

bulbar plexuses 3 to 5 hr after dosing were assayed³¹ for blood glucose using the method of Hoffman⁸ as adapted for the Technicon AutoAnalyzer. All the indolylpyridinium salts in Table II produced a hypoglycemic effect. Blood glucose was maximally reduced 32–91% by these compounds.

Experimental Section⁹

1-Alkyl-3-(4-pyridyl)indoles.—To a stirred mixture of 1.25 g (0.029 mole) of NaH (55% dispersion in mineral oil) and 4.85 g (0.025 mole) of 3-(4-pyridyl)indole (6) in 20 ml of DMF was added a solution of 0.025 mole of the appropriate alkyl halide in 10 ml of DMF. This mixture was stirred at room temperature for 16 hr, and poured onto cracked ice. The mixture was acidified with dil HCl and washed with Et₂O. The aq solution was made basic with dil NaOH and extracted with CHCl₃. The CHCl₃ solution was dried (MgSO₄) and concentrated under reduced pressure to the crude product which was purified by distillation and/or recrystallization. Compounds 12–14 were obtained by this procedure and are listed in Table I.

3-(4-Pyridyl)indoles.—To 0.02 mole of commercially available indole was added slowly 7.3 ml (0.022 mole) of 3 M ethereal MeMgBr. After gas evolution had subsided, a solution containing 0.03 mole of 4-chloropyridine in 20 ml of Et₂O was added to the mixture. This mixture was heated in a glass lined bomb at 160° for 20 hr. The reaction mixture was poured into a solution of 3 g of NH₄Cl in 150 ml of H₂O. The Et₂O phase was separated and the aq mixture was extracted with CHCl₃. The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to the crude products. Purification was accomplished by absorption chromatography (Al₂O₃) and/or recrystallization. Compounds 21–24 were obtained by this procedure, and are listed in Table I.

4-(3-Indolyl)pyridinium Salts.—The quaternary salts listed in Table II were prepared from the corresponding 3-(4-pyridyl)indole bases listed in Table I by heating with an alkyl halide in a refluxing alcoholic solvent² or in a glass-lined bomb.¹⁰

(8) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(9) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

Folic Acid Analogs. II.

p-{[(2,6-Diamino-8-purinylo)methyl]amino}-benzoyl-L-glutamic Acid and Related Compounds¹

LOUIS T. WEINSTOCK, BERNARD F. GRABOWSKI, AND C. C. CHENG

Midwest Research Institute, Kansas City, Missouri 64110, and University of Missouri-Kansas City, Kansas City, Missouri 64110

Received February 6, 1970

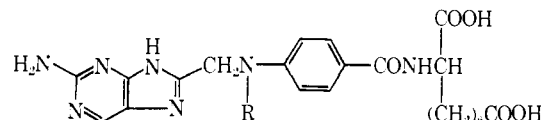
The biogenetic relationship between purines and pteridines has been described.² Since 2,6-diaminopurine, which inhibits the growth of leukemia,³ is

(1) (a) This investigation was supported by Contract No. PH-43-65-64 with Chemotherapy, National Cancer Institute, of the National Institutes of Health, Public Health Service; (b) presented in part before the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969 (Medi 66).

(2) (a) A. Albert, *Biochem. J.*, **65**, 124 (1957); (b) E. Vieira and E. Shaw, *J. Biol. Chem.*, **236**, 2507 (1961); (c) F. Weygand, H. Simon, G. Dahms, M. Waldschmidt, H. J. Schliep, and H. Wacker, *Angew. Chem.*, **73**, 402 (1961); (d) W. S. McNutt, *J. Biol. Chem.*, **238**, 1116 (1963); (e) W. S. McNutt and S. P. Damle, *ibid.*, **239**, 4272 (1964); (f) A. W. Burg and G. M. Brown, *Biochim. Biophys. Acta*, **117**, 275 (1966); *J. Biol. Chem.*, **243**, 2349 (1968).

(3) J. H. Burchenal, A. Bendich, G. B. Brown, G. B. Elion, G. H. Hitchings, C. P. Rhodes, and C. C. Stock, *Cancer*, **2**, 119 (1949).

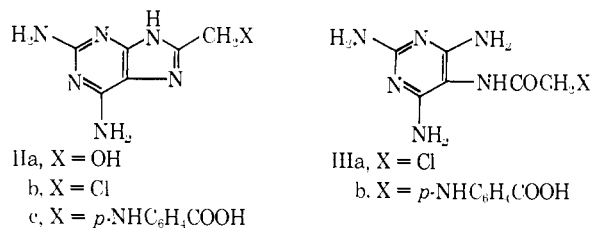
bound more tightly to dihydrofolic reductase than most pteridines,⁴ and since the 2,6-diaminopurine analog of pteric acid is more inhibitory to the growth of some bacteria than the parent 2,6-diaminopurine,⁵ synthesis of the 2,6-diaminopurine congeners of aminopterin and methotrexate, Ia and Ib, was investigated.



Ia. R = H
b. R = CH₃

A search of the literature revealed that, of the purine analogs synthesized in this group, the caffeine and the theophylline analogs of folic acid and pteric acids have been reported.³ These compounds were found to be without activity against the S-810, Ca-755, and L-1210 tumor systems.⁶ The guanine⁷ and 2,6-diaminopurine^{5,8} analogs of pteric acid as well as the 2,6-diaminopurine analog of homopteric acid⁸ were also prepared. The 2,6-diaminopurine derivatives were reported to be as inhibitory against dihydrofolic reductase as the parent 2,6-diaminopurine.⁸

Theoretically, two possible routes can be applied for the synthesis of compounds of this type. One utilizes the condensation of a 2,6-diamino-8-halomethylpurine with the appropriate *p*-aminobenzoyl compound; the other involves the reaction of 2,4,6-triamino-5-haloacetamidopyrimidine with the respective *p*-aminobenzoyl derivative with subsequent cyclization to the corresponding purine. Both routes were fruitful. Baker and Santi⁹ prepared 2,6-diamino-8-hydroxymethylpurine (IIa) by the treatment of 2,4,5,6-tetraaminopyrimidine with glycolic acid. Attempted bromination of IIa by these investigators was not successful. This was also found to be true in our hands. Nevertheless, a procedure reported for the chlorination of 2-methyl-4-amino-5-hydroxymethylpyrimidine with thionyl chloride in dimethylformamide⁹ was adopted for the chlorination of IIa. The resulting product IIb was then caused to react with appropriate *p*-aminobenzoyl derivatives to yield Ia, Ib, and related compounds.



Treatment of 2,4,5,6-tetraaminopyrimidine with chloroacetic acid followed by condensation of the resulting 5-chloroacetamidopyrimidine (IIIa) with *p*-aminobenzoic acid yielded IIIb. Cyclization of IIIb gave the diaminopurine analog of pteric acid IIc.

(4) S. F. Zakrzewski, *J. Biol. Chem.*, **238**, 1485 (1963).

(5) G. B. Elion, G. H. Hitchings, and H. VanderWerff, *ibid.*, **192**, 505 (1951).

(6) H. Zimmer and R. Atchley, *Arzneim. Forsch.*, **16**, 541 (1966).

(7) W. T. Caldwell and C.-S. Cheng, *J. Amer. Chem. Soc.*, **77**, 6631 (1955).

(8) B. R. Baker and D. V. Santi, *J. Heterocycl. Chem.*, **4**, 216 (1967).

(9) L. Suranyi and H. Wilk, German Patent, 1,150,987 (1963); *Chem. Abstr.*, **60**, 2971b (1964).

Compound Ia was then readily obtained from IIc by employing the mixed anhydride method.¹⁰

Compounds Ia and Ib were found to be without activity against the leukemia L-1210 system.¹¹ For direct comparison, antileukemic test results of *p*-{[2,4-diamino-5-pyrimidinyl)methyl]amino}benzoyl-L-glutamic acid¹² (IV) and the corresponding *N*-methylamino-benzoyl-L-glutamic acid derivative¹² (V) against leukemia L-1210, which were not reported in the preceding communication,¹² are listed in Table I. The concentration for 50% inhibition against chicken liver dihydrofolate reductase¹³ for compound Ia was found to be $2.8 \times 10^{-4} M$ and for Ib was $6.7 \times 10^{-5} M$, which suggests that these purine derivatives are less inhibitory toward this enzyme than the corresponding pyrimidine derivatives.¹²

TABLE I
ANTILEUKEMIC TEST RESULTS OF PURINE AND PYRIMIDINE
CONGENERS OF AMINOPTERIN AND METHOTREXATE
VS. LEUKEMIA L-1210^a

Compound	Dose (mg/kg)	Survivors	Wt diff (test - control)	Test/Control (%)
Ia	400	12/12	-2.1	102
Ib	400	12/12	1.0	108
IV	900	6/6	-1.8	133
	600	6/6	-2.1	139
	400	18/18	-1.0	144
	200	12/12	-2.1	125
	100	12/12	-1.5	129
V	400	12/12	-1.3	120

^a See ref 11.

Experimental Section¹⁴

2,6-Diamino-8-hydroxymethylpurine (IIa).—This compound was prepared from 119 g (0.50 mole) of 2,4,5,6-tetraaminopyrimidine sulfate and 152 g (2.0 mole) of glycolic acid by the procedure described for the preparation of the acetate of IIa⁹ with the exception of the isolation procedure. The syrupy reaction mixture was extracted three times with 800-ml portions of Et₂O and the remainder was dissolved in 1 l. of H₂O. The pH of the solution was adjusted to 9 with NH₄OH. On cooling, 72 g (73%) of 2,4,6-triamino-5-glycolamidopyrimidine was isolated, mp 255° dec. A small amount was recrystallized from H₂O for analysis; mp 255° dec; $\lambda_{\text{max}}^{\text{NH}^+}$ 271 m μ (ϵ 9,900); $\lambda_{\text{sh}}^{\text{NH}^+}$ 240 m μ (ϵ 5,800); $\lambda_{\text{max}}^{\text{OH}^-}$ 265 m μ (ϵ 16,800). *Anal.* (C₆H₁₀N₆O₂) C, H, N.

A solution of 70 g (0.35 mole) of the glycolamido intermediate in 500 ml of 2 N NaOH was refluxed for 6 hr. The reaction mixture was cooled and acidified to pH 5 with AcOH. The precipitated pale yellow solid was collected by filtration to give 45 g (71%) of IIa, mp >360°. Recrystallization from AcOH gave analytically pure material: $\lambda_{\text{max}}^{\text{NH}^+}$ 241 m μ (ϵ 9,200), 283 (11,000); $\lambda_{\text{sh}}^{\text{NH}^+}$ 241 m μ (5,400), 283 (7,900). *Anal.* (C₆H₈N₆O) C, H, N.

2,6-Diamino-8-chloromethylpurine (IIb).—To a suspension of 9 g (0.05 mole) of IIa in 50 ml of DMF was added portionwise 10 ml (16.6 g, 0.14 mole) of SOCl₂ at room temperature. The resulting solution was heated at 60–70° for 3 hr and subsequently allowed to stand at room temperature overnight. The solution was then

evaporated *in vacuo* and the residue triturated with EtOAc to give a yellow solid. The product was rapidly collected by filtration. Due to the hygroscopic nature of this material, it was used immediately for the preparation of the *p*-aminobenzoyl derivatives.

2,4,6-Triamino-5-chloroacetamidopyrimidine (IIIa).—A finely ground mixture of 24 g (0.1 mole) of 2,4,5,6-tetraaminopyrimidine sulfate and 47 g (0.5 mole) of CH₂ClCO₂H was heated under reduced pressure (water aspirator) on a steam bath for 1 hr. The resulting product was cooled and extracted three times with 300-ml portions of Et₂O. The remainder was dissolved in 500 ml of H₂O. The pH of the aq solution was adjusted to 8, at which point a yellow solid precipitated. This was collected by filtration to give 11 g (51%) of IIIa, mp 245–247° dec. This material was used in subsequent reactions without further purification.

***p*-{[(2,4,6-Triamino-5-pyrimidinyl)carbamylmethyl]amino}benzoic Acid (IIIb).**—A mixture of 4.5 g (0.021 mole) of IIIa and 5.7 g (0.042 mole) of *p*-aminobenzoic acid in 240 ml of H₂O was refluxed for 5 hr. During this time the solid reactants slowly dissolved followed by gradual precipitation of the product. It was collected by filtration from the still hot reaction mixture and dissolved in 200 ml of H₂O. The pH of the aq solution was adjusted to 10 with NaOH. The solution was heated to 60–70°, purified with charcoal, and filtered. The filtrate was acidified with AcOH to give 4 g (60%) of pure IIIb; mp 305–307° dec; $\lambda_{\text{max}}^{\text{NH}^+}$ 273 m μ (ϵ 19,000); $\lambda_{\text{sh}}^{\text{NH}^+}$ 295 m μ (ϵ 12,700); $\lambda_{\text{max}}^{\text{OH}^-}$ 267 m μ (ϵ 25,800). *Anal.* (C₁₃H₁₅N₇O₃) C, H, N.

***p*-{[(2,6-Diamino-8-puriny)methyl]amino}benzoic Acid (IIIc).** **Method A.**—A solution of 7.5 g (0.024 mole) of IIIb in 160 ml of 0.1 N NaOH was refluxed for 16 hr. The mixture was purified with charcoal and filtered. A pale yellow solid, which was formed upon acidification of the filtrate with AcOH, was collected by filtration. The product was purified through three successive reprecipitations from aq NaOH with AcOH to give 3.5 g (49%), mp 330–333° dec. The uv spectra of this product are as expected. *Anal.* (C₁₂H₁₃N₇O₂) C, H, N.

Method B.—A solution of 6.0 g (0.025 mole) of IIIb and 6.7 g (0.049 mole) of *p*-aminobenzoic acid in 250 ml of abs EtOH was refluxed for 16 hr. The HCl salt of the product gradually separated from the hot reaction mixture. This was collected, dissolved in aq NaOH, and reprecipitated with AcOH to give 3.5 g of IIIc. The melting point, uv and ir spectra were found to be identical with those of IIIc prepared by method A and similar to those reported by Baker and Santi.⁸

Ethyl *p*-{[(2,6-diamino-8-puriny)methyl]amino}benzoate (II, X = *p*-NHCH₂COOC₂H₅).—A solution of 4.1 g (0.025 mole) of ethyl *p*-aminobenzoate and 3.0 g (0.0125 mole) of IIb in 250 ml of abs EtOH was refluxed for 16 hr. The reaction mixture was evaporated under reduced pressure and the residue dissolved in 250 ml of H₂O. The pH of the aq solution was adjusted to 9 with NH₄OH. The solid product which separated was collected by filtration. It was recrystallized from MeOH-H₂O to give 1 g (25%) of the product; mp 272–275° dec; $\lambda_{\text{max}}^{\text{NH}^+}$ 292 m μ (ϵ 28,800); $\lambda_{\text{sh}}^{\text{NH}^+}$ 243 m μ (ϵ 10,100); $\lambda_{\text{max}}^{\text{OH}^-}$ 290 m μ (ϵ 29,100). *Anal.* (C₁₅H₁₇N₇O₂) C, H, N.

***p*-{[(2,6-Diamino-8-puriny)methyl]-*N*-methylamino}benzoic Acid (II, X = *p*-CH₃NC₆H₄COOH).**—A solution of 12 g (0.05 mole) of IIb and 11.3 g (0.075 mole) of *p*-*N*-methylaminobenzoic acid in 250 ml of abs EtOH was refluxed for 48 hr. The HCl salt of the product, which precipitated from the hot reaction mixture, was collected by filtration to give 9 g (50% yield) mp 277–280° dec. This was dissolved in hot H₂O, made alkaline with NaOH, treated with charcoal, and reprecipitated with AcOH to give 6 g (36%) of product; mp 330–334° dec; $\lambda_{\text{max}}^{\text{NH}^+}$ 300 m μ (ϵ 28,700); $\lambda_{\text{sh}}^{\text{NH}^+}$ 245 m μ (ϵ 10,900); $\lambda_{\text{max}}^{\text{OH}^-}$ 293 m μ (ϵ 28,200). *Anal.* (C₁₄H₁₇N₇O₂·0.5H₂O) C, H, N.

***p*-{[(2,6-Diacetamido-8-puriny)methyl]-*N*-acetamido}benzoic Acid.**—A mixture of 4.0 g (0.013 mole) of IIIc in 50 ml of Ac₂O was refluxed for 16 hr. The resulting solid was filtered from the hot reaction mixture and washed successively with H₂O, EtOH, and Me₂CO. The brown solid was recrystallized from AcOH to give 3 g (55%) of the product as a monohydrate, mp 275–278° dec. *Anal.* (C₁₆H₁₉N₇O₅·H₂O) C, H, N.

***p*-{[(2,6-Diamino-8-puriny)methyl]amino}benzoyl-L-glutamic Acid (Ia).** **Method A.**—A solution of 3.0 g (0.0125 mole) of IIb and 6.7 g (0.025 mole) of *p*-aminobenzoyl-L-glutamic acid in 125 ml of DMF containing a few crystals of KI was heated between 70 and 80° for 16 hr. The resulting solution was evaporated under reduced pressure and the residue was dissolved in

¹⁰ J. I. DeGraw, J. P. Marsh, Jr., E. M. Acton, O. P. Crews, C. W. Mosler, A. N. Fujiwara, and L. Goodman, *J. Org. Chem.*, **30**, 3404 (1965).

¹¹ Test results were provided by contract screeners of Cancer Chemotherapy National Service Center. Detailed interpretations of test data are provided in *Cancer Chemother. Rep.*, **25**, 1 (1962).

¹² L. T. Weinstein, D. E. O'Brien, and C. C. Cheng, *J. Med. Chem.*, **11**, 1238 (1968).

¹³ M. P. Mertes and N. R. Patel, *ibid.*, **9**, 868 (1966). We thank Professor Matthias P. Mertes of the University of Kansas for providing the information of dihydrofolate reductase inhibitory test.

¹⁴ All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. Uv spectra were determined with a Beckman DK-2 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

250 ml of H₂O. A gummy precipitate was produced when the pH of the aq solution was carefully adjusted to 4. The mixture was allowed to stand for 2 hr at room temperature, the supernatant liquid was decanted, and the residual gum was triturated with abs EtOH to give 1.2 g (18%) of Ia, mp 204–207° dec. The product was recrystallized from a large volume of H₂O and dried *in vacuo* at 135° to yield analytically pure product: mp 235–237° dec; $\lambda_{\text{max}}^{\text{NH}}$ 288 m μ (ϵ 27,800); $\lambda_{\text{NH}}^{\text{NH}}$ 245 m μ (ϵ 12,400); $\lambda_{\text{max}}^{\text{NH}}$ 290 m μ (ϵ 29,100). *Anal.* (C₁₈H₂₀N₈O₅) C, H, N.

Method B.—A solution of 7.4 g (0.025 mole) of dimethyl *p*-aminobenzoyl-L-glutamate,¹⁵ 3.0 g (0.0125 mole) of IIb and a few crystals of KI in 250 ml of abs EtOH was refluxed for 16 hr. The resulting solution was evaporated under reduced pressure and the residue was dissolved in 250 ml of H₂O. The pH of the aq solution was adjusted to 8–9 with NaHCO₃ which caused the precipitation of a gummy substance. No attempt was made to isolate the diester intermediate. The aq layer was decanted and to the residual gum was added 200 ml of 1 *N* NaOH. The mixture was allowed to stir at room temperature for 2 hr. The pH of the solution was carefully adjusted to 4 with 6 *N* HCl at which point the product precipitated. It was purified by recrystallization from H₂O to give 1.1 g (17%) of Ia. The product was found to be identical with that prepared by method A.

Method C.—To a solution of 3.1 g (0.007 mole) of *p*-{[(2,6-diacetamido-8-puriny)methyl]-*N*-acetamido}benzoic acid in 250 ml of DMF cooled at 0° was added 0.7 g (0.007 mole) of Et₃N followed by 0.8 ml (0.007 mole) of ethyl chloroformate. The mixture was stirred at 0° for 1 hr. A solution of 1.5 g (0.007 mole) of dimethyl L-glutamate-HCl and 0.7 g (0.007 mole) of Et₃N in 50 ml of DMF was then added to the mixture. The resulting suspension was stirred for 20 hr at room temperature. Excess solvent was evaporated under reduced pressure at ca. 45°. To the residue was added 200 ml of 1 *N* NaOH. The resulting dark solution was refluxed for 30 min, purified with charcoal, and filtered. The filtrate was acidified with 6 *N* HCl to give a light yellow solid, which was recrystallized twice from H₂O to give 1 g (33%) of Ia. The product was found to be identical with that prepared by method A.

***p*-{[(2,6-Diamino-8-puriny)methyl]-*N*-methylamino}benzoic acid (Ib).**—A solution of 34 g (0.1 mole) of diethyl *p*-methylaminobenzoyl-L-glutamate,¹⁶ 17 g (0.075 mole) of IIb, and a few crystals of KI in 500 ml of abs EtOH was refluxed for 48 hr. The reaction mixture was evaporated under reduced pressure and the diester intermediate was saponified by stirring the residue with 200 ml of 1 *N* NaOH at room temperature for 2 hr. The solution was then acidified to pH 4 with 6 *N* HCl and a gummy substance was formed. After decantation of the supernatant liquid, the residual gum was triturated with absolute EtOH. The resulting yellow solid was collected by filtration to give 10 g of crude product. Recrystallization from H₂O gave, after being dried at 135° *in vacuo*, 4.5 g (12%) of analytically pure Ib: mp 216–218°; $\lambda_{\text{max}}^{\text{NH}}$ 292 m μ (ϵ 29,200); $\lambda_{\text{NH}}^{\text{NH}}$ 249 m μ (ϵ 13,200); $\lambda_{\text{max}}^{\text{NH}}$ 295 m μ (ϵ 32,800). *Anal.* (C₁₉H₂₂N₈O₅) C, H, N.

Acknowledgment.—The authors wish to thank Mrs. Margaret L. Rounds and Mr. John R. Gravatt for the analytical and instrumental measurements.

(15) R. Koehler, L. Goodman, J. DeGraw, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5779 (1958).

(16) S.-C. J. Fu and M. Reiner, *J. Org. Chem.*, **30**, 1277 (1965).

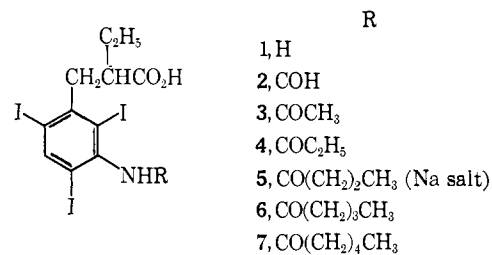
Sodium Tyropanoate,¹ a New Oral Cholecystographic Agent

J. O. HOPPE,^{2a} J. H. ACKERMAN,^{2b} A. A. LARSEN, and J. MOSS
Sterling-Winthrop Research Institute, Rensselaer, New York 12144

Received May 11, 1970

Cholecystography is the roentgenographic visualization of the gallbladder after an administered radioactive substance or its metabolite has been secreted in

the bile and collected in the gallbladder. We wish to report that sodium 3-butyramido- α -ethyl-2,4,6-triiodohydrocinnamate, sodium tyropanoate¹ (5), showed favorable characteristics in laboratory studies as an oral cholecystographic agent.



Sodium tyropanoate (5) is a derivative of iopanoic acid (1) and was found to excel iopanoic acid and other oral agents^{3–10} in one or more laboratory studies. Table I compares the acute toxicities in mice and the average cholecystographic indexes¹¹ (ACI) in cats of Na tyropanoate and other agents. Both iv and oral toxicities are given in Table I although there are shortcomings in the comparison of compounds by each method. Since only oral administration is used in the clinic for these agents, there is not necessarily a direct relationship between the acute iv toxicity and the adverse effects observed in the clinic. The acute oral toxicities may be ineffective for comparison purposes because of the difficulty of giving a massive dose which is required to produce mortality in animals in a manner which corresponds to the clinical administration. The method of Hoppe and Archer¹¹ was used for determining the acute oral toxicities reported in Table I. This consisted of administering the materials as a powder suspended in H₂O with gum tragacanth in a volume of 0.5 ± 0.35 ml by stomach tube. In the clinic iopanoic acid is administered in tablets and Na tyropanoate in capsules. Large variations in the acute oral toxicity can exist from sample to sample for some agents. For iopanoic acid the toxicities varied from 6.6 to 15.8 g/kg (24 hr) and 5.9 to 13.9 g/kg (7 days) for a series of more than 10 samples. Most 7-day values were between 6 and 10 g. The reason for this broad range was not readily determined. It is speculated that the cause is a combination of differences in particle size and crystalline habit. Other workers reported acute oral LD₅₀ values of 5.12¹² and 3.87¹³ g/kg in mice for iopanoic acid but did not describe their methods.

With samples of Na tyropanoate (5) values in the acute oral LD₅₀ toxicities ranged from 4.8 to 16.3 g/kg. This variation is believed to be due to different methods of crystallization which produced crystals with different

(3) E. A. Graham and W. H. Cole, *J. Amer. Med. Ass.*, **82**, 613 (1924).

(4) M. Dolirn and P. Diedrick, *Deut. Med. Wochenschr.*, **66**, 1133 (1940); N. Kleiber, *ibid.*, **66**, 1134 (1940); K. Junkmann, *Klin. Wochenschr.*, **20**, 125 (1941).

(5) T. R. Lewis and S. Archer, *J. Amer. Chem. Soc.*, **71**, 3753 (1949).

(6) D. Papa, H. F. Ginsberg, I. Lederman, and V. DeCamp, *ibid.*, **75**, 1107 (1953).

(7) M. Chao and P.-C. Hu, *Hua Hsueh Hsueh Pao*, **23**, 361 (1957); *Chem. Abstr.*, **52**, 15467g (1958).

(8) H. Prieue and A. Poljak, *Chem. Ber.*, **93**, 2347 (1960).

(9) British Patent 870,321; *Chem. Abstr.*, **55**, 24683f (1961).

(10) J. A. Korver, *Recl. Trav. Chim. Pays-Bas*, **87**, 308 (1968).

(11) J. O. Hoppe and S. Archer, *Amer. J. Roentgenol. Radium Ther. Nucl. Med.*, **69**, 630 (1953).

(12) R. Shapiro, *Radiology*, **60**, 687 (1953).

(13) K. Winzer, H. Langecker, and K. Junkmann, *Aertzt. Wochenschr.*, **9**, 950 (1954).

(1) Bilopaque.

(2) (a) Deceased; (b) author to whom inquiries should be addressed.