Tetraiodophthaloyl Amino Acids

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Aromatic iodo compounds are useful diagnostic agents since iodine is opaque to X-rays and because the particular type of carbon–iodine bonding minimizes generation of iodide ion.[1] Our interest in compounds with maximal content of iodine has prompted preparation of some tetraiodophthaloyl amino acids (Table I) that are

TABLE I

N,N-TETRAIODOPHTHALOYL AMINO ACIDS

Amino acid	Yield, %	Mp, °C	Formula[a]
DL-Alanine	49[b]	320–321	$C_{11}H_5I_4NO_4$
DL-Leucine	3[c]	275–278	$C_{14}H_{10}I_4NO_4$
p-Aminophenyl acetic acid	50[b]	321–322	$C_{16}H_7I_4NO_4$[d]
DL-Phenylalanine	62[b]	301–303	$C_{17}H_9I_4NO_4$

[a] Of N,N-tetraiodophthaloyl derivative. Analyses for iodine were within ±0.4% except where indicated. [b] Crude. [c] Purified. [d] I: calcd, 64.69; found, 64.42.

60–70% in iodine, a level comparable to that found in radiodiagnostic agents.[2] The syntheses involved treating tetraiodophthalic anhydride with appropriate amino acids at elevated temperature. This procedure is comparable to that used for condensing phthalic anhydride with amino acids.[3]

Experimental Section[4]

N,N-Tetraiodophthaloyl-DL-alanine.—A warm solution of 1.7 g (0.019 mole) of DL-alanine in 50 ml of HOAc was mixed with a solution of 6.3 g (0.0097 mole) of tetraiodophthalic anhydride in 35 ml of $PhNO_2$ at 180°. The solution was refluxed for 5 min at 117° and cooled to room temperature where yellow crystals formed. These were filtered and washed (Et_2O, H_2O) to yield 3.52 g (49%) of product, mp 320–321° (from dioxane–H_2O three times). *Anal.* ($C_{11}H_5I_4NO_4$) I.

N,N-Tetraiodophthaloyl-DL-leucine and N,N-tetraiodophthaloyl-DL-phenylalanine.—A solution of 2.8 g (0.02 mole) of DL-leucine in 100 ml of HOAc was added to a solution of 6.3 g (0.0097 mole) of tetraiodophthalic anhydride in dioxane. The solution was refluxed for 30 min and cooled to yield yellow crystals which were recrystallized twice from dioxane–H_2O to give 0.23 g (3.0%) of N,N-tetraiodophthaloyl-DL-leucine, mp 275–278°. *Anal.* ($C_{14}H_{10}I_4NO_4$) I. N,N-Tetraiodophthaloyl-DL-phenylalanine was prepared in a similar manner to give a 62% yield of white crystals, mp 301–303° (dioxane–H_2O). *Anal.* ($C_{17}H_9I_4NO_4$) I.

N,N-Tetraiodophthaloyl-*p*-aminophenylacetic Acid.—A solution of 1.7 g (0.011 mole) of *p*-aminophenylacetic acid and 6.3 g (0.0097 mole) of tetraiodophthalic anhydride in 100 ml of $PhNO_2$ was refluxed for 30 min. After 2 days at room temperature, a dark precipitate formed which was filtered and washed with Et_2O and H_2O to yield 3.9 g (50%) of yellow crystals, mp 321–322° (from dioxane–H_2O, four times). *Anal.* ($C_{16}H_7I_4NO_4$) I.

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(2) P. K. Knoefel in "Drill's Pharmacology in Medicine," J. R. DiPalma, Ed., 3rd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 1429.

(3) P. S. Tipson, *J. Org. Chem.*, **21**, 1353 (1956).

(4) Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of theoretical values. Analyses were performed by Micro Tech Laboratories, Skokie, Ill. Melting points were taken in capillary tubes and are uncorrected.

1-Substituted 4-Aryl- (or 4-Aralkyl-) phthalazines

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The disclosures of Laborit and coworkers[1] of the varied pharmacological activities of the aminoalkylpyridazones, together with the new class of synthetic analgetics[2] incorporating the quinazoline ring system, prompted us to investigate the potential of 1-substituted 4-aryl- (or 4-aralkyl-) phthalazines. The 1-hydrazino[3] and 1-diethylaminoalkyloxy[4] derivatives of this general structural type have been reported to have hypotensive and antihistaminic activities, respectively.

All the compounds were prepared by the action of the appropriate agent on the particular chlorophthalazine by the method indicated in Table I. Structures **2**, **3**, **8**, **29**, **31**, and **32** showed weak anorexic properties in starved mice. Compound **13** demonstrated antiinflammatory activity and had an MED of 32 mg/kg (30% inhibition of edema) when tested orally in rats using the carrageenin-induced edema technique.[5] All the other compounds were found to be devoid of significant pharmacological activity.

Experimental Section[6]

General Preparation of 1-Substituted 4-Aryl- (or 4-Aralkyl-) phthalazines. Method A.—A mixture of 1-chloro-4-phenylphthalazine,[7] amine, and Na_2CO_3 in molar equivalent amounts was refluxed in MIBK for 18 hr and worked up in the usual manner.

Method B.—A mixture of the appropriate chlorophthalazine,[7] amine, and Na_2CO_3 in molar equivalent amounts was heated in DMSO at 160° (**9** and **14** were heated at 130°) for 2–3 hr and worked up in the usual manner.

Method C.—A mixture of the appropriate chlorophthalazine,[7] amine, and Na_2CO_3 in molar equivalent amounts in DMSO was heated in a sealed pressure bottle for 4 hr (compound **38** was heated for 16 hr) on a steam bath and worked up in the usual manner.

Method D.—A solution of 1-chloro-4-phenylphthalazine[7] in excess amine was heated at 130–160° (**11** and **13** were heated at 200 and 60°, respectively) for 3–4 hr and worked up in the usual manner.

Method E.—A solution of the sodium alkoxide in the alkanol and the appropriate chlorophthalazine[7] was refluxed for 2–3 hr and worked up in the usual manner.

Method F.—The 1-chloro-4-phenylphthalazine[7] was added to a solution of the sodium cycloalkoxide (prepared with NaH) in DMF and heated at 70–80° for 3 hr.

Method G.—A mixture of the 1-chloro-4-phenylphthalazine,[7] amine, and Na_2CO_3 in molar equivalent amounts was refluxed in DMSO for 3 hr and worked up in the usual manner.

(1) (a) H. Laborit, C. G. Wermuth, B. Weber, B. Delbane, C. Chekler, C. Baron, and H. Rosengarten, *Agressologie*, **6**, 415 (1965); (b) H. Laborit, B. Weber, C. Baron, B. Delbane, and H. Pavlovichova, *ibid.*, **6**, 463 (1965); (c) H. Laborit, B. Weber, B. Delbane, and C. Baron, *ibid.*, **6**, 483 (1965); (d) C. G. Wermuth, *Chim. Ther.*, **2**, 130 (1967).

(2) H. M. Blatter and H. Lukaszewski, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 16N.

(3) J. Druey and A. Marxer, *J. Med. Chem.*, **1**, 1 (1959).

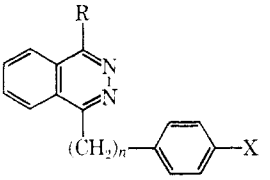
(4) H. J. Engelbrecht, D. Lenke, and H. Müller, German (East) Patent 17,319 (1959); *Chem. Abstr.*, **55**, 590 (1959).

(5) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(6) Melting points were determined in a Mel-Temp apparatus and are uncorrected. Nmr and ir spectra were obtained on all compounds described herein and were found to be consistent with structure.

(7) Prepared according to the procedure of A. Lieck, *Ber.*, **38**, 3918 (1905).

TABLE I: 1-SUBSTITUTED 4-ARYL- (OR 4-ARALKYL-) PHTHALAZINES



No.	R	n	X	Mp, °C	Crystn solvent[a]	Formula	Analyses[b]	Method
1	MeNH	0	H	195–197	A	$C_{15}H_{13}N_3$	C, H, N	C
2	Me_2N	0	H	111–113	B	$C_{16}H_{15}N_3$	C, H, N	C
3	EtNH	0	H	150–151	C–D	$C_{16}H_{15}N_3$	C, H, N	C
4	*n*-PrNH	0	H	103–104	E–D	$C_{17}H_{17}N_3$	C, H, N	C
5	*i*-PrNH	0	H	191–192	A–B	$C_{17}H_{17}N_3$	C, H, N	C
6	$HO(CH_2)_2NH$	0	H	161–163	C	$C_{16}H_{15}N_3O$	C, H, N	D
7	$Me_2N(CH_2)_2NH$	0	H	126–129	A–B	$C_{18}H_{20}N_4$	C, H, N	D
8	$Me_2N(CH_2)_3NH$	0	H	257–259	E	$C_{19}H_{22}N_4 \cdot 2HCl \cdot H_2O$	C, H, Cl, N	B
9	*i*-$PrCH_2NH$	0	H	143–144	C	$C_{18}H_{19}N_3$	C, H, N	B
10	$C_6H_5(CH_2)_2NH$	0	H	147–149	C	$C_{22}H_{19}N_3$	C, H, N	D
11	$C_6H_5CH_2NH$	0	H	219–220	C	$C_{21}H_{17}N_3$	C, H, N	D
12	$[CH_3(CH_2)_3]_2N$	0	H	173–175	A	$C_{22}H_{27}N_3 \cdot HCl$	C, H, Cl, N	D
13	C_3H_5NH[d]	0	H	188–190	C	$C_{17}H_{15}N_3$	C, H, N	D
14	C_5H_9NH[e]	0	H	189–191	E–B	$C_{19}H_{19}N_3$	C, H, N	B
15	$C_6H_{11}NH$[f]	0	H	303–305	F	$C_{20}H_{21}N_3 \cdot HCl$	C, H, N	G
16	C_4H_8N[g]	0	H	106–108	E–D	$C_{18}H_{17}N_3 \cdot 0.25H_2O$[b]	C, H, N	D
17	$C_5H_{10}N$[h]	0	H	152–153	C	$C_{19}H_{19}N_3$	C, H, N	A
18	$C_5H_{10}NO$[i]	0	H	159–160	E–D	$C_{19}H_{19}N_3O$	C, H, N	A
19	C_4H_8NO[j]	0	H	192–194	C	$C_{18}H_{17}N_3O$	C, H, N	D
20	$C_5H_{11}N_2$[k]	0	H	155–158	C	$C_{19}H_{20}N_4$	C, H, N	D
21	$C_{10}H_{13}N_2$[l]	0	H	217–219	F	$C_{24}H_{22}N_4$	C, H, N	D
22	$C_{11}H_{14}NO$[m]	0	H	208–210	C	$C_{25}H_{23}N_3O$	C, H, N	G
23	$C_{11}H_{13}ClNO$[n]	0	H	232–234	F	$C_{25}H_{22}ClN_3O$	C, H, N	G
24	EtO	0	H	91–93	B	$C_{16}H_{11}N_2O$	C, H, N	E
25	*n*-PrO	0	H	71–73	B	$C_{17}H_{16}N_2O$	C, H, N	E
26	*i*-PrO	0	H	102–104	F–D	$C_{17}H_{16}N_2O$	C, H, N	E
27	C_5H_9O[o]	0	H	120–121	B	$C_{19}H_{18}N_2O$	C, H, N	F
28	$C_6H_{11}O$[f]	0	H	111–113	F–D	$C_{20}H_{20}N_2O$	C, H, N	F
29	*i*-PrNH	0	Cl	199–202	F–B	$C_{17}H_{16}ClN_3$	C, H, Cl, N	C
30	$Me_2N(CH_2)_2NH$	0	Cl	265–267	F–G	$C_{18}H_{19}ClN_4 \cdot 2HCl$	C, H, Cl, N	B
31	$Me_2N(CH_2)_3NH$	0	Cl	269–270	F–G	$C_{19}H_{21}ClN_4 \cdot 2HCl$	C, H, Cl, N	B
32	C_3H_5NH[d]	0	Cl	189–191	A	$C_{17}H_{14}ClN_3$	C, H, Cl, N	C
33	EtO	0	Cl	156–157	A–B	$C_{16}H_{12}ClN_2O$	C, H, Cl, N	E
34	*i*-PrO	0	Cl	122–124	B	$C_{17}H_{15}ClN_2O$	C, H, Cl, N	E
35	Cl[p]	0	Cl	190–191	A–B	$C_{14}H_8Cl_2N_2$	C, H, Cl, N	
36	*i*-PrNH	1	H	229–231	F–G	$C_{18}H_{19}N_3 \cdot HCl$	C, H, Cl, N	C
37	$Me_2N(CH_2)_3NH$	1	H	234–236	E–G	$C_{20}H_{24}N_4 \cdot 2HCl$	C, H, Cl, N	B
38	C_3H_5NH[d]	1	H	149–150	A–B	$C_{18}H_{17}N_3$	C, H, N	C
39	*i*-PrO	1	H	91–93	B	$C_{18}H_{18}N_2O$	C, H, N	E

[a] A = EtOAc, B = Skellysolve B (bp 60–80°), C = MeCN, D = H_2O, E = *i*-PrOH, F = EtOH, G = Et_2O. [b] Analytical results obtained for the indicated elements were within ±0.3% of the theoretical values. Anal. (compound **16**) H_2O: calcd, 1.61; found, 1.98 (Karl Fischer). [c] See Experimental Section. [d] C_3H_5 = cyclopropyl. [e] C_5H_9 = cyclopentyl. [f] C_6H_{11} = cyclohexyl. [g] C_4H_8N = pyrrolidino. [h] $C_5H_{10}N$ = piperidino. [i] $C_5H_{10}NO$ = 4-hydroxypiperidino. [j] C_4H_8NO = morpholino. [k] $C_5H_{11}N_2$ = 4-methylpiperazino. [l] $C_{10}H_{13}N_2$ = 4-phenylpiperazino. [m] $C_{11}H_{14}NO$ = 4-hydroxy-4-phenylpiperidino. [n] $C_{11}H_{13}ClNO$ = 4-*p*-chlorophenyl-4-hydroxypiperidino. [o] See ref 7.

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Stereoisomeric 2,2′-Bithiiranes

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In the course of the work on bifunctional alkylating agents the title compounds were prepared by reaction of (2*R*:3*R*)-, (2*S*:3*S*)-, and *meso*-1,2:3,4-diepoxybutane[1] with KSCN, a known method[2] for the transformation of epoxides to episulfides. The mechanism of this conversion implies Walden inversions,[2] which in the present case afforded change in configuration at both of the two asymmetrical carbon atoms. The stereoisomeric 2,2′-bithiiranes polymerized readily. Only fresh sublimated samples were free of polymers. For this reason the biological properties of the compounds are not evaluated.

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(2) For a review see M. Sander, *Chem. Rev.*, **66**, 297 (1966).