five minutes in order to hydrolyze any C-3 enol ester.[6] The solution was concentrated *in vacuo* to half volume and extracted with ether. The ether solution was washed with 10% sodium hydroxide solution, water and dried over sodium sulfate. After taking to dryness the residue was taken up in 10 ml. of anhydrous ether by warming. On standing, prisms of progesterone separated and after cooling for forty-eight hours there was obtained 1.90 g. (60%), m. p. 118–122°. Recrystallization from a small volume of acetone raised the m. p. to 125–128° (prisms). Mixed with authentic progesterone there was no m. p. depression.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 80.09; H, 9.69.

(6) Westphal, *Ber.*, **70**, 2128 (1937).

Summary

1. Utilizing stigmasterol as a starting material a simplified procedure for the partial synthesis of progesterone is described. The number of steps has been reduced in comparison with present published methods and the yields for the types of reaction involved are excellent.

2. The enol acetates of 3-acetoxybisnor-5-cholenaldehyde and of 3-ketobisnor-4-cholenaldehyde have been prepared as new intermediates in the above synthesis.

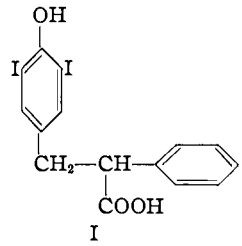
KALAMAZOO, MICHIGAN RECEIVED OCTOBER 10, 1949

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

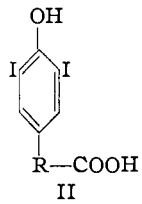
X-Ray Diagnostics. II. Cholecystographic Agents[1]

BY DOMENICK PAPA, ERWIN SCHWENK, HILDA BREIGER AND VIRGINIA PETERSON

Shortly after the discovery by Dohrn and Diedrich that α-phenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid[2] (I) was clinically efficacious as an oral cholecystographic agent,[3] we undertook an extended study on the correlation of chemical structure and cholecystographic property of several series of iodinated compounds.[4] This paper describes the synthesis and pharmacological data for a series of 3,5-diiodo-4-hydroxyphenyl aliphatic and alicyclic acids of general formula II, wherein R is a saturated or unsaturated straight or branched alkyl radical having 1 to 9 carbon atoms or an alkyl-alicyclic radical, the alicyclic group having 5 to 6 carbon atoms in the ring.

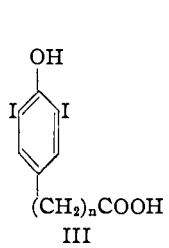


I

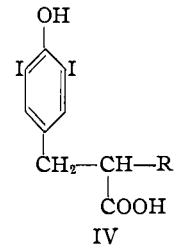


II

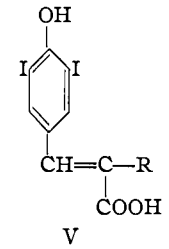
Three series of compounds[5] within the scope of formula II were synthesized for pharmacological investigation and may be represented by formulas III, IV and V, wherein n is an integer from 1 to 9 and R is an alicyclic group or a straight chain alkyl group having 1 to 8 carbon atoms.



III



IV



V

The diiodo compounds of formula III were secured from the known ω-(*p*-hydroxyphenyl) aliphatic acids[6] by iodination with potassium triiodide in alkaline solution. The iodinated acids IV and V, wherein R is aliphatic, were obtained as outlined in the equations.

The syntheses of a number of acids of formulas III and IV have been outlined by Natelson, *et al.*[5a]; but in no instance are yields indicated or any physical constants reported for either the intermediates or final products. Furthermore, the initial step in the synthesis of the acids IV as described by Natelson involves the condensation of *p*-methoxybenzaldehyde with the anhydrous alkali metal salt of the appropriate aliphatic acid at 100° for four hours. Under these conditions, we have not been able to secure any of the Perkin condensation products.[7] However, with the more reactive *p*-hydroxybenzaldehyde at 135–140° for thirty to forty

(1) Presented in abstract before the Division of Medicinal Chemistry, American Chemical Society Meeting, Atlantic City, September 21, 1949.

(2) (a) Dohrn and Diedrich, *Deutsche Med. Wchnschr.*, **66**, 1133 (1940); (b) Grunke and Finger, *Klin. Wchnschr.*, **19**, 1187 (1940); (c) Junkmann, *ibid.*, **20**, 125 (1941); (d) Dohrn and Diedrich, U. S. Patent 2,345,384, March 28, 1944.

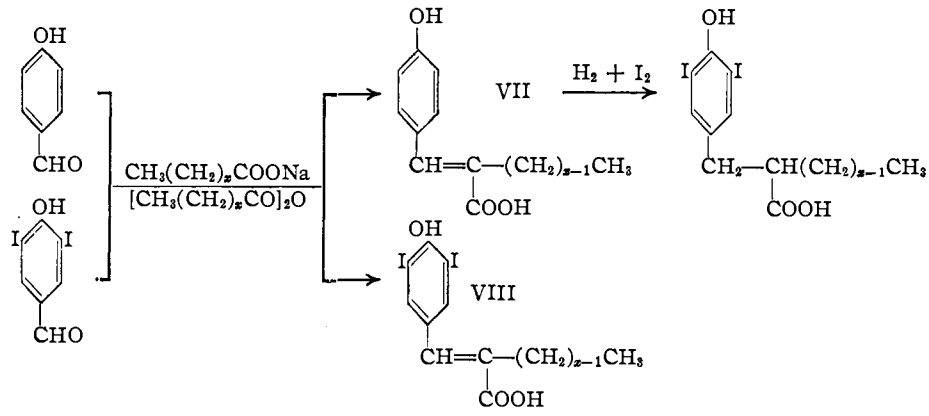
(3) This compound, Priodax, has been extensively used clinically as a gall bladder contrast agent: (a) Einsel and Einsel, *Am. J. Digest. Dis.*, **10**, 206 (1943); (b) Vaughan and Eichwald, *Radiology*, **43**, 578 (1948); (c) Dannenberg, *Am. J. Roent.*, **51**, 328 (1944).

(4) For previous investigations on cholecystographic agents reported from this Laboratory, see (a) Schwenk and Papa, U. S. Patent 2,436,270, Feb. 17, 1948; (b) Papa, *Arch. Biochem.*, **23**, 163 (1949); (c) Papa, Schwenk and Klingsberg, THIS JOURNAL, **72**, 2623 (1950); (d) Papa, *ibid.*, in press.

(5) Other investigators have reported on the synthesis and pharmacology of compounds within the scope of formula II: (a) Natelson, Kramer and Tekel, U. S. Patent 2,400,433, May 14, 1946; (b) Epstein, Natelson and Kramer, *Am. J. Roent.*, **56**, 201 (1946); (c) Grayzel and Natelson, *J. Lab. and Clin. Med.*, **32**, 292 (1947); (d) Pratt, Hoppe and Archer, *J. Org. Chem.*, **13**, 576 (1948).

(6) Papa, Schwenk and Hankin, THIS JOURNAL, **69**, 3018 (1947).

(7) Compare, "Organic Reactions," "The Perkin Reaction," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 224, 251.



hours, fair yields of crude condensation products were obtained in all the reactions studied. As reported for cycloalkene,[8] aryloxy and arylmercapto[9] and naphthyl and tetralyl[10] acetic acids, aliphatic carboxylic acids condense in fair yield with aromatic aldehydes in the presence of equimolecular amounts of anhydrous triethylamine. Anhydrous potassium acetate was not employed as condensing catalyst in this investigation since it is known to undergo an exchange reaction with the aliphatic acid anhydrides to yield mixtures of cinnamic acid and α-alkylcinnamic acids.

The reduction of the substituted cinnamic acids VII to the propionic acids proceeded in practically quantitative yield by the Raney alloy-aqueous alkali method.[11] Iodination to the acids IV was carried out as described for the isomeric acids III.

The Perkin condensation of the 3,5-diiodo-4-hydroxybenzaldehyde and the anhydrous alkali metal salts of the aliphatic acids proceeded smoothly to give compounds VIII in fair yields. In the case of the α-methyl (VIII, $x = 0$) and the α-*n*-butyl (VIII, $x = 4$) compounds, the corresponding 4-propionoxy and 4-caproxy derivatives were secured notwithstanding mild alkaline hydrolysis of the crude Perkin condensation product. These esters, however, were converted to the free hydroxy compounds by prolonged hydrolysis with hot 10% aqueous sodium hydroxide.

The intermediates for the cyclopentyl and the cyclohexyl compounds of formula IV were prepared by the Perkin reaction[12] employing Δ^1-cyclopentenyl and Δ^1-cyclohexenylacetic acids, respectively, followed by reduction of the diene condensation products with Raney alloy and aqueous alkali[11]. Iodination to the cyclopentyl and cyclohexyl compounds of general formula IV was carried out as described for compounds of general formula III. The Δ^1-cyclohexenyl-3,5-diiodo-4-hydroxycinnamic acid (general formula V) was secured by the Perkin condensation of 3,5-diiodo-4-hydroxybenzaldehyde and cyclohexylideneacetic acid.

It is of interest to note that all the compounds of general formula III and IV, except the first member of the series of formula III, had relatively low melting points. In addition, these compounds and the mono- and di-sodium salts exhibited solubility properties in water and alcohol reminiscent of the fatty acids. In contrast, the compounds of formula V melted between 196–246° and in general did not show the solubility characteristics of compounds of formula III and IV.

Pharmacology.—Preliminary toxicity data for the compounds are as follows: oral LD/50 in mice for compounds 1, 2, 3, 5, 9, 11, 12, 13, 16, 17 and 18, greater than 5 mg./g.; compounds 4, 8, 10, 14, 15 and 19, 2 to 4 mg./g.; compound 7, 1 mg./g.

The cholecystographic property of the compounds was studied in dogs, each compound being administered orally in 2-g. doses in gelatin capsules. "Priodax," α-phenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid (I), was used as standard.

In general, the compounds of formula III gave poor gall bladder contrast, particularly compounds 6, 7 and 9. Although compound 8 gave a more intense shadow than the homologous compounds of this series, the dog vomited and was disturbed for twelve hours following administration of the drug.

Only compounds 12, 13, 14, 17 and 18 of formula IV gave adequate gall bladder contrast. However, the animal data[5b] indicated that compounds 12, 13 and 14, in carefully controlled experiments, did not give density of shadow equal to that obtained with I. Compounds 17 and, particularly, 18 were well tolerated and gave gall bladder contrast comparable to that of I. The other members of this series either did not concentrate in the gall bladder or were preferentially excreted by the colon.

Compounds of general formula V gave fair gall bladder contrast, but without exception poor absorption of the compounds resulted in interfering shadows in the cholecystograms. The animal data for these compounds was confirmed by a limited clinical study of compound 2.

Experimental

The Perkin syntheses were carried out in a three-necked flask equipped with stirrer, thermometer and condenser

(8) Schwenk and Papa, THIS JOURNAL, **67**, 1432 (1945).
(9) Papa and Schwenk, *ibid.*, **69**, 3022 (1947).
(10) Papa, Breiger and Peterson, *J. Org. Chem.*, **14**, 362 (1949).
(11) Schwenk, Papa, Whitman and Ginsberg, *ibid.*, **9**, 175 (1944).
(12) (a) Ref. 8; (b) Schwenk and Papa, U. S. Patent 2,469,415, May 10, 1949.

carrying a calcium chloride tube. The caprylic and capric acids were obtained from Neo Fat 7 and Neo Fat 15, respectively (Armour and Co., Chicago, Ill.), by fractionation *in vacuo* using a 60-cm. Vigreux column, the foreruns and residues being discarded. The caproic, heptylic, caprylic and capric anhydrides were secured by the reaction of the acids and the corresponding acid chlorides in pyridine.[13] The 3,5-diiodo-4-hydroxybenzaldehyde was secured by the reaction of iodine monochloride and *p*-hydroxybenzaldehyde in hydrochloric acid solution.[14] The iodine analyses[15] reported herein and the reduction of the substituted cinnamic acids were carried out using the Raney alloy–aqueous alkali method.[11] The yields reported herein represent single experimental runs and not the maximum obtainable under the conditions of the reactions. All melting points are corrected.

(1) α-Methyl-3,5-diiodo-4-hydroxycinnamic acid: a mixture of 187 g. (0.5 mole) of 3,5-diiodo-4-hydroxybenzaldehyde, 56 g. (0.5 mole) of freshly fused potassium propionate and 195 g. (1.5 moles) of propionic anhydride was heated for twenty-four hours at 120–125°. The reaction mixture was cooled to 60–70° and water cautiously added to decompose the excess anhydride. After pouring the reaction mixture into 1500 cc. of 5% hydrochloric acid, the solid which separated was filtered and then dissolved in dilute sodium hydroxide. The alkaline solution was treated with Norite, filtered and the filtrate acidified. The crude α-methyl-3,5-diiodo-4-propionoxycinnamic acid was obtained in a yield of 191 g. (78%), m. p. 176–180°; recrystallized from benzene for analysis, m. p. 190–191°.

Anal. Calcd. for $C_{13}H_{11}O_4I_2$: C, 32.09; H, 2.49. Found: C, 32.21; H, 2.57.

Hydrolysis of the propionoxy derivative with hot 10% sodium hydroxide gave the hydroxy compound which after recrystallization from chloroform–petroleum ether melted at 247–248° with decomposition.

Anal. Calcd. for $C_{10}H_8O_3I_2$: C, 27.91; H, 1.88. Found: C, 28.27; H, 1.52.

(2) α-Ethyl-3,5-diiodo-4-hydroxycinnamic acid: this compound was secured as described for the α-methyl compound except that anhydrous potassium butyrate and butyric anhydride were used and the reaction mixture was heated for thirty hours at 135°. The crude diiodo acid was dissolved in 10% sodium hydroxide, the solution heated for one hour on the steam-bath, filtered and then acidified; yield 55%, m. p. 179–186°; recrystallized from benzene for analysis, m. p. 209–210°.

Anal. Calcd. for $C_{11}H_{10}O_3I_2$: C, 29.73; H, 2.27. Found: C, 30.17; H, 2.07.

(3) α-*n*-Butyl-3,5-diiodo-4-hydroxycinnamic acid: a mixture of 14.8 g. (0.1 mole) of anhydrous sodium caproate, 37.4 g. (0.1 mole) of 3,5-diiodo-4-hydroxybenzaldehyde and 70 g. (0.33 mole) of caproic anhydride was heated at 130–140° for thirty hours. The reaction mixture was poured into 5% hydrochloric acid and the excess caproic anhydride decomposed. The crude solid reaction product was either filtered or extracted with chloroform. In the latter case, the caproic acid was removed by steam distillation. The crude α-*n*-butyl-3,5-diiodo-4-caproxycinnamic acid was obtained in a yield of 24 g. (42%), m. p. 166–170°; recrystallized from chloroform–petroleum ether for analysis, m. p. 181–182°.

Anal. Calcd. for $C_{19}H_{24}O_4I_2$: C, 40.00; H, 4.24. Found: C, 40.37; H, 4.52.

Hydrolysis with hot 10% sodium hydroxide gave the hydroxy diiodo acid, m. p. 220–221° after recrystallization from chloroform–petroleum ether.

Anal. Calcd. for $C_{13}H_{14}O_3I_2$: C, 33.04; H, 4.58. Found: C, 33.04; H, 4.56.

(4) α-*n*-Amyl-3,5-diiodo-4-hydroxycinnamic acid: the condensation of 187 g. (0.5 mole) of 3,5-diiodo-4-hydroxybenzaldehyde, 363 g. (1.5 moles) of heptylic anhydride and 76 g. (0.5 mole) of anhydrous sodium heptylate for thirty hours at 135° gave 49.2 g. (21%) of the cinnamic acid after hydrolysis melting at 200–202°; recrystallized from benzene for analysis, m. p. 208–209°.

Anal. Calcd. for $C_{14}H_{16}O_3I_2$: C, 34.56; H, 3.32. Found: C, 34.43; H, 3.73.

(5) α-*n*-Hexyl-3,5-diiodo-4-hydroxycinnamic acid: a mixture of 37.4 g. (0.1 mole) of 3,5-diiodo-4-hydroxybenzaldehyde, 16.6 g. of anhydrous sodium caprylate and 81 g. (0.3 mole) of caprylic anhydride was heated for thirty hours at 140–145°. The reaction mixture was worked up as described for the α-*n*-butyl compound and 25 g. (50%) of the crude cinnamic acid was obtained, m. p. 190–194°; recrystallized from aqueous alcohol for analysis, m. p. 195–196°.

Anal. Calcd. for $C_{15}H_{18}O_3I_2$: C, 36.02; H, 3.63. Found: C, 36.27; H, 3.76.

(6) 3,5-Diiodo-4-hydroxyphenylacetic acid: *p*-hydroxyphenylacetic acid[16] and the homologous acids were iodinated as follows[24]: To a solution of 0.1 mole of *p*-hydroxyphenylaliphatic acid in 800 cc. of 0.5 *N* sodium hydroxide, there was added dropwise with stirring a solution of 50.8 g. of iodine and 50.8 g. of potassium iodide in 250 cc. of water. The reaction mixture was then filtered through Supercel filter aid cooled to 0–5° and sufficient 5% sodium bisulfite solution slowly added with stirring until the mixture was acid to litmus paper. The crude iodinated acid was filtered, dissolved in 5% sodium bicarbonate solution, filtered, reprecipitated as described above and then recrystallized from aqueous ethanol, yield 92%, m. p. 216.5–217.5°; recrystallized from aqueous acetone for analysis, m. p. 218–219°.

Anal. Calcd. for $C_8H_6O_3I_2$: I, 62.85. Found: I, 62.51.

(7) γ-(3,5-Diiodo-4-hydroxyphenyl)-butyric acid was secured from γ-(*p*-hydroxyphenyl)-butyric acid[6] in quantitative yield; recrystallized from acetone–water, m. p. 105–106°, literature[5d] m. p. 105–107°.

Anal. Calcd. for $C_{10}H_{12}O_3I_2$: I, 58.70. Found: I, 58.70.

(8) ω-(3,5-Diiodo-4-hydroxyphenyl)-hexoic acid was obtained from ω-(*p*-hydroxyphenyl)-hexoic acid[6] in 96% yield; recrystallized from a mixture of acetone and water for analysis, m. p. 117–118°, literature[5d] m. p. 117–119°.

Anal. Calcd. for $C_{12}H_{16}O_3I_2$: I, 55.20. Found: I, 54.90.

(9) ω-(3,5-Diiodo-4-hydroxyphenyl)-capric acid was secured from ω-(*p*-hydroxyphenyl)-capric acid[6] in 88% yield, m. p. 78–79° after recrystallization from a mixture of acetone and water.

Anal. Calcd. for $C_{16}H_{24}O_3I_2$: I, 49.23. Found: I, 49.60.

(10) α-Methyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: a mixture of 52.4 g. (0.4 mole) of freshly fused potassium propionate, 48.8 g. (0.4 mole) of *p*-hydroxybenzaldehyde and 100 g. of propionic anhydride was heated for thirty hours at 130–135°. The reaction mixture was worked up as described for the unsaturated iodo compounds to yield 54 g. (75%) of α-methyl-*p*-hydroxycinnamic acid melting at 204–204.5° after recrystallization from aqueous ethanol. Reduction of the cinnamic acid gave a quantitative yield of α-methyl-β-(*p*-hydroxyphenyl)-propionic acid, m. p. 102–102.5° after recrystallization from water; neut. equiv. 180; found 179.5.

Iodination as described for the isomeric acids yielded the diiodo acid in quantitative yield, m. p. 111–114°; recrystallized for analysis from a mixture of chloroform and petroleum ether, m. p. 118–119°.

Anal. Calcd. for $C_{10}H_{10}O_3I_2$: I, 58.70. Found: I, 58.49.

(11) β-Methyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: the requisite intermediate, β-methyl-β-(*p*-hydroxyphenyl)-propionic acid was secured by demethyla-

(13) *Org. Syn.*, **26**, 1 (1946).

(14) Dohrn and Diedrich, U. S. Patent 2,116,104, May 3, 1938.

(15) Schwenk, Papa and Ginsberg, *Ind. Eng. Chem., Anal. Ed.*, **15**, 376 (1943).

(16) Schwenk and Papa, *J. Org. Chem.*, **6**, 801 (1946).

tion of the corresponding methoxy compound[16] with hydrobromic and acetic acids, m. p. 136–137° after recrystallization from water; neut. equiv. 180; found 180. The diiodopropionic acid was obtained in a crude yield of 94%, m. p. 116–119°; recrystallized from chloroform–petroleum ether, m. p. 122–123°.

Anal. Calcd. for $C_{10}H_{10}O_3I_2$: I, 58.70. Found: I, 59.04.

(12) α-Ethyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: the intermediate α-ethyl-*p*-hydroxycinnamic acid was secured as described for the homologous α-methyl compound by using anhydrous potassium butyrate and butyric anhydride and heating the reaction mixture for thirty-five hours at 135°. After decomposing the excess anhydride, the butyric acid was removed by steam distillation. The crude α-ethyl compound was obtained in a yield of 61%, m. p. 152–153°; recrystallized from water for analysis, m. p. 154–155°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.71; H, 6.29. Found: C, 68.90; H, 6.51.

Reduction gave the α-ethyl-β-(*p*-hydroxyphenyl)-propionic acid in quantitative yield, m. p. 99–104°; recrystallized for analysis from water, m. p. 105–105.5°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.00; H, 7.26. Found: C, 68.26; H, 7.07.

Iodination was carried out as described, yield 90%, m. p. 102–104°. Recrystallized from chloroform–petroleum ether or carbon tetrachloride, m. p. 133–134°.

Anal. Calcd. for $C_{11}H_{12}O_3I_2$: C, 29.60; H, 2.91. Found: C, 29.31; H, 2.90.

(13) α-*n*-Butyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: the requisite intermediate, α-*n*-butyl-*p*-hydroxycinnamic acid, was obtained by heating for thirty-five hours at 135° a mixture of 77 g. (0.5 mole) of anhydrous potassium caproate, 61 g. (0.5 mole) of *p*-hydroxybenzaldehyde and 321 g. (1.5 moles) of caproic anhydride. After decomposing the excess anhydride with sodium hydroxide, the alkaline solution was acidified and extracted with chloroform. The chloroform extracts were dried, the solvent removed and the caproic acid distilled off *in vacuo*. The distillation residue was dissolved in sodium hydroxide, heated and then filtered. Acidification with hydrochloric acid gave 46 g. (42%) of crude α-*n*-butyl-*p*-hydroxycinnamic acid, m. p. 114–119°; recrystallized from benzene–petroleum ether for analysis, m. p. 123–124°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.87; H, 7.33. Found: C, 70.41; H, 7.39.

The condensation of 58 g. (0.5 mole) of caproic acid, 61 g. (0.5 mole) of *p*-hydroxybenzaldehyde, 321 g. (1.5 moles) of caproic anhydride and 50.5 g. (0.5 mole) of anhydrous triethylamine for thirty-five hours at 135° gave a 34% yield of the α-*n*-butyl-*p*-hydroxycinnamic acid melting at 115–117°.

The α-*n*-butyl-β-(*p*-hydroxyphenyl)-propionic acid was obtained in 88% yield from the cinnamic acid, m. p. 110–111° after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.39; H, 8.17. Found: C, 69.86; H, 7.97.

Iodination yielded the diiodo acid in 82% yield, m. p. 84–86°; recrystallized for analysis from benzene–petroleum ether, m. p. 91–91.5°.

Anal. Calcd. for $C_{13}H_{16}O_3I_2$: C, 32.90; H, 3.40. Found: C, 33.14; H, 3.52.

(14) α-*n*-Amyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: the α-*n*-amyl-*p*-hydroxycinnamic acid was obtained in 36% yield from *p*-hydroxybenzaldehyde, anhydrous potassium heptylate and heptylic anhydride as described for the α-*n*-butyl compound; m. p. 129–130° after recrystallization from benzene. The analytical sample melted at 131–132°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.75; H, 7.75. Found: C, 71.92; H, 7.81.

Reduction of the substituted cinnamic acid gave the α-*n*-amyl-β-(*p*-hydroxyphenyl)-propionic acid in 90% yield, m. p. 92–93.5°. Recrystallized from a mixture of ether and ligroin (b. p. 65–70°), the propionic acid was obtained as fine white needles, m. p. 97–98°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.15; H, 8.54. Found: C, 71.10; H, 8.63.

The diiodo acid was obtained in 76% yield, m. p. 84–85° after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{14}H_{18}O_3I_2$: I, 52.05. Found: I, 52.46.

(15) α-*n*-Hexyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: the α-*n*-hexyl-*p*-hydroxycinnamic acid was obtained by condensing 61 g. (0.5 mole) of *p*-hydroxybenzaldehyde, 83 g. (0.5 mole) of anhydrous sodium caprylate and 405 g. (1.5 moles) of caprylic anhydride for thirty-five hours at 140°. The crude α-*n*-hexyl-*p*-hydroxycinnamic acid was secured in 35% yield, m. p. 109–112°; recrystallized from benzene–petroleum ether, m. p. 123.5–124.5°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.53; H, 8.12. Found: C, 72.85; H, 8.37.

Reduction gave the α-*n*-hexyl-β-(*p*-hydroxyphenyl)-propionic acid in 93% yield, m. p. 84–88°; recrystallized from benzene–petroleum ether, m. p. 98–99°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 72.32; H, 8.93.

The diiodo acid was obtained in the usual manner in 76% yield; recrystallized from a mixture of ether–petroleum ether, m. p. 79.5–80.5°.

Anal. Calcd. for $C_{15}H_{20}O_3I_2$: C, 35.86; H, 4.02. Found: C, 36.07; H, 4.30.

(16) α-*n*-Octyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: the α-*n*-octyl-*p*-hydroxycinnamic acid was obtained in 22% yield by the condensation of *p*-hydroxybenzaldehyde, anhydrous potassium caprate and capric anhydride as described for the α-*n*-hexyl compound, m. p. 100–103°; recrystallized from chloroform–petroleum ether, m. p. 109–110°.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.89; H, 8.76. Found: C, 73.56; H, 9.09.

The α-*n*-octyl-β-(*p*-hydroxyphenyl)-propionic acid was obtained in 77% yield. After recrystallization from benzene–petroleum ether, the propionic acid melted at 102–103°.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.31; H, 9.42. Found: C, 73.33; H, 9.37.

The diiodo acid was secured in 68% yield, m. p. 70–72°; recrystallized from a mixture of ether–petroleum ether, m. p. 74–75°.

Anal. Calcd. for $C_{17}H_{24}O_3I_2$: C, 38.48; H, 4.56. Found: C, 38.76; H, 4.67.

(17) α-Cyclohexyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid was secured by iodination of α-cyclohexyl-β-(*p*-hydroxyphenyl)-propionic acid[11] as described for the aliphatic compounds, yield 84%, m. p. 150–152°. After dissolving the iodinated acid in 5% sodium bicarbonate solution, reprecipitating with sulfur dioxide, and drying, it was recrystallized from carbon tetrachloride or a mixture of chloroform–petroleum ether, m. p. 156.5–157.5°.

Anal. Calcd. for $C_{15}H_{18}O_3I_2$: I, 50.75. Found: I, 50.57.

(18) α-Cyclopentyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid: the requisite intermediate, α-cyclopentyl-β-(*p*-hydroxyphenyl)-propionic acid, was obtained from the corresponding cinnamic acid[8] by reduction with Raney alloy, yield 95%, m. p. 179–180°; recrystallized for analysis from aqueous ethanol, m. p. 180–181°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.75; H, 7.74. Found: C, 71.32; H, 7.63.

Iodination was carried out as described for the homologous cyclohexyl compound, yield 86%, m. p. 128–130°; recrystallized from aqueous acetone, m. p. 131–132°.

Anal. Calcd. for $C_{14}H_{16}O_3I_2$: I, 52.30. Found: I, 52.50.

(19) α-(Δ¹-Cyclohexenyl)-3,5-diiodo-4-hydroxycinnamic acid: a mixture of 17.9 g. (0.1 mole) of anhydrous potassium cyclohexylidineacetate,[8] 37.4 g. (0.1 mole) of 3,5-diiodo-4-hydroxybenzaldehyde and 100 cc. of acetic anhydride was heated for twenty-five to thirty hours at 105 to 110°. After decomposing the excess anhydride with water, the reaction mixture was poured on ice. The crude substituted cinnamic acid was taken up in 5% sodium carbonate solution, the solution filtered and the filtrate acidified with sulfur dioxide, yield 12.5 g. (25%), m. p. 201–203°; recrystallized from benzene–petroleum ether for analysis, m. p. 203–204°.

Anal. Calcd. for $C_{15}H_{14}O_3I_2$: C, 36.28; H, 2.84. Found: C, 36.39; H, 3.12.

Acknowledgment.—The authors wish to express their appreciation to Dr. Richard Tislow and Mrs. Annette La Belle for the pharmacological data reported herein.

Summary

Three series of aliphatic acids having the 3,5-diiodo-4-hydroxyphenyl radical have been synthesized for pharmacological study as cholecystographic agents. Preliminary toxicity data and cholecystographic properties of the compounds are discussed.

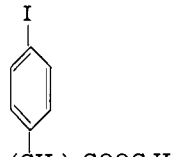
BLOOMFIELD, N. J. RECEIVED OCTOBER 8, 1949

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

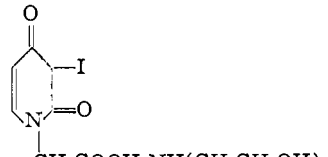
X-Ray Diagnostics. III. Iodinated Alkoxyaryl Aliphatic Acids and Ethyl Esters[1]

BY DOMENICK PAPA, ERWIN SCHWENK AND ERWIN KLINGSBERG[2]

Halogenated vegetable oils[2] have been used clinically for many years for visualization of body cavities such as spinal cord, urethra, seminal vesicles, uterine cavity and tubes, fistulas and sinuses. In recent years, radiopaque substances of greater opacity and increased safety have been developed. The latter substances, in contrast to the halogenated vegetable oils, are iodinated compounds in which the iodine atoms are firmly bound to aromatic or heterocylic ring systems. Two compounds of this type are shown in formulas I and II; the former is used clinically for



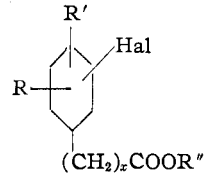
I



II

myelography,[3] the latter for hysterosalpingography.[4]

In continuation of studies[5] on the correlation of structure and pharmacological action of X-ray diagnostic agents, we prepared a series of iodinated alkoxyaryl aliphatic acids (III) (Table I) and esters (IV) (Table II) of the following general formula, wherein R is hydrogen, a methyl or methoxy group, R′ is a methoxy or ethoxy group



(III) R″ = H; (IV) R″ = C_2H_5
Hal = Br or I

and x is an integer from 1 to 10. The acids (III) were secured readily by the iodination of the previously described alkoxyaryl aliphatic acids[6] (V), whereas the esters (IV) were secured from III by esterification or by direct iodination of the esters of V.

Four iodination procedures were studied in this investigation, namely, mercuric acetate and iodine, iodine chloride, silver acetate and iodine, and iodine plus the anhydrous silver salt of the acids V. After several exploratory experiments, the mercuric acetate–iodine procedure was abandoned because the by-product, mercuric iodide, being soluble in the usual organic solvents, had to be removed with hydrogen sulfide, an unsatisfactory and time consuming procedure. Furthermore, in several instances, the iodinated acids or esters were found to contain mercury, notwithstanding repeated treatment of the crude iodinated products with hydrogen sulfide. Iodination with iodine chloride[7] proceeded smoothly and good yields were obtained in the majority of cases.

The iodination procedures utilizing silver ace-

(1) This is part of a paper presented before the Division of Organic Chemistry at the Chicago Meeting of the American Chemical Society, April, 1948.

(2) Lipidol, iodized poppy seed oil, and Iodochloral, iodinated and chlorinated peanut oil are representative of these types of substances. Recently, Olsson and Ekman (*Acta Radiologica*, **31**, 33 (1949)) have described the use of emulsified brominated sesame oil in rats for liver visualization.

(3) Strain, Plati and Warren, U. S. Patent 2,348,231, May 9, 1944; THIS JOURNAL, **64**, 1436 (1942); Steinhausen, *et al.*, *Radiology*, **43**, 230 (1944).

(4) Schnider, U. S. Patent 2,212,187, August 20, 1940; Norment, *Am. J. Obst. and Gynec.*, **49**, 253 (1945); Montgomery and Lang, *ibid.*, **51**, 702 (1946).

(5) For previous investigations on X-ray diagnostic agents reported from this Laboratory, see Schwenk and Papa, U. S. Patent 2,436,270, Feb. 17, 1948; Papa, *Arch. Biochem.*, **23**, 163 (1949); Papa, Schwenk, Breiger and Peterson, THIS JOURNAL, 2619 (1950); Papa, *ibid.*, in press.

(6) Papa, Schwenk and Hankin, *ibid.*, **69**, 3018 (1947).

(7) Iodination with iodine chloride has been employed by Pratt, Hoppe and Archer (*J. Org. Chem.*, **13**, 576 (1948)) for the preparation of compounds 4 and 7 in Table I.