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Iodinated 1-Phenyl*cyclo*alkane-1-carboxylic Acids

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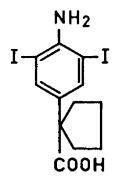
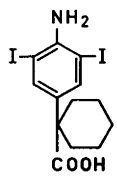
Dedicated to Professor *Holger Erdtman* on his 60th birthday

Some iodinated amino- and hydroxysubstituted 1-phenyl*cyclo*alkane-1-carboxylic acids have been synthesised for investigation as X-ray contrast media.

Iodinated phenylsubstituted alkanoic acids are used clinically as diagnostic agents for visualization of X-rays [1]. The present paper describes the preparation of some related compounds, *viz.* iodinated amino- and hydroxy-substituted 1-phenyl*cyclo*alkane-1-carboxylic acids (I—IV).



I



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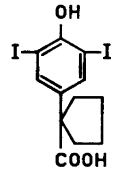
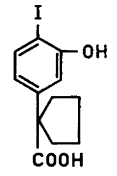
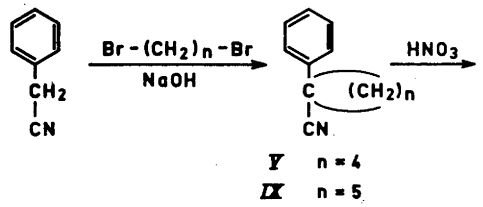


III



IV

The aminosubstituted acids were prepared according to the following sequence of reactions:



V n = 4
IX n = 5

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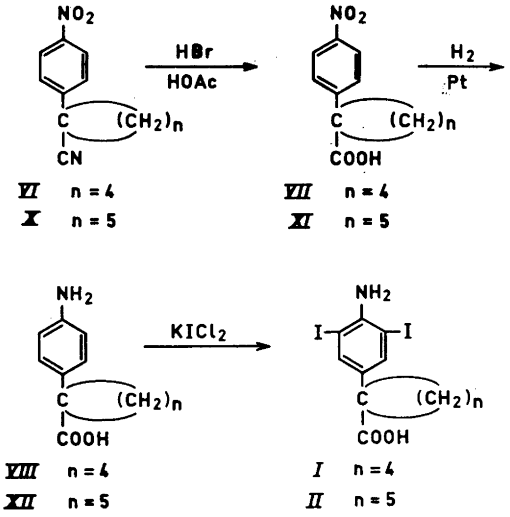
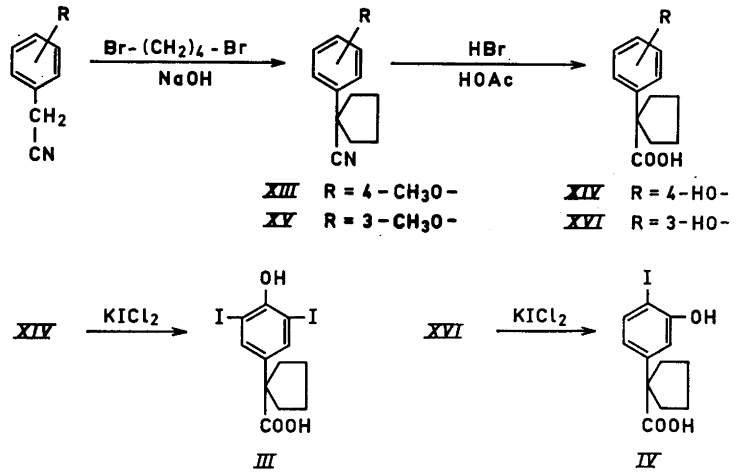


The hydroxysubstituted acids were prepared from *m*- and *p*-methoxybenzylcyanide as follows:



Iodination of 1-(3-hydroxyphenyl)-*cyclo*pentane-1-carboxylic acid yielded only a monoiodo derivative and not a di- or triiodosubstituted product as is the case with several (3-hydroxyphenyl)-alkanoic acids [2]. However, the 2- and 6-positions in the benzene ring of the 1-(3-hydroxyphenyl)-cyclopentane-1-carboxylic acid are hindered sterically by the bulky *cyclo*pentyl group, as is evident from examination of molecular models. We have therefore assumed, that the iodine has entered the 4-position.

The compounds I—IV were tested pharmacologically. No affinity for any special organ was observed, and their toxicities were rather high.

EXPERIMENTAL

*1-Phenyl*cyclo*pentane-1-carbonitrile (V).* This compound has been prepared from benzyl cyanide and 1,4-dibromobutane in the presence of sodium amide [3]. We found that sodium amide could be replaced by sodium hydroxide. A mixture of benzyl cyanide (117 g, 1 mole), 1,4-dibromobutane (216 g, 1 mole) and powdered sodium hydroxide (200 g, 5 mole) was heated at 100—110° in an oil bath with vigorous mechanical stirring. After about half an hour a violent reaction started, which subsided in a few minutes. Stirring was continued at the same temperature for 3 h. The hot reaction mixture was then poured on *ca.* 1 kg of crushed ice. The organic layer was separated and the aqueous solution was extracted with ether (2 × 100 ml). The organic layer and the ether extract were combined and dried over sodium sulphate. The solvent was evaporated and the residue was distilled *in vacuo* giving a colourless oil (132 g, 77 %), b.p. 139—140°/10 mm (lit.[3] 148—153°/20 mm); n_D^{22} 1.5333.

1-(4-Nitrophenyl)-cyclo*pentane-1-carbonitrile (VI).* The nitrile V (34.2 g) was added dropwise with stirring to nitric acid (115 ml, *d* 1.50) at a temperature of −10° to −15° during one hour. The stirring was continued at 0° for 2 h, and the mixture was then poured on 250 g of crushed ice. The precipitated nitro compound was collected, washed with water and crystallised from ethanol, m.p. 76—78° (29 g, 67 %). Recrystallisation from the same solvent raised the m.p. to 77.5—78.5°. (Found: C 66.5; H 5.37; N 13.2. Calc. for $C_{12}H_{12}N_2O_2$: C 66.6; H 5.59; N 13.0).

1-(4-Nitrophenyl)-cyclo*pentane-1-carboxylic acid (VII).* The nitrile VI (29 g) was refluxed for 3 h with a mixture of 48 % hydrobromic acid (150 ml) and glacial acetic acid (100 ml). During the reaction the acid formed gradually crystallised. After cooling the product was collected (28 g, 89 %); m.p. 181—182°. (Found: C 60.9; H 5.59. Calc. for $C_{12}H_{13}NO_4$: C 61.3; H 5.57).

1-(4-Aminophenyl)-cyclo*pentane-1-carboxylic acid (VIII).* The nitro compound VII (26 g) was dissolved in ethanol (250 ml) and hydrogenated at 50° in a Parr hydrogenation apparatus with PtO_2 as catalyst at a pressure of 3—4 kg/cm². The calculated amount of hydrogen was consumed in one hour. During the hydrogenation the amino compound partly separated as white needles. The ethanol was removed *in vacuo* and the residue was dissolved in 2 N hydrochloric acid and the solution was filtered through theorite. The solution was made alkaline with ammonia, and the reaction product was then precipitated with acetic acid and recrystallised from ethanol (22 g, 97 %), m.p. 197—199°. (Found: C 70.0; H 7.49; N 6.79. Calc. for $C_{12}H_{15}NO_2$: C 70.2; H 7.37; N 6.82).

1-(4-Amino-3,5-diiodophenyl)-cyclo*pentane-1-carboxylic acid (I).* The preceding amino compound (20.5 g) was dissolved in 0.1 N hydrochloric acid (4 l) and 2 M potassium iodochloride solution (120 ml, prepared according to the method of Larsen *et al.*[4]) was added with vigorous stirring in one portion. The reaction product started to separate immediately. Stirring was continued for 2 h, and saturated sodium hydrogen sulphite solution was then added in order to remove excess of iodine. The product was collected (40 g, 87 %) and recrystallised from ethanol to give yellow plates, m.p. 180—181° (decomp.). (Found: C 31.5; H 2.84; I 55.1. Calc. for $C_{12}H_{13}I_2NO_2$: C 31.5; H 2.87; I 55.5).

*1-Phenyl*cyclo*hexane-1-carbonitrile (IX).* This compound was prepared from benzyl cyanide, 1,5-dibromopentane and sodium hydroxide by the same method as described for the *cyclo*pentyl analogue V. Formation of solid condensation products lowered the yield to 30 %. The nitrile hade b.p. 148—149°/10 mm; n_D^{22} 1.5334 (lit.[5] b.p. 110—115°/0.7 mm; n_D^{25} 1.5327).

1-(4-Nitrophenyl)-cyclo*hexane-1-carbonitrile (X)* was obtained by nitration of the foregoing nitrile as described for VI. Yield 60 %, m.p. 73—74° (from ethanol). (Found: C 67.6; H 6.11. Calc. for $C_{13}H_{14}N_2O_2$: C 67.8; H 6.13).

1-(4-Nitrophenyl)-cyclo*hexane-1-carboxylic acid (XI).* The nitrile X was refluxed for 3 h with 48 % hydrobromic acid (200 ml) and glacial acetic acid (150 ml). After cooling the separated reaction product was filtered off and recrystallised from ethanol to give colourless crystals (33 g, 78 %) of m.p. 175—177°. This acid has earlier been prepared in 33 % yield by nitration of 1-penyl*cyclo*hexane-1-carboxylic acid [6], m.p. 176—177°.

1-(4-Aminophenyl)-cyclo*hexane-1-carboxylic acid (XII).* The above nitro compound XI (25 g) was hydrogenated in a Parr hydrogenation apparatus as described for compound

VIII. The solution of the amino compound in hydrochloric acid was used directly in the next step. Only one tenth of the solution was worked up and the acid XII was isolated and characterised. It melted at 201—203° after recrystallisation from ethanol. (Found: C 70.7; H 7.40; N 6.38. Calc. for $C_{13}H_{17}NO_2$: C 71.2; H 7.28; N 6.39).

1-(4-Amino-3,5-diiodophenyl)-cyclo*hexane-1-carboxylic acid (II)*. The solution of XII in hydrochloric acid obtained in the foregoing experiment was diluted to 4 l and 2 M potassium iododichloride solution (150 ml) was added. The reaction mixture was stirred at room temperature for 2 h and was then decolourised with saturated sodium hydrogen sulphite solution. The reaction product was collected and recrystallised from ethanol giving light yellow crystals (20 g, 47 % calc. on XI), m.p. 177—178°. (Found C 33.1; H 3.42; I 53.6; N 3.22. Calc. for $C_{13}H_{15}I_2NO_2$: C 33.1; H 3.21; I 53.9; N 2.97).

1-(4-Methoxyphenyl)-cyclo*pentane-1-carbonitrile (XIII)*. 4-Methoxybenzyl cyanide was alkylated with 1,4-dibromobutane in the presence of sodium hydroxide as described for the nitrile V. Yield 76 %, b.p. 121—122°/0.2 mm; n_D^{20} 1.5382. The compound has earlier been prepared [7] using sodium amide as condensation agent.

1-(4-Hydroxyphenyl)-cyclo*pentane-1-carboxylic acid (XIV)*. The nitrile XIII was hydrolysed in the usual way by refluxing it with 48 % hydrobromic acid and glacial acetic acid. Yield 65 %, m.p. 194—196° (from ethanol-water). (Found: C 69.4; H 7.00. Calc. for $C_{12}H_{14}O_3$: C 69.9; H 6.84).

1-(4-Hydroxy-3,5-diiodophenyl)-cyclo*pentane-1-carboxylic acid (III)*. The foregoing acid (31 g) was dissolved in water (7.5 l) at 60°. 2 M potassium iododichloride solution (230 ml) was added, and the mixture was stirred at this temperature for one hour. Excess iodine was removed by addition of sodium hydrogen sulphite solution, and the reaction product was then collected and recrystallised from ethanol-water to give light yellow crystals (35 g, 51 %) of m.p. 205—206°. (Found: C 31.5; H 2.63; I 54.8. Calc. for $C_{12}H_{12}I_2O_3$: C 31.5; H 2.64; I 55.4).

1-(3-Methoxyphenyl)-cyclo*pentane-1-carbonitrile (XV)* was prepared from 3-methoxybenzyl cyanide, 1,4-dibromobutane and sodium hydroxide as described for the nitrile V. Yield 83 %, b.p. 113—114°/ 0.2 mm; n_D^{22} 1.5365. (Found: C 77.7; H 7.48; N 6.90. Calc. for $C_{13}H_{15}NO$: C 77.6; H 7.51; N 6.96).

1-(3-Hydroxyphenyl)-cyclo*pentane-1-carboxylic acid (XVI)*. The nitrile XV was hydrolysed in the usual way by refluxing it with 48 % hydrobromic acid and glacial acetic acid. Yield 68 %, m.p. 168—169° after recrystallisation from water. (Found: C 69.3; H 6.80. Calc. for $C_{12}H_{14}O_3$: C 69.9; H 6.84).

1-(3-Hydroxy-4-iodophenyl)-cyclo*pentane-1-carboxylic acid (IV)*. The foregoing acid (5 g) was dissolved in glacial acetic acid (60 ml) to which had been added some conc. hydrochloric acid (5 ml). 2 M potassium iododichloride solution (50 ml) was then added, and the reaction mixture was heated on the steam bath for 4 h. After cooling, the product which had precipitated was collected. It was then dissolved in alkali and treated with sodium hydrogen sulphite to remove excess of iodine. Precipitation with acid yielded a crystalline product, which was purified further by recrystallisation from ethanol-water to give almost colourless crystals (5 g, 63 %) of m.p. 192—194°. Analysis indicated that only one iodine atom had entered the benzene ring. (Found: C 43.9; H 4.08; I 37.9. Calc. for $C_{12}H_{13}IO_3$: C 43.4; H 3.94; I 38.2).

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