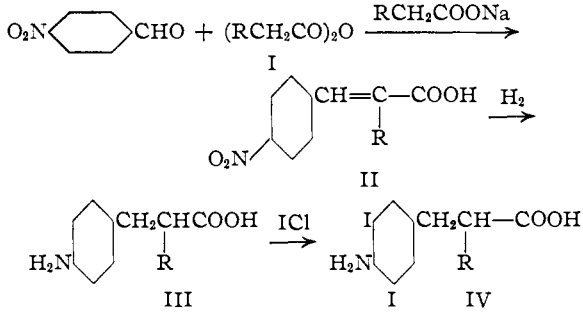
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Some Iodinated Aminophenylalkanoic Acids

BY T. R. LEWIS AND S. ARCHER

In a previous communication the synthesis of three isomeric (amino-diiodophenyl)-phenylpropionic acids was reported.[1] It was found that two of these concentrated sufficiently in the gall-bladder so as to render this organ opaque to X-rays.[2] It seemed advisable to determine whether one of the phenyl radicals may be replaced by another hydrocarbon group without impairing the efficiency of the compounds as contrast media. While this work was in progress two papers appeared in which it was shown that certain (diiodo-hydroxyphenyl)-alkanoic acids did provide visualization of the gall-bladder for radiological examination.[3,4] The compounds reported below were fed orally to animals and after a suitable interval cholecystograms were obtained. The compounds represented by IV produced adequate visualization of the gall-bladder except in the cases where R contained a cyclohexyl group.

The (4-amino-3,5-diiodophenyl)-alkanoic acids were prepared according to the following general equations.



The anhydrides, I, were prepared according to the general procedure of Allen, *et al.*[5] These condensed with *p*-nitrobenzaldehyde in the presence of the sodium salt of the corresponding acid to give II in yields varying from 25–80%. In one preparation (R = *i*-amyl) we employed triethylamine in place of sodium isoheptanoate and secured the acid II (R = *i*-amyl) in 52% yield. In contrast to the aromatic series in no instance were we able to isolate more than one isomer corresponding to II.

Reduction of the unsaturated nitro acids was carried out with the aid of Raney nickel catalyst and the iodination of the resulting amino acids was carried out as described previously.[1]

(1) Lewis, Pratt, Homiller, Tullar and Archer, THIS JOURNAL, **71**, 3749 (1949).

(2) Hoppe and Archer, *Fed. Proc.*, **8**, 303 (1949).

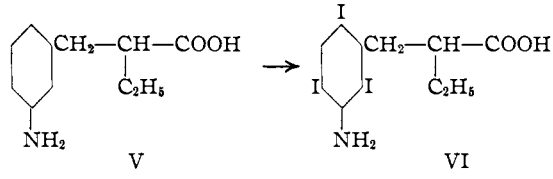
(3) Epstein, Natelson and Kramer, *Am. J. Roentgenol.*, **56**, 202 (1946).

(4) Pratt, Hoppe and Archer, *J. Org. Chem.*, **13**, 576 (1948).

(5) Allen, Kibler, McLachlin and Wilson, *Org. Syntheses*, **26**, 1 (1946).

Condensation of *m*-nitrobenzaldehyde with butyric anhydride in the presence of sodium butyrate resulted in the formation of α-ethyl-*m*-nitrocinnamic acid in 72% yield. When triethylamine was used as the condensing agent the yield fell off to 52% of the theoretical.

Reduction of the acid gave V, which, surprisingly, was quite low melting and difficult to obtain analytically pure. Both methods A and



B were tried but the latter did not seem to offer any advantages with respect to yield. The substance which was isolated from the reaction mixture proved to be the triiodoacid, VI. It may be recalled that when β-(*m*-aminophenyl)-α-phenylpropionic acid was iodinated only the diiodo acid was secured.[1] It is probable that the bulkier phenyl group prevented the third iodine atom from entering the remaining position ortho to the amino group.

Experimental[6]

Preparation of the Acid Anhydrides (I).—Without exception, the method described in "Organic Syntheses"[5] was used. Most of the anhydrides have been described previously.

β-Cyclohexylpropionic anhydride was obtained in 71% yield. It boiled at 154–158° at 0.5 mm., $n^{25}D$ 1.4720.

Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.74; H, 10.15.

γ-Cyclohexylbutyric anhydride was obtained in 68% yield. It boiled at 169–172° at 0.5 mm., $n^{25}D$ 1.4730.

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.34; H, 10.45.

α-Ethyl-*m*-nitrocinnamic Acid.—A mixture of 100 g. of *m*-nitrobenzaldehyde, 210 g. of butyric anhydride and 73 g. of dry sodium butyrate was heated with stirring at 140° for seven hours. The red reaction mixture was cooled and then steam distilled for four hours, when crystals appeared in the flask. These were filtered and dried, wt., 130 g. The product was dissolved in 2 *N* sodium hydroxide and the solution filtered. After acidification with hydrochloric acid, the acid which separated was collected and recrystallized from dilute ethanol. In this way there was obtained 105 g. of the acid which melted at 140–142° (uncor.).

Anal. Calcd. for $C_{11}H_{11}NO_4$: N, 6.33. Found: N, 6.35.

The nitrocinnamic acids listed in Table I were prepared by essentially the same method. In the cases wherein the alkanoic acids were not volatile with steam, the hydrolyzed reaction mixture was dissolved in sodium hydroxide solution and then extracted with ether. The basic layer was acidified and the organic acids removed with ether. The solution was concentrated and the residue leached with a

(6) Analyses were performed under the supervision of Mr. M. E. Auerbach of this Laboratory.

TABLE I

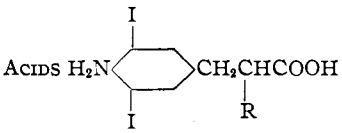
PROPERTIES OF THE α-ALKYL-*p*-NITROCINNAMIC ACIDS AND THE α-ALKYL-*p*-AMINOPHENYLPROPIONIC ACIDS

	α-Alkyl-*p*-nitrocinnamic acids					α-Alkyl-*p*-aminophenylpropionic acids					
R =	Yield, %[b]	M. p., °C.[c]	Formula	Nitrogen, % Calcd.	Found	Yield, %	Solvent	M. p., °C.[e]	Formula	Nitrogen, % Calcd.	Found
C_2H_5	80	168–169	$C_{11}H_{11}NO_4$	6.33	6.17	92	C_6H_6	129–130	$C_{11}H_{15}NO_2$	7.25	7.28
n-C_3H_7	39	132–134	$C_{12}H_{13}NO_4$	5.96	5.86	82	CH_3OH–H_2O	151–153	$C_{12}H_{17}NO_2$	6.76	6.73
n-C_4H_9	70	162–163	$C_{13}H_{15}NO_4$	5.62	5.55	79	C_2H_5OH–H_2O	151.5–152	$C_{13}H_{19}NO_2$	6.33	6.28
n-C_5H_{11}	37	167–169	$C_{14}H_{17}NO_4$	5.36	5.32	93	C_6H_5–Lig.[d]	140–142	$C_{14}H_{21}NO_2$	5.95	5.92
i-C_5H_{11}	52	163–164	$C_{14}H_{17}NO_4$	5.36	5.13	99	C_2H_5OH–H_2O	161–162.5	$C_{14}H_{21}NO_2$[f]		
C_6H_{11}[a]	25	181–183	$C_{15}H_{17}NO_4$	5.09	5.04	95	C_2H_5OH	215–216	$C_{15}H_{21}NO_2$	5.66	5.64
$C_6H_{11}CH_2$[a]	42	195–196.5	$C_{16}H_{19}NO_4$	4.84	4.60	97	C_6H_6	176–177	$C_{16}H_{23}NO_2$[g]		
$C_6H_{11}CH_2CH_2$[a]	45	170–172	$C_{17}H_{21}NO_4$	4.62	4.64	95	C_2H_5OH	176–177	$C_{17}H_{25}NO_2$	5.09	5.05

[a] C_6H_{11} = Cyclohexyl. [b] All the nitro acids were purified by recrystallization from either ethanol or dilute ethanol. The yields are calculated on the basis of purified compounds. [c] Uncorrected. [d] Lig. = Ligroin. [e] Corrected. [f] *Anal.* Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.65; H, 8.40. [g] *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.87. Found: C, 73.91; H, 8.80.

TABLE II

PROPERTIES OF THE α-ALKYL-β-(4-AMINO-3,5-DIIODOPHENYL)-PROPIONIC ACIDS



R =	Yield, %	M. p. (cor.), °C.	Method[a]	Solvent	Morpholine salt M. p. (uncor.), °C.	Formula	Iodine, % Calcd.	Found
C_2H_5	54	114.2–115.1	A	Dil. methanol	130–132	$C_{11}H_{13}I_2NO_2$	57.03	57.00
n-C_3H_7	54	121–121.8	A	Dil. methanol	131–133	$C_{12}H_{15}I_2NO_2$	55.29	55.68
n-C_4H_9	60	108–109.2	B	Dil. methanol		$C_{13}H_{17}I_2NO_2$	53.65	53.75
n-C_5H_{11}	40	104–105.7	A	Benzene–ligroin	117–119	$C_{14}H_{19}I_2NO_2$	52.11	51.90
i-C_5H_{11}	20	100–102	B	Dil. methanol	105–107	$C_{14}H_{19}I_2NO_2$	52.11	52.40
C_6H_{11}[b]	81	172–174.3	B	Dil. ethanol		$C_{15}H_{19}I_2NO_2$	50.87	50.32
$C_6H_{11}CH_2$[b]	83	142–144	B	Dil. ethanol		$C_{16}H_{21}I_2NO_2$	49.46	49.30
$C_6H_{11}CH_2CH_2$[b]	62	123–123.6	A	Dil. ethanol	129–133	$C_{17}H_{23}I_2NO_2$	48.14	47.95

[a] Details of Methods A and B are found in the Experimental Part. [b] C_6H_{11} = Cyclohexyl.

large volume of petroleum ether. The insoluble material was the desired α-alkyl-*p*-nitrocinnamic acid.

α-Ethyl-β-(*m*-aminophenyl)-propionic Acid.—Fifty grams of the nitro acid was dissolved in 500 ml. of ether containing 9.1 g. of sodium hydroxide and reduced at 70° with Raney nickel catalyst. After two hours reduction was complete. The filtered solution was made slightly acidic with acetic acid and concentrated to about 200 ml. A few ml. of acetic acid was added whereupon an oil separated which gradually solidified. It weighed 20 g. The supernatant liquid was decanted and concentrated to dryness *in vacuo*. The residue was leached with boiling ether. The leachings were concentrated to leave a viscous oil which crystallized on cooling and seeding (wt. 20 g.). The solids were combined and recrystallized from benzene–petroleum ether (Darco). The product, which melted at 67–70° weighed 34.5 g. and was suitable for use in the iodination. Further purification raised the m. p. to 78–80°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.21.

The amino acids listed in Table II were prepared by the same procedure. In all cases careful acidification of the filtered reduction mixture caused the compounds to separate in the yields indicated and in satisfactory condition for use in the next step. The analytical samples were obtained after one or two crystallizations from the solvents noted.

β-(Amino-2,4,6-triiodophenyl)-α-ethylpropionic Acid.—A solution of 34.0 g. of β-(*m*-aminophenyl)-α-ethylpropionic acid in 110 ml. of 6 *N* hydrochloric acid was warmed to 70°. Then a solution of 94.3 g. of iodine monochloride in 220 ml. of 6 *N* hydrochloric acid was added in one portion. A dark oil separated almost immediately. After one hour 500 ml. of water was added over a fifteen-minute period. The oil solidified. While the temperature was kept at 70°, 1000 ml. of water and 28.5 g. of iodine monochloride was added during the next five hours. The whole was cooled and filtered. The crude, dried solid which weighed 103 g. was crystallized from chloroform–ligroin. It then weighed 74 g. and melted at 147–150°. After three crystallizations from dilute methanol (Darco was used in the first two) there was obtained 42 g. of cream-colored needles melting at 155.2–157° (cor.) (42%).

Anal. Calcd. for $C_{11}H_{13}I_2NO_2$: I, 66.68. Found: I, 66.70.

β-(4-Amino-3,5-diiodophenyl)-α-propylpropionic Acid (Method A).—A solution of 26.2 g. of iodine monochloride in 200 ml. of 6 *N* hydrochloric acid was warmed to 70°. To the stirred solution there was added over a period of ninety minutes a solution of 16.0 g. of β-(*p*-aminophenyl)-α-propylpropionic acid in 440 ml. of 0.12 *N* hydrochloric acid. After one-half hour an oil separated. It gradually solidified. After one hour more at 70° the mixture was cooled, diluted with 500 ml. of water and saturated with sulfur dioxide. The product was filtered and dried. It melted at 111–113° and amounted to 32 g. It was recrystallized from dilute methanol with practically no change in melting point. The compound (29.5 g.) was dissolved in ether and treated with a slight excess of morpholine. The salt was filtered and recrystallized twice from benzene–ligroin. The pink plates melted at 130–132°. The crystals were dissolved in methanol and the solution diluted with water. It was then saturated with sulfur dioxide and further diluted to the point of incipient crystallization. On slow cooling 19.0 g. of the product separated which melted at 121–121.8° (cor.).

Anal. Calcd. for $C_{12}H_{15}I_2NO_2$: C, 31.39; H, 3.29. Found: C, 31.52; H, 3.18.

β-(4-Amino-3,5-diiodophenyl)-α-ethylpropionic Acid (Method B).—A solution of 87.4 g. of iodine monochloride in 150 ml. of 8 *N* hydrochloric acid and 300 ml. of chloroform was stirred and warmed to maintain a gentle reflux. A solution of β-(*p*-aminophenyl)-α-ethylpropionic acid in dilute hydrochloric acid prepared by acidifying the reduction mixture from 50 g. of α-ethyl-*p*-nitrocinnamic acid was added over a forty-minute period. After refluxing for forty minutes more the two-phase system was cooled and the layers separated. The aqueous portion was washed with chloroform. The combined organic layers were washed with two 150-ml. portions of water, two 120-ml. portions of 5% aqueous sodium hydrosulfite and again with water. The chloroform solution was dried over Drierite and diluted with petroleum ether. On standing 66.5 g. of the crude diiodo acid separated. After recrystallization from dilute methanol with the aid of Darco there was obtained 58.7 g. of pure product which melted at 114.2–115.1° (cor.).

Summary

1. The preparation of several β-(4-amino-3,5-diiodophenyl)-α-alkylpropionic acids has been described. These were obtained by iodination of the corresponding α-alkyl-β-(aminophenyl)-propionic acids which in turn were secured by catalytic reduction of the α-alkyl-*p*-nitrocinnamic acids.

2. α-Ethyl-β-(*m*-aminophenyl)-propionic acid gave a triiodo acid when treated with iodine monochloride.

RENSSELAER, NEW YORK RECEIVED MAY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE, SCHOOL OF MEDICINE]

Reaction of Aliphatic Amines with 3-Nitro-4-chlorophenylarsonic Acid

BY ROBERT L. MCGEACHIN

In the study of the preparation of organic arsenicals of possible therapeutic use against protozoa and spirochetes, it has been found[1,2,3,4] that 3-nitro-4-chlorophenylarsonic and 3-nitro-4-bromophenylarsonic acids will react with certain amines and phenols to give 3-nitro-4-alkylaminophenylarsonic and 3-nitro-4-phenoxyphenylarsonic acids. There are a number of amines that have not been used in this type reaction, however, particularly the polyethylenepolyamines, so it was decided to investigate the preparation of these substituted 4-amino compounds.

In all cases the products of these condensation reactions were yellow solids, soluble in dilute alkali giving blood-red solutions. The product obtained from tetraethylenepentamine, however, precipitated from solution as a heavy oil and resisted all attempts to crystallize it. For this reason it was isolated as the dipicrate. The products obtained from aminoethylethanolamine and aminoethylmorpholine were very soluble in water, probably due to the character of the side-chains, so that the yields here were low and the products were isolated as hydrates. In the condensation with dipropylenetriamine the product obtained constantly contained more arsenic than the theoretical amount for the product from one mole of amine and one mole of arsonic acid. Though several runs with increasing amounts of amine were tried, the desired product was not obtained.

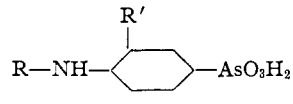
The condensation of 2-amino-2-methyl-1-propanol with 3-nitro-4-chlorophenylarsonic acid did not proceed satisfactorily under standard conditions but was successful when an excess of the amine was heated with the arsonic acid at 160–170° for six hours. Apparently the amino group in 2-amino-2-methyl-1-propanol, which is linked to a tertiary carbon atom, is not reactive enough to allow condensation in aqueous solution at the lower temperatures. An attempt at a similar condensation using 2-amino-2-methyl-1,3-propanediol was unsuccessful.

(1) Maclay and Hamilton, THIS JOURNAL, **54**, 3310 (1932).
(2) Fourneau and Funke, *Bull. soc. chim.*, **43**, 889 (1928).
(3) King, *J. Chem. Soc.*, 1094 (1927).
(4) Cragoe and Hamilton, THIS JOURNAL, **67**, 536 (1945).

Experimental

General Procedure for the Condensation of 3-Nitro-4-chlorophenylarsonic Acid with Amines in Aqueous Alkali.—Five grams of 3-nitro-4-chlorophenylarsonic acid, 15 ml. of 10% sodium hydroxide, 10 ml. of water and 3–5 ml. of the amine were heated, under reflux, at 135–140° for three to eight hours. The solution was cooled, made neutral to congo red with concd. hydrochloric acid. The product precipitated out as a yellow solid (except in the case of tetraethylenepentamine where the product was a thick brown oil). The product was redissolved in 5% sodium hydroxide, the solution charcoaled, filtered, and the yellow solid reprecipitated by addition of concd. hydrochloric acid to the congo red neutral point. The

TABLE I



R	R'	Formula	% Arsenic[a] Calcd.	Found
$-CH_2CH_2NHCH_2CH_2NH_2$	NO_2	$C_{10}H_{17}O_5N_4As$	21.53	21.64
$-CH_2CH_2NHCH_2CH_2NH_2$	NH_2	$C_{10}H_{19}O_3N_4As$	23.57	23.48
$-(CH_2CH_2NH)_2CH_2CH_2NH_2$	NO_2	$C_{12}H_{22}O_5N_5As$	19.15	18.94
$-(CH_2CH_2NH)_2CH_2CH_2NH_2$	NH_2	$C_{12}H_{24}O_3N_5As$	20.77	20.98
$-(CH_2CH_2NH)_3CH_2CH_2NH_2$	NO_2	$C_{26}H_{33}O_{19}N_{12}As$[b]	8.41	8.60
$-CH_2CH_2NHCH_2CH_2OH$	NO_2	$C_{10}H_{16}O_6N_3As$[d]	20.41	20.29
$-CH_2CHNH_2CH_3$	NO_2	$C_9H_{14}O_5N_3As$	23.49	23.17
$-CH_2CHNH_2CH_3$	NH_2	$C_9H_{16}O_3N_3As$	25.95	25.61
$-CH_2CHOHCH_3$	NO_2	$C_9H_{13}O_6N_2As$	23.41	23.30
$-CH_2CH_2NC_4H_8O$	NO_2	$C_{12}H_{18}O_6N_3As$[d]	19.08	18.75
$-CH_2CH_2NC_4H_8O$	NO_2	$C_{18}H_{21}O_{12}N_6As$[c]	12.40	11.93
$-CH_2CH=CH_2$	NO_2	$C_9H_{11}O_5N_2As$	24.81	24.56
$-CH_2CH=CH_2$	NH_2	$C_9H_{13}O_3N_2As$	27.54	27.36
$-CH_2CHOHCH_2NH_2$	NO_2	$C_9H_{14}O_6N_3As$	22.37	21.98
$-C(CH_3)_2CH_2OH$	NO_2	$C_{10}H_{15}O_6N_2As$	22.45	22.39
$-C(CH_3)_2CH_2OH$	NH_2	$C_{10}H_{17}O_4N_2As$	24.67	24.17

[a] Arsenic was determined by a modification of the method of Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930). [b] Isolated as the dipicrate. [c] Isolated as the monopicrate. [d] Plus one molecule of water.