The reaction has been carried out in the presence of excess dimethylformamide or ethylene dichloride as solvents. Styrene, *p*-methylstyrene, α-methylstyrene, *p*,α-dimethylstyrene, *p*-isopropyl-α-methylstyrene, anethole and isosafrole have been employed to give cinnamaldehyde, *p*-methylcinnamaldehyde, β-methylcinnamaldehyde, *p*,β-dimethylcinnamaldehyde, *p*-isopropyl-β-methylcinnamaldehyde, *p*-methoxy-α-methylcinnamaldehyde and α-piperonylidenepropionaldehyde, respectively.

Acknowledgment.—To Mr. C. W. Nash for analytical data reported.

Experimental

Method A. Formylation Using Excess Dimethylformamide.—Seventy-seven grams (0.5 mole) of phosphorus oxychloride was added dropwise with stirring and cooling to 146 g. (2 moles) of dimethylformamide while the temperature was kept below 20°. One-half mole of the olefin was then added. The mixture was heated slowly to 55°. An exothermic reaction took place and cooling was necessary to maintain the temperature at 55–60°. After the exotherm had ceased, the mixture was heated and kept at 75–80° for 1 hr. The mixture was cooled in an ice-bath and a solution of 278 g. (2.75 moles) of anhydrous sodium acetate in 700 ml. of water was added to the mixture slowly at first and then rapidly with stirring and cooling. The mixture was heated to 70–75° for 15 minutes and cooled. The aldehyde was extracted with ether, washed with water, dried over anhydrous magnesium sulfate and distilled.

Method B. Formylation Using Ethylene Dichloride as Solvent.—The procedure of Silverstein, Ryskiewicz, *et al.*,[4] for the formylation of pyrrole was utilized for the formylation of olefins. To 40 g. (0.55 mole) of dimethylformamide, cooled to 5°, was added 84.5 g. (0.55 mole) of phosphorus oxychloride; 125 ml. of ethylene dichloride was then added and the mixture was stirred for 15 minutes while it was cooled to 5°. One-half mole of the olefinic compound dissolved in 125 ml. of ethylene dichloride was added dropwise with stirring over the course of 40 minutes. The mixture was then refluxed for 15 minutes and cooled to room temperature. A solution of 278 g. (2.75 moles) of anhydrous sodium acetate in 600 ml. of water was added to the mixture slowly at first and then rapidly with stirring and cooling. The mixture was refluxed for 15 minutes, cooled and extracted with ether. The upper (organic) layer was separated, washed with water, dried over anhydrous magnesium sulfate and distilled.

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Iodinated 3,5-Diaminobenzoic Acid Derivatives[1]

BY A. A. LARSEN, CHARLENE MOORE, J. SPRAGUE, BETTY CLOKE, J. MOSS AND J. O. HOPPE

RECEIVED DECEMBER 30, 1955

Thirty-two di- and triiodo-3,5-diaminobenzoic acid derivatives have been prepared and evaluated for use as urographic contrast media. Among this group of compounds 3,5-diacetamido-2,4,6-triiodobenzoic acid is noteworthy as a urographic agent. Investigations into the structures of the diiodo-3,5-diaminobenzoic acid derivatives are reported. Iodination of 3-acylamino-5-aminobenzoic acids was found to be a two-step process wherein the introduction of the third iodine was found to be dependent on the acidity of the media. Directions are given for the preparation of aqueous solutions of potassium iododichloride and some of the advantages of this reagent over iodine chloride are indicated.

As part of a continuing program related to the development of new and useful radiopaques, we have prepared a number of iodinated 3,5-diaminobenzoic acid derivatives and within this group of compounds several have been found which possess the requisite properties for use in urography.

A number of iodinated benzoic and monoaminobenzoic acid derivatives have been prepared in past and investigated for use as radiopaques. The culmination of these various efforts with regard to urography was achieved by Wallingford[2] who prepared 3-acetamido-2,4,6-triiodobenzoic acid and found that it fulfilled in large measure the requirements for visualizing the kidneys. No results, however, had been published previous to the initiation of this present work on the investigation and use of iodinated 3,5-diaminobenzoic acid derivatives as radiopaque agents. In 1896 Lütgens[3] iodinated 3,5-diaminobenzoic acid, isolating 3,5-diamino-2,4,6-triiodobenzoic acid. This compound is, however, much too unstable to be employed as a radiopaque. Subsequent to the start of our investigation Langecker, Harwart and Junkmann[4] reported on the physical and physiological properties of one of the compounds included in this study, 3,5-diacetamido-2,4,6-triiodobenzoic acid.

Two different approaches were employed for the preparation of the iodinated compounds. One of these, used for the preparation of the diiodo and triiodo unsymmetrical diamides (III and V), involved introduction of one of the N-acyl variants prior to iodination. The second procedure was for the preparation of the triiodo symmetrical diamides (VIII), and here the N-acyl groups were introduced following iodination. In connection with the first method, initial attempts to iodinate 3-acylamino-5-aminobenzoic acid (I) in dilute hydrochloric acid media with iodine chloride gave only the diiodo derivative II. Extending the time of reaction and the increasing of the amount of iodine chloride or substitution of acetic acid for the hydrochloric acid were to no avail in isolating the 3-acylamino-5-amino-2,4,6-triiodobenzoic acids (IV). Heating the reaction mixture for any length of time resulted in amide hydrolysis and isolation of 3,5-diamino-2,4,6-triiodobenzoic acid.[5] Successful introduction of the third iodine atom was found to be dependent on reducing the acidity of the reaction media. When an aqueous solution of an alkali or amine salt of 3-

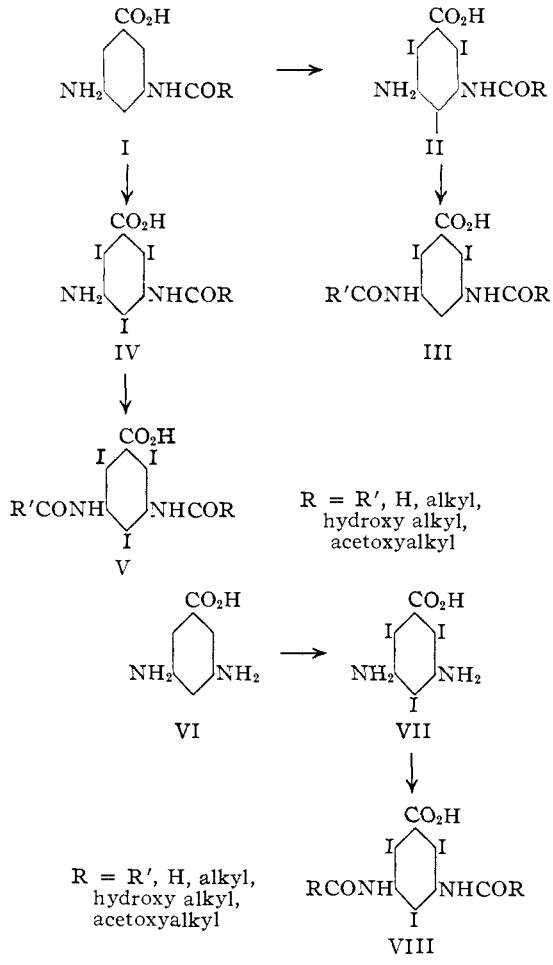
(1) Presented in part at the 126th meeting of the American Chemical Society, New York, September, 1954, Abstracts, p. 11-N.

(2) V. H. Wallingford, Harriet Decker and Margaret Kruty, THIS JOURNAL, **74**, 4365 (1952).

(3) J. Lütgens, *Ber.*, **29**, 2836 (1896).

(4) H. Langecker, A. Harwart and K. Junkmann, *Arch. Exper. Path. Pharmakol.*, **222**, 584 (1954).

(5) Iodination of 3-amino-5-formamidobenzoic acid, even under the most gentle conditions, gave only the hydrolysis product, 3,5-diamino-2,4,6-triiodobenzoic acid.



acetamido-5-amino-2,6-triiodobenzoic acid (II, R = CH_3) was treated with a solution of potassium iododichloride, there was obtained in good yield, 3-acetamido-5-amino-2,4,6-triiodobenzoic acid (IV, R = CH_3). The success of this procedure may be due in part to the enhanced reactivity of the aromatic system toward electrophilic substitution when the amino group is present as the base and the carboxyl group is present as the anion. In addition, the possibility of complex formation between the iodine chloride and the aminoamide is diminished in the less acidic media.[6] With the introduction of the third iodine atom dependent upon a neutral reaction medium, it was found more convenient to employ potassium iododichloride as an iodinating agent rather than the more commonly used iodine chloride, which is rapidly decomposed in water unless excess acid is present. Compounds of the second type, 3,5-diacylamino-2,4,6-triiodobenzoic acid (VIII) were prepared by catalytic reduction of 3,5-dinitrobenzoic acid, iodination of a dilute hydrochloric acid solution of the 3,5-diaminobenzoic acid with potassium iododichloride or iodine chloride in dilute hydrochloric acid and then acylation of the triiodo derivative.

The acylation of the weakly basic, hindered amines in the iodobenzoic acids was generally effected by a brief heating with the appropriate acid anhydride in the presence of a catalytic amount of a strong mineral acid, usually concd. sulfuric acid. In some instances, with the larger acyl derivatives, the corresponding acid chloride was employed for the acylation.

Intermediates for the iodinated unsymmetrical diamides (III and V) were obtained from 3-amino-5-nitrobenzoic acid.[7] The amino group was acylated to give the 3-acylamino-5-nitrobenzoic acids listed in Table I. Reduction of these nitroamides to the corresponding aminoamides was accomplished by either catalytic hydrogenations with Raney nickel or by reduction with hydrazine and Raney nickel.[8] This latter method was quite convenient for laboratory sized preparations, since the reduction can be run in an open vessel and requires little care or attention. With either method of reduction, the yields of 3-acylamino-5-aminobenzoic acids, listed in Table II, were comparable.

Although the structure of the diiodo acid (II) is not known with absolute certainty, it would appear that the two iodine atoms are substituted mainly *ortho* to the carboxyl group. Deamination of 3-acetamido-5-amino-2,6-diiodobenzoic acid (IX)[9] gave a 3-acetamido-diiodobenzoic acid which was not identical with an authentic sample of 3-acetamido-2,4-diiodobenzoic acid. This non-identity was established on the basis of infrared spectral data and mixed melting points. The sequence of reactions used for the preparation of 3-acetamido-2,4-diiodobenzoic acid from 3-amino-6-nitrobenzoic acid, diiodination, acetylation, reduction and deamination, was not applicable to the preparation of 3-acetamido-4,6-diiodo- or 2,6-diiodo-benzoic acids from 2- or 4-nitro-3-aminobenzoic acids, respectively. Additional insight into the structure of the diiodinated product IX was obtained by converting it to the unsymmetrical diamide X. This was found to be identical, after purification, to the diamide obtained by acetylation of 3-amino-5-butyramido-2,6-diiodobenzoic acid (XI). This is not an absolute structure proof in itself, as it is possible that the orientation of the iodine atoms in the ring may vary depending upon the size of the N-acyl group in the acylaminobenzoic acid (I). Coupled, however, with the fact that the deamination product of IX was not

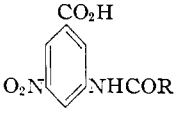
(6) Evidence for complex formation between 3-acetamido-5-amino-2,6-diiodobenzoic acid and iodine chloride was obtained by the addition of iodine chloride to a suspension of the benzoic acid in 6*N* hydrochloric acid. The new solid, so obtained, when added to water decomposed with the recovery of the starting substituted benzoic acid. This is not unlike the behavior of the iodine chloride complexes of iodinated acetamidothiazoles as reported by Garreau (Yvonne Garreau, *Bull. soc. chim. France*, 1048 (1954)).

(7) H. Hübner, *Ann.*, **222**, 81 (1884).

(8) D. Balcom and A. Furst, THIS JOURNAL, **75**, 4334 (1953).

(9) Since the crude diiodo compound II was a mixture and no solvent was found suitable for crystallization, it was necessary to standardize the iodination procedure so that a reproducible diiodo compound could be isolated. The ratio of isomers appeared to vary somewhat with the acidity of the reaction media. Iodination of I in 6 *N* hydrochloric acid with iodine chloride consistently gave a product with a lower melting and decomposition point than the diiodo product obtained from iodinations with potassium iododichloride in water. Furthermore, the neutral equivalent of the product obtained from the less acidic iodination tended to be higher than the neutral equivalents of the diiodo acid (II) obtained from the iodination run in the more acid media. Both these observations, higher melting point and neutral equivalent, are in accord with there also being some triiodo acid (III) in the product from the less acidic iodinations. Rather arbitrarily, the iodination of 3-acetamido-5-aminobenzoic acid (I, R = CH_3) and its homologs was done on the hydrochloride of the amino acid with solutions of potassium iododichloride.

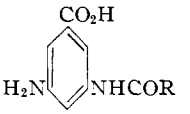
TABLE I

3-ACYLAMIDO-5-NITROBENZOIC ACIDS, 

R	Formula	Method[a]	M.p., °C.[b]	Yield, %	Mol. wt.	Neut.[c] equiv.	Analyses N by $TiCl_3$[d] Calcd.	Found
—CH_3	$C_9H_8N_2O_5$	I	291–295	97	224.2	223	6.24	6.20
—CH_2CH_3	$C_{10}H_{10}N_2O_5$	I	242–243	75	238.2	240	5.88	5.88
—$CH_2CH_2CH_3$	$C_{11}H_{12}N_2O_5$	I	243–245	76	252.2	251	5.55	5.62
—$(CH_2)_3CH_3$	$C_{12}H_{14}N_2O_5$	II	206–208	84	266.3	267	5.26	5.30
—$CH_2CH(CH_3)_2$	$C_{12}H_{14}N_2O_5$	II	223–224	82	266.3	267	5.26	5.34
—$(CH_2)_4CH_3$	$C_{13}H_{16}N_2O_5$	II	184–186	50	280.3	285	5.00	5.00
—$CH_2CH_2CH(CH_3)_2$	$C_{13}H_{16}N_2O_5$	II	206–207	82	280.3	283	5.00	5.03
—$(CH_2)_5CH_3$	$C_{14}H_{18}N_2O_5$	II	170–171	62	294.3	296	4.77	4.76
—CH_2OH	$C_9H_8N_2O_6$	III	231–233	77	240.2	242	5.83	5.84

[a] Method I, acid anhydride and aqueous sodium hydroxide. Method II, acid chloride and refluxing toluene. Method III, aqueous acid and heating. [b] Melting points are corrected. [c] For calcd. neutral equivalent see molecular weight column. [d] Titanous chloride titration of the nitro group.

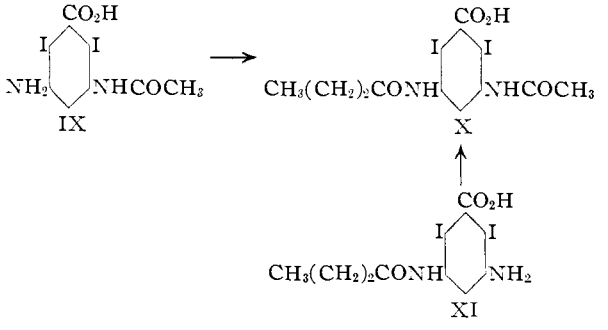
TABLE II

3-ACYLAMIDO-5-AMINOBENZOIC ACIDS, 

R	Formula	Method[a]	M.p., °C.[b]	Yield, %	Mol. wt.	Neut.[c] equiv.	Analyses Nitrogen Calcd.	Found
—CH_3	$C_9H_{10}N_2O_3$	II	222–224	97	194.2	195	14.40	14.38
—CH_2CH_3	$C_{10}H_{12}N_2O_3$	I	206–208	73	208.2	209	13.50	13.50
—$CH_2CH_2CH_3$	$C_{11}H_{14}N_2O_3$	I	237–238	75	222.2	223	12.60	12.76
—$(CH_2)_3CH_3$	$C_{12}H_{16}N_2O_3$	II	230–231	86	236.3	235	11.86	11.88
—$CH_2CH(CH_3)_2$	$C_{12}H_{16}N_2O_3$	II	242–244	67	236.3	232	11.86	11.72
—$(CH_2)_4CH_3$	$C_{13}H_{18}N_2O_3$	II	203–204	80	250.3	244	11.20	11.16
—$CH_2CH_2CH(CH_3)_2$	$C_{13}H_{18}N_2O_3$	II	224–225	61	250.3	250	11.20	11.31
—$(CH_2)_5CH_3$	$C_{14}H_{20}N_2O_3$	II	183–185	65	264.3	264	10.61	10.65
—CH_2OH	$C_9H_{10}N_2O_4$	I	204–207	85	210.2	210	13.32	13.16

[a] Method I, catalytic reduction of the ammonium salt with Raney nickel. Method II, reduction with hydrazine and Raney nickel. [b] Melting points are corrected. [c] For calcd. neutral equivalent see molecular weight column.

3-acetamido-2,4-diiodobenzoic acid, it is highly probable that the 2,6-diiodo isomer is the predominant one.



In this present work two different complexes of iodine chloride were employed for iodinations, pyridine–iodine chloride and potassium iododichloride. Although potassium iodochloride has been the subject of numerous investigations, it has not, up to this time, been used for iodinations. The equilibria involved in aqueous solutions of potassium iododichloride have been investigated by Cremer and Duncan,[10] who found that the following equation best fits the over-all equilibrium

$$5ICl_2^- + 3H_2O = 2I_2 + IO_3^- + 10Cl^- + 6H^+$$

Both increased acidity and chloride ion concentration have a stabilizing effect on solutions of iodine chloride in aqueous potassium chloride. Since in this work it was necessary to avoid excess acidity, we employed the potassium chloride in excess. Although the potassium iododichloride solutions were most conveniently prepared by the addition of commercial iodine chloride to a solution of potassium chloride, it was possible to modify the procedure of Gleu and Jagemann,[11] wherein an iodide solution was oxidized with the calculated quantity of iodate in the presence of excess potassium chloride

$$KIO_3 + 2KI + 6HCl \underset{}{\overset{KCl}{\rightleftharpoons}} 3KICl_2 + 3H_2O$$

The pyridine–iodine chloride complex was prepared directly from pyridine and potassium iododichloride. This procedure avoided the separate isolation of the pyridine–iodine chloride–hydrogen chloride complex as reported by Gleu and Jagemann.[11]

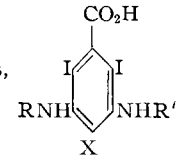
The various iodinated 3,5-diaminobenzoic acid derivatives are listed in Table III together with the intravenous toxicity values as determined in the pharmacological laboratories of this Institute. Outstanding in this series of compounds was 3,5-

(10) H. W. Cremer and D. R. Duncan, *J. Chem. Soc.*, 2031 (1932).

(11) K. Gleu and W. Jagemann, *J. prakt. Chem.*, **145**, 257 (1936).

TABLE III

IODINATED 3,5-DIAMINOBENZOIC ACID DERIVATIVES,



X	R	R'	Formula	Procedure	M.p., °C.[a]	Yield, %	Solvent[b]	Mol. wt.	Neut. equiv.	Analyses Iodine Calcd.	Iodine Found	i.v. LD_{50} mice, g./kg.[c]
H	H	$COCH_3$	$C_9H_8I_2N_2O_3$	1	215–218	70	...	446.0	444	56.9	57.1	9.5 ± 0.5
H	H	$COCH_2CH_3$	$C_{10}H_{10}I_2N_2O_3$	1	210–212	41	1	460.0	460	55.2	55.7	10.0
H	H	$COCH_2CH_2CH_3$	$C_{11}H_{12}I_2N_2O_3$	1	204–205	40	1	474.0	474	53.6	53.8	6.94
H	H	$COCH_2OH$	$C_9H_8I_2N_2O_4$	1	225–227	38	2	462.0	473	55.0	54.6	7.35
H	$COCH_3$	$COCH_3$	$C_{11}H_{10}I_2N_2O_4$	2	266–268	60	EtOH	488.1	485	52.1	52.2	9.80 ± 0.8
H	$COCH_2CH_3$	$COCH_3$	$C_{12}H_{12}I_2N_2O_4$	2	241–242	33	DMF	502.1	497	50.6	49.6	12.66
H	$COCH_2CH_2CH_3$	$COCH_3$	$C_{13}H_{14}I_2N_2O_4$	2	220–221	42	Acetone	516.1	510	49.2	48.9	13.00
H	$COCH_2OH$	$COCH_3$	$C_{11}H_{10}I_2N_2O_5$	3	223–225	61	dil. EtOH	504.1	505	50.4	50.4	>3.6
H	$COCH_2O_2CCH_3$	$COCH_3$	$C_{13}H_{12}I_2N_2O_6$	2	238–239	50	HOAc	546.1	[d]	46.5	45.8	8.5
I	H	$COCH_3$	$C_9H_7I_3N_2O_3$	4	258–259	65	dil. EtOH	571.9	572	66.6	66.5	7.20 ± 0.66
I	H	$CO(CH_2)_3CH_3$	$C_{12}H_{13}I_3N_2O_3$	4	236–237	50	dil. EtOH	614.0	590	62.1	62.2	5.66
I	H	$COCH_2OH$	$C_9H_7I_3N_2O_4$	4	263–264	71	dil. EtOH	587.9	587	64.9	64.5	4.32
I	COH	$COCH_3$	$C_{10}H_7I_3N_2O_4$	7	261–262	40	dil. EtOH	599.9	597	63.5	63.0	10.8 ± 0.46
I	$COCH_2CH_3$	$COCH_3$	$C_{12}H_{11}I_3N_2O_4$	2	>300	77	3	628.0	602	60.7	61.0	10.0 ± 0.57
I	$CO(CH_2)_2CH_3$	$COCH_3$	$C_{13}H_{13}I_3N_2O_4$	2	>300	65	3	642.0	641	59.4	59.5	8.70 ± 0.44
I	$COCH(CH_3)_2$	$COCH_3$	$C_{13}H_{13}I_3N_2O_4$	5	>300	46	dil. EtOH	642.0	636	59.4	59.8	6.87
I	$CO(CH_2)_3CH_3$	$COCH_3$	$C_{14}H_{15}I_3N_2O_4$	5	290–293	47	dil. EtOH	656.0	646	58.2	58.0	6.20 ± 0.40
I	$COCH_2CH(CH_3)_2$	$COCH_3$	$C_{14}H_{15}I_3N_2O_4$	5	>290	40	dil. EtOH	656.0	653	58.2	57.9	3.12
I	$CO(CH_2)_4CH_3$	$COCH_3$	$C_{15}H_{17}I_3N_2O_4$	5	276–278	60	dil. EtOH	670.1	665	56.8	57.2	3.20 ± 0.16
I	$CO(CH_2)_2CH(CH_3)_2$	$COCH_3$	$C_{15}H_{17}I_3N_2O_4$	5	291–292	45	dil. EtOH	670.1	669	56.8	56.3	2.38
I	$CO(CH_2)_5CH_3$	$COCH_3$	$C_{16}H_{19}I_3N_2O_4$	5	294–295	79	dil. EtOH	684.1	673	55.7	56.5	1.32 ± 0.84
I	$CO(CH_2)_6CH_3$	$COCH_3$	$C_{17}H_{21}I_3N_2O_4$	5	278–279	60	dil. EtOH	698.1	704	54.5	54.6	0.48 ± 0.03
I	$COCH_2OH$	$COCH_3$	$C_{11}H_9I_3N_2O_5$	3	249–251	50	H_2O	630.0	625	60.5	59.8	8.50 ± 0.70
I	$COCH_2O_2CCH_3$	$COCH_3$	$C_{13}H_{11}I_3N_2O_6$	2	284–289	55	HOAc	672.0	[e]	56.7	56.6	8.50 ± 0.74
I	H	H	$C_7H_5I_3N_2O_2$	6	154–158	89	2	529.9	529	71.9	72.8	1.31 ± 0.13
I	COH	COH	$C_9H_5I_3N_2O_4$	7	>300	48	4	585.9	[f]	65.0	64.7	7.40 ± 0.44
I	$COCH_3$	$COCH_3$	$C_{11}H_9I_3N_2O_4$	2	>300	67	dil. DMF	614.0	614	62.1	62.3	13.40 ± 0.86
I	$COCH_2CH_3$	$COCH_2CH_3$	$C_{13}H_{13}I_3N_2O_4$	2	>300	59	dil. DMF	642.0	647	59.3	59.7	11.80 ± 0.54
I	$COCH_2CH_2CH_3$	$COCH_2CH_2CH_3$	$C_{15}H_{17}I_3N_2O_4$	2	>300	33	EtOH	670.1	674	56.8	56.9	7.20 ± 0.58
I	$CO(CH_2)_3CH_3$	$CO(CH_2)_3CH_3$	$C_{17}H_{21}I_3N_2O_4$	2	>300	33	dil. MeOH	698.1	[g]	52.9[f]	52.3	2.65 ± 0.18
I	$COCH_2CH(CH_3)_2$	$COCH_2CH(CH_3)_2$	$C_{17}H_{21}I_3N_2O_4$	2	>300	45	dil. MeOH	698.1	677	54.6	54.5	3.57
I	$CO(CH_2)_4CH_3$	$CO(CH_2)_4CH_3$	$C_{19}H_{25}I_3N_2O_4$	2	>300	35	dil. MeOH	726.2	[h]	50.9[g]	51.4	0.60 ± 0.06

[a] Decomposition accompanied by iodine liberation is characteristic of all of these compounds. [b] (1) crystallized di-*n*-butylamine salt from water and then liberated the acid; (2) crystallized ammonium salt from water and then liberated the acid; (3) the acid was refluxed with abs. ethanol and the mixture filtered hot to separate alcohol soluble material; (4) crystallized sodium salt from 75% ethanol; DMF, dimethylformamide; HOAc, glacial acetic acid; EtOH, 95% ethanol; MeOH, methanol. [c] Where no standard error is indicated the toxicity values are ALD_{50}. [d] Carbon: Calcd., 28.56; found, 28.50. [e] Carbon: Calcd., 23.2; found, 23.7. [f] Carbon: Calcd., 18.45; found, 18.57. [g] Sodium salt: nitrogen: calcd., 3.89; found, 3.71. [h] Sodium salt: nitrogen: calcd., 3.75; found, 3.60.

diacetamido-2,4,6-triiodobenzoic acid[12] which had a toxicity, calculated on the basis of the acid, of 13.4 g./kg. when injected as an aqueous solution of the sodium salt in mice.[13] This intravenous toxicity is one of the lowest observed for any organic compound.

Experimental

Potassium Iododichloride.—Iodine chloride, 55 ml. (1 mole), was added to a solution of 120 g. (1.6 moles) of potassium chloride in 350 ml. of water. The volume was then adjusted to 500 ml. to give a 2 *N* solution. In the event the iodine chloride was either under or over chlorinated, the solution was either filtered or the calculated quantity of potassium iodide added.[2] Over chlorination was more to be avoided than under chlorination since iodine trichloride can serve as a chlorinating agent. Alternatively the solution of potassium iododichloride could be made as follows. A mixture of 71 g. (0.33 mole) of potassium iodate, 40 g. of potassium chloride and 5 ml. of concd. hydrochloric acid in 80 ml. of water was stirred vigorously and treated simultaneously with 111 g. (0.66 mole) of potassium iodide in 100 ml. of water and with 170 ml. of concd. hydrochloric acid. The rate of addition of the hydrochloric acid and potassium iodide solutions were so regulated that no chlorine was evolved. After addition was completed, the volume was brought to 500 ml. with water to give a 2 *N* solution of potassium iododichloride.

Pyridine–Iodine Chloride.—To a stirred soln. of 45 ml. of pyridine in 1 l. of water was added 250 ml. of 2 *N* potassium iododichloride. A cream colored solid separated, the *p*H of the mixture was adjusted to 5 with pyridine and the solid collected, washed with water and air-dried, 117 g. (97.5%), m.p. 130–133°. This can be crystallized from 700 ml. of benzene to give 87 g. of light yellow solid, m.p. 135–136°.

3-Amino-5-nitrobenzoic Acid.[7]—A mixture of 212 g. (1 mole) of 3,5-dinitrobenzoic acid in 1.4 l. of water and 210 ml. of concd. aqueous ammonia was heated to 70° with stirring. Heating was stopped and a stream of hydrogen sulfide passed into the solution at a rate sufficient to maintain the temperature at 75–80°. When after 40–50 min. an acidified test portion showed no dinitrobenzoic acid to be left, the mixture was diluted with 800 ml. of water and 300 ml. of concd. hydrochloric acid. The cooled mixture was filtered and the filtrate neutralized to a *p*H of 3 with solid sodium carbonate. The orange solid was collected and crystallized from 3.5 l. of water to give 160 g. of product (88%), m.p. 211–213°.

3-Acylamido-5-nitrobenzoic Acids (Table I). Method I.—A solution of 78 g. (0.38 mole) of sodium 3-amino-5-nitrobenzoate in 750 ml. of water was warmed to 40°, heat removed and 43 ml. of acetic anhydride added with vigorous stirring. After 1 hr. the yellow 3-acetamido-5-nitrobenzoic acid was collected, washed with water and dried, wt. 80 g. (93%), m.p. 291–295°.

Method II.—A mixture of 91 g. (0.5 mole) of 3-amino-5-nitrobenzoic acid in 1.25 l. of toluene was dried azeotropically. To this was added 65 ml. (62.5 g., 0.5 mole) of isovaleryl chloride and the whole refluxed for 1.5 hours, cooled, filtered and the solid washed with benzene and then dil. hydrochloric acid. The air-dried product weighed 110 g. (82%), m.p. 220–222°. This material was of suitable purity for subsequent reactions. It could be crystallized from ethanol.

Method III.—The clear melt obtained by heating a mixture of 100 g. (0.55 mole) of 3-amino-5-nitrobenzoic acid and 110 g. of 70% glycolic acid to 150° was poured onto 3 l. of crushed ice. The separated solid was collected, dissolved in dil. sodium hydroxide solution, filtered and the organic acid precipitated with dil. hydrochloric acid. The yellow air-dried 3-amino-5-hydroxyacetamidobenzoic acid weighed 63 g. (77%), m.p. 228–231°.

3-Acylamino-5-aminobenzoic Acids (Table II). Method I.—A solution of 98 g. (0.41 mole) of 3-nitro-5-propionamidobenzoic acid in 750 ml. of water and sufficient aqueous ammonia to give solution was reduced at room temperature at 500 lb. hydrogen pressure with Raney nickel catalyst. After 2 hr. the reduction was complete. The catalyst was filtered off and the filtrate acidified with acetic acid. The 3-amino-5-propionamidobenzoic acid, which was crystallized from ethanol, weighed 63 g. (73%), m.p. 206–208°.

Method II.—To a solution of 112 g. (0.42 mole) of 3-nitro-5-valerylaminobenzoic acid in 750 ml. of water and 77 ml. of hydrazine hydrate, was added 12 g. of Raney nickel in 6 portions. After the final addition the mixture was heated on the steam-bath until foaming stopped. Upon working up the reaction, as above, there was obtained 3-amino-5-valerylaminobenzoic acid weighing 86 g. (86%), m.p. 227–230°. Crystallization was from ethanol, 80% recovery, m.p. 230–231°.

3-Acetamido-5-amino-2,6-diiodobenzoic Acid (II, R = CH_3). (**Procedure No. 1**).—To a stirred suspension of 38.8 g. (0.2 mole) of 3-acetamido-5-aminobenzoic acid in 1 l. of water and 16 ml. of concd. hydrochloric acid, there was added, over a 20-min. period, 210 ml. of 2 *N* potassium iododichloride. After stirring for 3 hr., the gray solid was collected and washed with water, 86 g. (95%), m.p. 208–211° dec. The product was taken up in 1 l. of water with ammonia, 5 g. of sodium bisulfite added and the acid precipitated with 6 *N* hydrochloric acid. The collected acid was redissolved in dilute ammonia, charcoaled and reprecipitated. After washing and air-drying the material weighed 57 g., m.p. 215–217° dec. The color of the product was light tan and all attempts to crystallize the compound were unsuccessful.

3,5-Diacetamido-2,6-diiodobenzoic Acid (III, R = R′ = CH_3). (**Procedure No. 2**).—A mixture of 100 g. (0.222 mole) of 3-acetamido-5-amino-2,6-diiodobenzoic acid, 900 ml. of acetic anhydride and 2 ml. of concd. sulfuric acid was heated on the steam-bath for 3 hr. The soln. was poured onto 3 kg. of ice and the mixture left to stand until the excess anhydride was hydrolyzed. The product was collected, washed with water and air-dried, 102 g. This material was dissolved in dil. sodium hydroxide soln., filtered and the filtrate acidified to give 85 g., dull white solid, m.p. 241–243°. A crystallization from 1.5 l. of ethanol and then a precipitation of the acid from the ammonium salt gave 65 g. of white product, m.p. 266–268° dec.

3-Acetamido-5-butyramido-2,6-diiodobenzoic Acid (III, R = CH_3, R′ = C_3H_7). (**Procedure No. 2**).—A mixture of 33 g. (0.074 mole) of 3-acetamido-5-amino-2,6-diiodobenzoic acid, 145 ml. of butyric anhydride and 10 drops of concd. sulfuric acid was heated on the steam-bath for 2.5 hr. After cooling the solid was collected and washed with *n*-pentane, 21 g., m.p. 213–216° dec. Solution as the ammonium salt, charcoaling, reprecipitation of the acid and a crystallization from 75 ml. of acetone gave 16 g. of white product, m.p. 220–221° dec.

The infrared spectra, in potassium bromide discs, of this compound and the one prepared by acetylation of 3-amino-5-butyramido-2,6-diiodobenzoic acid were identical in all respects.

3-Acetamido-2,6-diiodo-5-hydroxyacetamidobenzoic Acid (III, R = CH_3, R′ = $HOCH_2^-$) (**Procedure No. 3**).—A paste of 23 g. (0.042 mole) of 3-acetamido-5-acetoxyacetamido-2,6-diiodobenzoic acid in water was gradually treated with 84 ml. of 1 *N* sodium hydroxide soln. Toward the end of the alkali addition, it was necessary to gently warm the solution to effect consumption of the alkali. After filtering, the filtrate was acidified to give 20 g. of crude product, m.p. 220–225°. After a crystallization from 500 ml. of water and 200 ml. of ethanol, there was obtained 13 g. of white product, m.p. 223–225° dec.

3-Acetamido-5-amino-2,4,6-triiodobenzoic Acid (IV, R = CH_3). (**Procedure No. 4**).—To a stirred suspension of 97 g. (0.5 mole) of 3-acetamido-5-aminobenzoic acid in 2.5 l. of water, there was added, over a 30-min. period, 550 ml. of 2 *N* potassium iododichloride soln. Solution resulted and a new solid separated. The mixture was stirred for 3 hr. at room temp., the excess hydrochloric acid was neutralized with 155 ml. of 35% sodium hydroxide soln. and the reaction soln. was then treated with 250 ml. more of 2 *N* potassium iododichloride soln. over a 0.5-hr. period. The brown solid was collected, washed with water and the air-dried product was heated to 90° with 400 ml. of satd. ammonium

(12) Hypaque is the registered trade mark of Winthrop-Stearns Inc. for 3,5-diacetamido-2,4,6-triiodobenzoic acid.

(13) For a discussion of the toxicology and pharmacology of these compounds, see "Observations on the Toxicity of a New Urographic Contrast Medium, Sodium 3,5-Diacetamido-2,4,6-triiodobenzoate (Hypaque Sodium) and Related Compounds," James O. Hoppe, A. A. Larsen and F. Coulston, *J. Pharm. Exper. Therap.*, **116**, 394 (1956).

chloride and then the mixture made ammoniacal. After filtering and cooling the separated ammonium salt was collected and washed with satd. ammonium chloride soln. The air-dried ammonium salt was dissolved in 3 l. of hot water, charcoaled and the organic acid precipitated with concd. hydrochloric acid. The collected, water washed, vacuum dried product weighed 220 g., m.p. 255–257° dec. This product is cream colored and is satisfactory for subsequent reactions. Additional purification can be achieved by either a crystallization of the ammonium salt from water or a crystallization of the acid from ethanol. The product so purified is almost white, m.p. 258–259° dec.

3-Acetamido-5-isobutyramido-2,4,6-triiodobenzoic Acid (V, R = CH_3, R′ = $CH_2CH(CH_3)_2$). (**Procedure No. 5**).—A mixture of 28.6 g. (0.05 mole) of 3-acetamido-5-amino-2,4,6-triiodobenzoic acid and 70 ml. of isobutyryl chloride was heated on the steam-bath for 4 hr. After cooling, the crude solid was collected, washed with *n*-pentane and then air-dried. This material was dissolved in dil. ammonia, charcoaled, the organic acid precipitated from the filtrate with dil. hydrochloric acid, collected, washed well with water and air-dried, 27 g., m.p. >290°. A recrystallization from dil. ethanol yielded 15 g., m.p. >300°.

3,5-Diamino-2,4,6-triiodobenzoic Acid.[3] (**Procedure No. 6**).—A suspension of 212 g. (1 mole) of 3,5-dinitrobenzoic acid in 1.4 l. of water and 168 ml. of concd. hydrochloric acid was hydrogenated in 0.5 hour with 30 g. of 10% Pd–C at 1500 p.s.i. initial hydrogen pressure. The resultant soln. was filtered and diluted to 12 l. with water and to this soln. was added 1.6 l. of 2 *N* potassium iodochloride. After stirring for 0.5 hour, the brown solid was collected, washed with water and air-dried, wt. = 475 g., m.p. 130–140° dec. The melting range of this crude acid varies somewhat but it was pure enough for subsequent reactions. For purification 53 g. of the crude iodinated product was suspended in 100 ml. of satd. ammonium chloride soln., the mixture heated on the steam-bath, concd. ammonia added to solution, filtered and the filtrate cooled to 0°. The collected brown ammonium salt was dissolved in water, treated in the cold for 2 hr. with charcoal, filtered and the cream-colored organic acid precipitated with acetic acid, 42 g., m.p. 148–155° dec. Repetition of the above procedure yielded a dull white solid, 28.5 g., m.p. 154–158° dec.

3,5-Diformamido-2,4,6-triiodobenzoic Acid (VIII, R = H) (**Procedure No. 7**).—To 400 ml. of cold stirred acetic anhydride, there was added 610 ml. of 98% formic acid as rapidly as possible and yet maintain the temp. below 15°. The cooling was removed and 53 g. (0.1 mole) of 3,5-diamino-2,4,6-triiodobenzoic acid was added. The mixture was warmed slowly to 50°, solution was practically complete at 35° and then a new solid started to separate. The mixture was held at 50–55° for one hour, diluted with 250 ml. of warm water and left to stand overnight. The gray solid was collected, washed thoroughly with warm water and air-dried, 47 g., m.p. >300°. This acid was suspended in 400 ml. of 70% isopropyl alcohol and sufficient 5% sodium hydroxide soln. added to effect solution of the sodium salt at the boil. After decolorization with charcoal, the separated solid was collected from the chilled filtrate, 34 g. This sodium salt was dissolved in water and the acid precipitated with dil. hydrochloric acid to yield after drying 28 g., m.p. >300°.

3,5-Diacetamido-2,4,6-triiodobenzoic Acid (VIII, R = CH_3) (**Procedure No. 2**).—A stirred solution of 145 g. (0.25 mole) of 3,5-diamino-2,4,6-triiodobenzoic acid in 750 ml. of acetic anhydride at 70–75° was cooled to 45–50° and 10 drops of concd. sulfuric acid was added. A brief exothermic reaction followed, the mixture was heated on the steam-bath for 15 min. and then cooled in ice. The collected product was well washed with water and dried at 50 *in vacuo*, wt. 137 g., m.p. >300°. Solution of this solid in dil. ammonia water, charcoaling and reprecipitation of the acid yielded 130 g. of practically white product, m.p. >300°. A final purification was effected by crystallization from 300 ml. of 50% aqueous dimethylformamide with charcoaling to yield 103 g. of white product, m.p. >300°.

3-Acetamido-2,4-diiodo-6-nitrobenzoic Acid.—A mixture of 24 g. (0.132 mole) of 3-amino-6-nitrobenzoic acid and 70 g. (0.29 mole) of pyridine–iodine chloride in 1 l. of water was stirred for 6 hr. at room temperature and then for 6 hr. on the steam-bath. After cooling, excess ammonia was added to dissolve the benzoic acid and the red mixture filtered several times to remove the black nitrogen triiodide. The filtrate was heated on the steam-bath and made acid with dil. hydrochloric acid. The collected yellow solid was washed with water and air-dried, 45.3 g. (79%), neut. equiv. calcd. 434, found 429, m.p. 280 ± indef. dec.[14] This solid was added to 125 ml. of acetic anhydride and 10 drops of concd. sulfuric acid, heated on the steam-bath for 0.5 hr., the excess anhydride destroyed cautiously with hot water and the final soln. of about 280 ml. left to stand at room temp. overnight. The collected yellow crystals after washing with water and air-drying weighed 43.6 g. (88%), m.p. 266–267° dec.

Anal. Calcd. for $C_9H_6I_2N_2O_5$: I, 53.3; N_{Tl}, 2.93. Found: I, 52.7; N_{Tl}, 3.04.

3-Acetamido-6-amino-2,4-diiodobenzoic Acid.—A soln. of 9 g. (0.02 mole) of 3-acetamido-6-nitro-2,4-diiodobenzoic acid in 50 ml. of water and 8 ml. of concd. aq. ammonia was treated with 15 g. of sodium hydrosulfite. The temperature was held at 15–20°, and after 12 g. of the hydrosulfite had been added, heat was no longer liberated from the reaction. The water white soln. was heated for 10 min. on the steam-bath, cooled, *p*H adjusted with ammonia to 8–9, Filtercel added and the mixture filtered. The filtrate was made acid with concd. hydrochloric acid and heated on the steam-bath to expel the sulfur dioxide. A solid separated from the heated filtrate, cooled and the white solid collected and again precipitated from the ammonium salt to yield 5.2 g., m.p. 239–240° dec.

Anal. Calcd. for $C_9H_8I_2N_2O_3$: I, 56.9; neut. equiv., 446. Found: I, 57.3; neut. equiv., 442.

3-Acetamido-2,4-diiodobenzoic Acid.—A cold, stirred suspension of 30 g. (0.067 mole) of 3-acetamido-6-amino-2,4-diiodobenzoic acid in 100 ml. of water and 50 ml. of concd. sulfuric acid was treated, over a 75-min. period, with 5 g. of sodium nitrite in 20 ml. of water. The mixture was stirred for an additional hour and then treated with sulfamic acid to destroy the excess nitrous acid. To the mixture was added 100 ml. of cold 50% hypophosphorous acid and the whole stirred for 10 hr. at 0°. After air-drying, the collected brown solid weighed 21 g., m.p. 219–235° dec. Precipitation of this acid from a soln. of the ammonium salt gave 13.5 g. of off-white product, m.p. 244–250° dec. Further purification by a crystallization from acetic acid, soln. as the ammonium salt and reprecipitation and finally a crystallization from isopropyl alcohol gave 2.5 g., white solid, m.p. 264° dec.

Anal. Calcd. for $C_9H_7I_2NO_2$: I, 58.9; O, 11.10; neut. equiv., 431. Found: I, 58.6; O, 11.35; neut. equiv., 428.

3-Acetamido-2,6-diiodobenzoic Acid.—A cold stirred suspension of 44 g. (0.1 mole) of 3-acetamido-5-amino-2,6-diiodobenzoic acid in 25 ml. of concd. hydrochloric acid and 200 ml. of water was treated, over a 0.5-hr. period, with 7 g. of sodium nitrite in 20 ml. of water. The mixture was stirred for another 1.5 hr., the excess nitrous acid destroyed with sulfamic acid and then treated with 100 ml. of hypophosphorous acid and left to stir at 0° for 8 hr. The collected brown solid was reprecipitated from a charcoaled soln. of the ammonium salt to yield 27 g. of pink material, m.p. 254–255° dec. A crystallization from acetic acid and then two precipitations from solutions of the ammonium salt gave 10.5 g., m.p. 256° dec.

Anal. Calcd. for $C_9H_7I_2NO_3$: I, 58.9; neut. equiv., 431. Found: I, 58.8; neut. equiv., 429.

The infrared spectra, potassium bromide discs, of this compound and that of 3-acetamido-2,4-diiodobenzoic acid were completely different in the fingerprint region, 8–11 μ, and in the region of 12–15 μ the aromatic bands were shifted with respect to each other. The mixed melting point of the two samples was 254° dec., that of the individual components, 256 and 264° dec.

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(14) L. Kalb, F. Schweizer, H. Zellner and E. Berthold, *Ber.*, **59**, 1868 (1926).

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Structure and Properties of Cyclic Compounds. V.[1] Strain Effects in the Ultraviolet Light Absorption of Cyclic Compounds

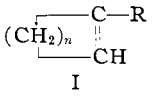
BY OWEN H. WHEELER

RECEIVED APRIL 19, 1955

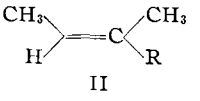
New and previous data on the ultraviolet light absorption of cyclic systems containing double bonds are discussed in terms of strain effects in the rings. Simple α,β-unsaturated amides and nitriles have, in general, absorption similar to that of the corresponding acids.

It has been observed by a number of workers that the presence of a carbon ring in, or at the end of a conjugate chromophore, affects the characteristic wave length of absorption of that chromophore.[2] In this investigation the absorption of a series of cyclic acids and amides, with both endo- and exocyclic double bonds, has been measured under standard conditions, and these results, together with previous literature data, are discussed in terms of the strain effects produced by these endo- and exocyclic double bonds.

Compounds with Endocyclic Double Bond.— The ultraviolet light absorption of cycloalkenylcarboxylic acids (I, R = CO_2H), carboxamides (I, R = $CONH_2$) and nitriles (I, R = CN) of ring size 5 to 7 carbon atoms (I, n = 3 to 5), has been measured and is given in Table I, together with published data on the corresponding carboxaldehydes (I, R = CHO) and methyl ketones



I

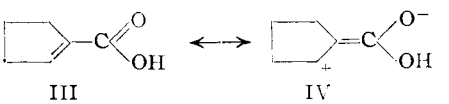


II

(I, R = $COCH_3$). It is seen that the cyclopentenyl and cycloheptenyl derivatives all absorb at higher wave lengths than the cyclohexenyl compounds, and that the latter absorb at similar wave lengths to the acyclic analogs (*cf. cis*-α,β-dimethylacrylic acid (tiglic acid) (II, R = CO_2H) and amide (II, R = $CONH_2$)).

The absorption of light by a molecule in the near ultraviolet region of the spectrum results in electronic transitions from a hybrid ground state, in which ionic resonance forms normally play little part, to an excited state to which ionic resonance forms make a large contribution.[3] If there is a structural change in the molecule which raises the energy of the excited state more than that of the ground state, then the energy of the transition will be increased and absorption will take place at lower wave length. Such effects are well known in sterically hindered molecules,[4] where there is inhibition of resonance stabilization in the excited state. However, if some effect in the molecule raises the energy level of the ground state with little effect on the energy level of the excited state, the energy of the absorption transition will be lowered, and the absorption peak displaced to a longer wave length. It is proposed that this last effect offers an explanation of the spectral differences in cycloalkenyl compounds.

The presence of a double bond in a cyclopentane ring leads to considerable strain in the ring, since the angles about the double bond are considerably compressed.[5] However, when the double bond is exocyclic to the ring, this angle strain is greatly relieved.[5] As a result of this the endocyclic double bond in cyclopentenylcarboxylic acid (III) makes this a strained molecule, relative to its acyclic



III IV

analog (II, R = CO_2H), and increases the energy level of its ground state. Absorption of light causes a transition to a higher energy level, to which polar resonance forms (*e.g.* IV) contribute. Resonance of this type (III–IV) will give some single bond character to the endocyclic double bond, and produce a partial double bond exocyclic to the ring. This leads to a delocalization of the endocyclic double bond with relief of strain in the ring and the energy level of the excited state will be lowered relative to that of an unstrained molecule. Hence the energy level of the ground state is raised and that of the excited state lowered, decreasing the energy of the transition and causing absorption at longer wave length. It can be seen (Table I) that cyclopentenylcarboxylic acid (I, n = 3; R = CO_2H) shows a bathochromic shift over its acyclic strainless analog, tiglic acid (II, R = CO_2H). A similar explanation holds for the other cyclopentenyl compounds (I, n = 3, R = $CONH_2$, CN, CHO, $COCH_3$).

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