perature of the reaction mixture increased from 24 to 29°. After standing at room temperature for 2 hr, the mixture was heated to reflux for 1 hr, then cooled and filtered. The filtrate was distilled *in vacuo* over a 15-cm glass-bead-packed column to provide 49 g (60% yield) of pure hexamethylene 1,6-bis(isocyanidedichloride).

X-Ray Media. II. Synthesis of Alkanoylbis(isophthalamic Acids) as X-Ray Contrast Agents[1]

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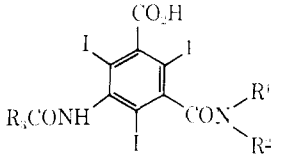
Received March 17, 1966

We recently reported[1] that certain triiodoisophthalamic acids (**1**) had been found potentially useful as X-ray diagnostic agents by virtue of the low toxicity and high water solubility of their sodium and N-methylglucamine salts. Subsequent, extensive clinical experience has shown **1** (R_1 = H; R_2 = R_3 = CH_3; iothalamic acid) to be a safe and effective diagnostic agent in the visualization of the kidney, heart, and cerebrovascular system.[2]



1

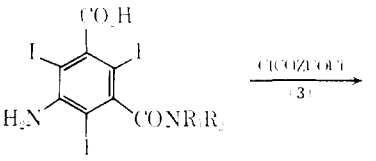
We now wish to describe the synthesis of further compounds of this type wherein our efforts have been directed toward the development of useful intravenous cholangiographic agents for visualization of the gall bladder. 5-Amino-2,4,6-triiodo-N-alkylisophthalamic acids (**2**) have been condensed with acid chlorides (**3**) to give alkanoylbis(isophthalamic acids) (**4**) (Scheme I). Salts of **4** have been found to possess generally low toxicity and high water solubility.

The compounds and their properties are summarized in Table I. The toxicities and solubilities of the lower members of the series compare favorably with those reported earlier for the 5-acylamino analogs.[1]

A toxicologic study[3] of the sebacoyl analog **4a** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_8$) as the N-methylglucamine salt (75% solution) gave the results shown in Table II.

When tested in the cat,[4] several of these compounds showed promise as cholangiographic agents. Subsequent clinical investigations on the sebacoyl analog **4a** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_8$) showed it to be substantially free of side effects and to opacify the gall bladder and biliary ducts in a high percentage of cases.[5,6] Unexpectedly, this compound also showed a high degree of kidney excretion.[5] The adipoyl analog **4b** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_4$) has also been found to be nontoxic and excreted *via* the kidneys.[7] The synthesis and biological testing of additional compounds of this general type will be reported at a later date.

SCHEME I



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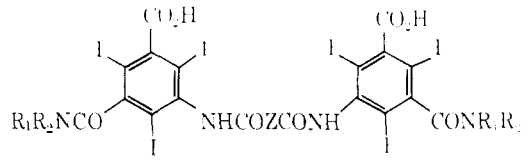


4a, R_1 = H; R_2 = CH_3; Z = $(CH_2)_8$
b, R_1 = H; R_2 = CH_3; Z = $(CH_2)_4$

Experimental Section[8]

The following procedure illustrates the general method of synthesis employed. Analyses and yields are given in Table I.

5,5′-Adipoyldiiminobis(2,4,6-triiodo-N-methylisophthalamic acid) (**4**, R_1 = H; R_2 = CH_3; Z = $(CH_2)_4$).—5-Amino-2,4,6-triiodo-N-methylisophthalamic acid (228 g, 0.4 mole) was heated and stirred in dimethylacetamide (400 ml). When the temperature reached 95°, adipoyl chloride (55.0 g, 0.30 mole) was added, half at once, followed by the remainder over a period of 15 min. When addition was complete, the solution was stirred at about 95° for another 15 min, then poured into 2 l. of hot water. As the mixture cooled to room temperature, a gum separated. The mother liquor was discarded and the gum was dissolved in 2 l. of water with sufficient solid NaOH added to complete solution. This solution was acidified with HCl and acetic acid to *ca.* pH 5, treated with decolorizing charcoal, and filtered. The filtrate was then strongly acidified with HCl, and the resulting amorphous granular solid was filtered, digested 0.5 hr with 0.5 l. of hot ethanol, filtered, washed with ethanol, and dried at 110°. The yield of crude 5,5′-adipoyldiiminobis(2,4,6-triiodo-N-methylisophthalmic acid) (**5**) was 183 g.

The acid obtained was reprecipitated twice again from its sodium salt solution. This solid was dissolved in hot dimethylformamide (400 ml), and 1.5 l. of water was added slowly. After digestion, filtration, and cooling, a crystalline product was obtained which, after drying at 110°, weighed 126 g. This solid was dissolved in 1 l. of 10% aqueous NaOH solution, acidified (pH 5), and filtered into a hot stirred solution of 1:3 concentrated HCl–water (100 ml). The mixture was chilled and the solid was

(1) (a) Paper I in this series: G. B. Hoey, R. D. Rands, G. DeLaMater, D. W. Chapman, and P. E. Wiegert, *J. Med. Chem.*, **6**, 24 (1963). (b) See G. B. Hoey, Canadian Patent 720,826 (1965), for a portion of the work described herein.

(2) (a) T. R. Marshall and J. T. Ling, *Southern Med. J.*, **56**, 1424 (1963); (b) J. W. Linhart, R. E. Whalen, and H. D. McIntosh, *ibid.*, **58**, 793 (1965); (c) A. C. Beall, Jr., G. C. Morris, Jr., H. E. Garrett, W. S. Henly, G. L. Hallman, E. S. Crawford, D. A. Cooley, and M. E. DeBakey, *Arch. Internal Med.*, **60**, 843 (1964), and references therein.

(3) D. H. Baeder, T. W. Tusing, M. Beu, and W. Reiter, *Federation Proc.*, **32**, 182 (1963).

(4) J. O. Hoppe and S. Archer, *Am. J. Roentgenol. Radium Therapy Nucl. Med.*, **69**, 630 (1953).

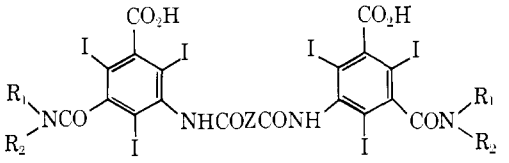
(5) T. R. Marshall and J. T. Ling, *ibid.*, **90**, 854 (1963).

(6) Private communications from E. R. Jolly and F. P. Hallett, Research and Development Department, Medicinal Division, Mallinckrodt Chemical Works.

(7) S. Hilal, VIIth Symposium Neuroradiologicum, New York, N. Y., Sept 1964.

(8) All melting points are corrected and were determined in a capillary tube in a Thomas–Hoover or similar melting point apparatus. Neutral equivalents were determined by potentiometric titration; iodine analyses and spectral determinations were carried out by Dr. Perry King and staff of the Analytical Development Group. Solubility measurements were done as described previously.[1] The acute toxicity studies were carried out either in our own laboratories or at Hazleton Laboratories, Falls Church, Va. We thank Dr. David H. Baeder for making biological data available to us. The infrared spectra of all compounds prepared were compatible with postulated structures.

TABLE I
BIS(ISOPHTHALAMIC ACIDS)



R_1	R_2	Z	Time, hr	Temp, °C	Yield, %	Mp,[a] °C	Neut equiv Calcd	Neut equiv Found	Iodine, % Calcd	Iodine, % Found	LD_{50},[b] g/kg iv	Solubility[c]
H	H	$(CH_2)_4$	1.75	95	28[d]	290–291	613	606	62.1	60.3	12.2	53
H	H	$(CH_2)_8$	0.75	120	36[e]	268	641	635	59.4	58.1	...	>68[h]
H	CH_3	$(CH_2)_4$	0.5	95	45[d]	302	627	619[f]	60.7	60.2[f]	14–17.5	51, 65[h]
H	CH_3	$(CH_2)_6$	0.5	90–105	34[d]	278–280	641	631	59.4	57.9	19.5	...
H	CH_3	$(CH_2)_8$	0.5	120	54[e]	279–279.5	655	652	58.2	59.7	13.1	47
H	CH_3	$(CH_2)_{10}$	0.5	120	33[e]	288	669	666	56.9	55.8	4.8	50
H	CH_3	p-C_6H_4	2.0	118	17[d]	316–320	637	649[g]	59.8	58.6[g]	10.3	...
H	n-C_3H_7	$(CH_2)_6$	2.0	128	60[e]	286.5	669	671	56.9	55.7	8.4	>93
H	n-C_3H_7	$(CH_2)_8$	0.5	90–105	35[d]	286–286.5	683	682	55.7	54.6	3.5	...
H	n-C_4H_9	$(CH_2)_8$	...	100	26[e]	269.5–271	697	708	54.7	53.7	2.3	...
H	CH_3	$(CH_2)_8$[i]	7	85	16	278.5–279.5	...	...	54.6	54.3	...	...
H	CH_3	$(CH_2)_{10}$[i]	7.5	85	23	255.5–257	...	...	53.6	53.5	...	...

[a] All compounds melted with decomposition. [b] In mice. [c] As the disodium salt in water, g/100 ml of solution at 25°. [d] Dimethylacetamide as solvent. [e] Dimethylformamide as solvent. [f] After correction for 1.2% water. [g] After correction for 3.5% water. [h] Di-N-methylglucamine salt. [i] Dipropyl ester, see Experimental Section.

TABLE II
TOXICOLOGIC STUDY OF **4a**

Animal	LD_{50}, g/kg iv
Mice	13.1
Rat	6.6
Dog	10.0
	Intracerebral LD_{50}, mg/kg
Mice	1120

collected, washed with water, and dried at 110°, yield 114 g, mp 302° dec.

5-Nitro-N-propylisophthalamic Acid.—*n*-Propylamine (100 g, 1.70 moles) was added to a solution of methyl hydrogen 5-nitroisophthalate (153 g, 0.68 mole) in 0.7 l. of methanol. The container was tightly closed and the reaction mixture was put aside for 4 days. At the end of this time the solvent was evaporated and the remaining oil was dissolved in 1.5 l. of dilute NaOH solution. The solution was adjusted to pH 5–6 and slowly added to 80 ml of concentrated HCl in 400 ml of water. The solid was collected and twice reprecipitated by acidifying a solution of the sodium salt. This solid was recrystallized from 0.5 l. of 50% ethanol, washed with water, and dried at 110°; the yield was 98 g (57.5%), mp 181.1–184.1°.

Anal. Calcd for $C_{11}H_{12}N_2O_5$: neut equiv, 252. Found: neut equiv, 247.

5-Amino-N-propylisophthalamic Acid.—An alcoholic solution of 5-nitro-N-propylisophthalamic acid (80 g, 0.32 mole) was hydrogenated at 2.8 kg/cm² in the presence of 5% Pd–C catalyst. After removal of the catalyst and evaporation of the solvent, the residue was dissolved in dilute NaOH solution and reprecipitated by addition of dilute HCl. This solid was collected, washed with water, and dried at 70°; the yield was 42 g (59%), mp 194.7–195.7°.

5-Amino-2,4,6-triiodo-N-propylisophthalamic Acid (2, R_1 = C_3H_7; R_2 = H).—Iodine monochloride (160.5 g of 95% ICl in 160 ml of concentrated HCl) was slowly added to a stirred mixture of 5-amino-N-propylisophthalamic acid (42 g, 0.19 mole) and 45 ml of concentrated HCl in 400 ml of water. Sufficient water was added to bring the volume to 1.3 l., and the mixture was stirred and heated on a steam bath for 20 hr. The reaction mixture was cooled and the solid was collected and dissolved in 0.5 l. of 4% NaOH solution. The pH was adjusted to 5 with acetic acid and the solution was treated with decolorizing charcoal and filtered into hot stirred dilute HCl. Upon cooling, the resulting crystals were collected, washed with water, and dried at 70°. The yield was 109 g (95%), mp 242–243° dec.

Anal. Calcd for $C_{11}H_{11}I_3N_2O_3$: neut equiv, 600. Found: neut equiv, 594.

N-*n*-Butyl-5-nitroisophthalamic Acid.—A solution of methyl hydrogen 5-nitroisophthalate (225 g, 1 mole) and *n*-butylamine (250 ml) in 1 l. of absolute methanol was heated under reflux for 16 hr. The solvent was evaporated, leaving an oil, which was dissolved in dilute aqueous NaOH. The product was precipitated by the addition of excess HCl and this treatment was repeated twice more with little improvement in quality. Finally, the product was dissolved in 1 l. of hot acetone and filtered, and an equal volume of water was added. The solvents were slowly evaporated and, when the concentrated solution was cooled, a solid separated. The crystals were collected, washed with water, and dried at 110°. The yield was 103 g (39%).

Anal. Calcd for $C_{12}H_{14}N_2O_5$: neut equiv, 266. Found: neut equiv, 268.

A second preparation yielded a product of neut equiv 263, mp 174.2–175.2°.

5-Amino-N-*n*-butylisophthalamic Acid.—A solution of N-*n*-butyl-5-nitroisophthalamic acid (103 g, 0.39 mole) in ethanol (400 ml) was hydrogenated at 2.8 kg/cm² in the presence of 5% Pd–C catalyst. The catalyst was removed by filtration and the solvent by evaporation to yield 86 g (94%) of product, mp 199.2–199.7°.

5-Amino-N-*n*-butyl-2,4,6-triiodoisophthalamic Acid (2, R_1 = n-C_4H_9; R_2 = H).—A solution of iodine monochloride (205 g of 95% ICl in 205 ml of concentrated HCl) was added slowly to a stirred slurry of 5-amino-N-butylisophthalamic acid (86 g, 0.36 mole), water (800 ml), and concentrated HCl (89 ml). The mixture was diluted to 27 l. and stirred and heated on a steam bath for 20 hr. The reaction mixture was chilled and the separated solid was collected and washed with water. It was then dissolved in 1.3 l. of dilute NaOH solution and the pH was adjusted to 5 with acetic acid. This solution was treated with $NaHSO_3$, then decolorizing charcoal, and filtered into a hot, stirred 1:5 HCl solution (240 ml). After cooling, the separated solid was collected. This treatment was repeated, yielding 192 g (86%) of material, mp 247–249° dec.

Anal. Calcd for $C_{12}H_{13}I_3N_2O_3$: neut equiv, 614. Found: neut equiv, 606.

Dipropyl 5,5′-Sebacoyldiiminobis(2,4,6-triiodo-N-methylisophthalamate).—A solution of 328 g (0.25 mole) of **4a** in 20 g of NaOH in H_2O–ethanol (0.6:1.2 l.) and 105 ml of *n*-propyl iodide was heated at reflux with stirring for 7 hr. The precipitated NaI was removed by filtration and washed with ethanol. The filtrate and washings were diluted with 3 l. of H_2O, and the resulting slurry was stirred for 1 hr with sufficient NaOH added to maintain alkalinity. After filtration the solid was dissolved in 2.5 l. of hot dimethylformamide (DMF), filtered, diluted with 5 l. of H_2O, and cooled. This solid, after filtration, was dissolved in 2 l. of DMF and diluted with 7 l. of H_2O at 50°. This solid after filtration was digested with 3 l. of anhydrous ethanol for 2

hr. After filtration, this solid was dissolved in 1.5 l. of DMF and diluted with 7 l. of 1:6 AcOH–H_2O. After filtration, digestion with 2 l. of ethanol, and filtration, the solid was dried at 110°, yield 111 g (16%) of the ester.

Dipropyl 5,5'-Dodecanedioyldiiminobis(2,4,6-triiodo-N-methylisophthalamate).—A solution of 208.5 g (0.223 mole) of **4** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_{10}$) and 17.9 g of NaOH in EtOH–H_2O (1.2:0.6 l.) containing 100 ml of *n*-propyl bromide and 25 g of NaI was refluxed with stirring for 7.5 hr. The ester was isolated as described in the preceding experiment; yield 74 g (23%).

Acknowledgment.—The authors wish to thank Messrs. Elmer Eberhardt, William Blade, Miss Evelyn Lare, and Mrs. Julie Macksey for their technical assistance.

L-, D-, and DL-Ephedrine Phosphates

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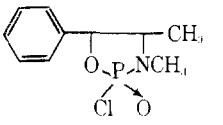
Received June 11, 1966

As a part of our program of synthesis of therapeutically or physiologically active compounds,[1,2] we have prepared L- (IVa), D- (IVb), and DL-ephedrine phosphates (IVc) starting from L- (Ia), D- (Ib), and DL-ephedrines (Ic).

The reaction of L-ephedrine (Ia) with phosphorus oxychloride gave L-2-chloro-3,4-dimethyl-5-phenyl-1,3,-2-oxazophospholidine 2-oxide[3] (IIa). Hydrolysis of



IIa

IIa yielded L-ephedrine phosphate (IVa) hydrochloride (IIIa) the structure of which was confirmed by catalytic hydrogenation[4] to D-*N*,α-dimethylphenethylamine. L-Ephedrine was obtained from the corresponding phosphate by hydrolysis; this indicates that in the course of the reactions Ia → IVa the original configuration was retained. Physical and chemical data of the compounds synthesized are reported in Table I.

Experimental Section[5]

L-2-Chloro-3,4-dimethyl-1,3,2-oxazaphospholidine 2-Oxide (IIa).—Under protection from moisture, freshly distilled L-ephedrine (16.5 g, 0.1 mole) was dissolved in triethylamine (30 ml, 0.21 mole) and in 500 ml of anhydrous benzene. With vigorous stirring, $POCl_3$ (10 ml) previously dissolved in 50 ml of anhydrous benzene was added dropwise at such a speed that the temperature of the reaction mixture remained below 50°. After stirring for 4–5 hr, the reaction mixture was filtered and the solvent was removed under reduced pressure. The dry residue was repeatedly extracted with boiling petroleum ether (bp 60–80°) and the combined extracts (about 600 ml) were cooled in the freezer for 24 hr. The precipitated white crystalline product (16.5 g) melted at 99–91° and was stable only in a dry, inert atmosphere.

L-α-[1-(Methylamino)ethyl]benzyl Phosphate Hydrochloride (L-Ephedrine Phosphate Hydrochloride, IIIa).—IIa (20 g) was suspended in 100 ml of 1 *N* HCl and heated on a water bath for 1 hr. The reaction mixture became clear after this time and was decolorized with 1 g of charcoal. The solution was evaporated under reduced pressure at 40–45° (bath temperature). The residue was suspended in acetone, filtered, and recrystallized from ethanol–ether. The white crystals (17.3 g) melted at 178–179°.

L-α-[1-(Methylamino)ethyl]benzyl Phosphate (L-Ephedrine Phosphate, IVa). A.—To a solution of IIIa (56 g) in 200 ml of distilled water, Amberlite IRA-410 (OH⁻ form) was added until the supernatant was pH 4. The suspension was decanted and the resin was repeatedly washed with distilled water. The supernatant and the washings were evaporated under reduced pressure to dryness and from the residue, after washing with absolute ethanol and ether, 41.2 g of white crystals were obtained, mp 242–243°.

B.—Diethylamine (1.5 g) dissolved in 10 ml of ethanol was added to a solution of IIIa (5.5 g) in 30 ml of ethanol. After 12 hr at room temperature the precipitated crystals were filtered, washed with ethanol and ether, and dried; yield 4.2 g, mp 242–243°.

D-*N*,α-Dimethylphenethylamine by Catalytic Hydrogenation of IIIa.—IIIa (2.8 g) in 40 ml of ethanol was hydrogenated at atmospheric pressure and room temperature (22°) in the presence of 0.28 g of 5% Pd–C. After the uptake of the theoretical amount of hydrogen (*ca.* 2 hr), the hydrogenation was interrupted and the mixture was filtered. The solution was evaporated under reduced pressure and the residue was dissolved in 30 ml of water. The cold aqueous solution made alkaline with 30% NaOH solution was extracted with three 50-ml portions of ether. The residue, after evaporation of the solvent, distilled at 91–93° (15 mm), yield 1.2 g (84%).

The hydrochloride had mp 168–170° (lit.[6] 172°) and $[\alpha]^{20}D$ +17.2° (*c* 3.3, H_2O) [lit.[6] +17.2° (*c* 2.3, H_2O)].

The picrate had mp 142–144° (lit.[7] 145°).

Stability of L-Ephedrine Phosphate (IVa) in Aqueous Solution.—IVa was dissolved in water, and the pH was adjusted in four different solutions to 2, 4, 5, and 6.5, respectively, the final concentration of IVa being always 2% w/v. The four solutions thus obtained, either by addition of NaOH or HCl, were heated separately at 100° for 10 hr. Controls by paper electrophoresis every hour showed that L-ephedrine appeared only in traces after 4 hr.

Hydrolysis of L-Ephedrine Phosphate Hydrochloride (IIIa).—A solution of IIIa (5 g) in water (50 ml) was heated in a sealed tube at 120° for 3 hr. After cooling and neutralization, the water was evaporated at reduced pressure and the residue repeatedly was extracted with ether. The solvent was evaporated from the organic extracts and the residue was distilled. The fraction boiling at 132° (12 mm) was L-ephedrine (2.3 g), which was dissolved in absolute ethanol (30 ml) and mixed with normal ethanolic HCl (15 ml). The solution gave a precipitate (2.5 g) of L-ephedrine hydrochloride upon addition of 45 ml of ether; mp 215–216°; $[\alpha]D$ −36.1° (*c* 2, water).

Enzymatic Hydrolysis of L-Ephedrine Phosphate (IVa).—IVa (133 mg) was dissolved in water (5 ml) and acetate buffer pH 4.5 (2 ml) containing in suspension five powdered Taka-Diastase® (Parke-Davis) tablets. After 15 hr at 40° the suspension was centrifuged, and the supernatant was analyzed by thin layer chromatography. An identical treatment was carried out on a similar reaction mixture, but without IVa. The only different spot in the first reaction mixture was L-ephedrine.

Paper Electrophoresis.—The paper used was Munktell 20 (Paperworks, Gryksbo, Sweden), the buffer employed was acetate pH 5.1, the ionic strength was 0.007, and the time was 2 hr at 200 mv. L-Ephedrine phosphate migrated slowly toward the anode; L-ephedrine migrates faster toward the cathode.

Thin Layer Chromatography.—The adsorbent used was silica gel (Merck, Darmstadt), 250 μ; the solvents were A,

(1) A. Segre and A. Larizza, *Gazz. Chim. Ital.*, **87**, 519 (1957).

(2) E. Cutolo and A. Larizza, *ibid.*, **91**, 964 (1961).

(3) For a similar reaction see: T. Bersin, H. G. Moldtmann, H. Nafiger, B. Marchand, and W. Leopold, *Z. Physiol. Chem.*, **269**, 241 (1941); Kh. Fel'dmen and A. I. Berlin, *Zh. Obshch. Khim.*, **32**, 3379 (1962); *Chem. Abstr.*, **58**, 12563*g* (1963).

(4) Ia hydrochloride was unaffected under the same reaction conditions.

(5) Infrared absorption spectra were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer and ultraviolet absorption spectra on a Beckman DK-2 spectrophotometer. Melting points were determined on a Kofler block. Optical rotations were measured on a Zeiss 0.01° Kreispolarimeter. We are indebted to Miss A. De Leonibus, for microanalysis, and to Miss M. L. Reviglio for absorption spectra, chromatograms, and enzymatic hydrolysis.

(6) H. Emde, *Helv. Chim. Acta*, **12**, 373 (1929).

(7) H. Ogata, *J. Pharm. Soc. Japan*, 151 (1919); *Chem. Abstr.*, **14**, 745 (1920).