOAc-pyridine, 15:5:3:2) *R*<sub>f</sub> 0.62. Com-

pound 6 gave a positive ninhydrin test: λ max (0.01 N HCl) 226 mμ (log ε 3.81) and 275 (3.58). Corresponding data for dl-Dopa: λ max (0.01 N HCl) 224 mμ (log ε 3.79) and 279 (3.40). *Anal.* (C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>) C, H, N.

**Procedure B.** To a cooled mixture of 7 (7.6 g, 0.02 mol) and purified red P (4.65 g, 0.15 mol) in Ac<sub>2</sub>O (60 ml) was added dropwise with stirring 55% HI (50 g, 0.2 mol). The mixture was refluxed for 1 hr and then cooled. The excess P was removed by filtration; the solvent was evaporated under reduced pressure to give a solid. The solid was partitioned between H<sub>2</sub>O-Et<sub>2</sub>O (400 ml, 1:1) and after separation the aqueous solution was adjusted to pH 6 with dilute NH<sub>4</sub>OH. The solution was concentrated and the precipitated crystals were filtered and washed with H<sub>2</sub>O, MeOH, and then Me<sub>2</sub>CO to give 6 described in procedure A.

**Acknowledgment.** We wish to express our thanks to Dr. John Reinhard, Department of Pharmacology, Graduate School of Pharmacy, Northeastern University, Boston, Mass., for the antitremorine assay, Dr. Nicolas Zenker, University of Maryland, School of Pharmacy, for the tyrosine hydroxylase enzyme assay, and E. H. Gerry of Kendall Co. for the Dopa decarboxylase enzyme assay.

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## Amino-Imino Tautomerism in the Antibiotic Formycin A as Studied by CNDO/2 Molecular Orbital Theory

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In a recent communication Krugh<sup>1</sup> reported that carbon-13 nmr studies of the nucleoside antibiotic formycin A (1) show that this molecule is involved in prototropic tautomeric equilibria. These results for formycin A, which is a cytotoxic adenosine analog, are particularly interesting since adenosine does not give any evidence of tautomerization in its <sup>13</sup>C spectra and is known to exist in the amine form.<sup>2,3</sup> In the present communication we show that CNDO/2 molecular orbital calculations indicate that, relative to adenine, there are significant changes in the stability of the amino and imino forms of formycin A and that this suggests a possible mechanism for the biological activity of this drug.

Using the Pople and Segal<sup>4</sup> version of CNDO/2, we have computed the total ground-state energy of formycin