for $C_{15}H_{13}O_2N$: C, 75.28; H, 5.48. Found: C, 75.44; H, 5.39. This cinnamic acid yielded the propionic acid on treatment with sodium amalgam in ethanol after refluxing for 6–8 hours; melting point and mixed melting point with product from Raney catalyst reduction, 205–206.5°.

Iodination of the α-(*p*-aminophenyl)-β-phenylpropionic acid by the procedure of Barnett, Robinson and Wilson[5a] gave 28% of the α-(3,5-diiodo-4-aminophenyl)-β-phenylpropionic acid, m. p. 133–138°. After several recrystallizations from ether-petroleum ether, the product was obtained as tan crystals, m. p. 139–141° after sintering at 135°, previously reported 144–146.2°.[5b] *Anal.* Calcd. for $C_{15}H_{13}O_2NI_2$: I, 51.5. Found: I, 50.9.

Acknowledgment.—The authors wish to express their appreciation to Dr. Richard Tislow for permission to publish the preliminary data on the pharmacology of the compounds and to Mr. Edwin Conner for most of microanalyses reported herein.

Summary

A series of α-(dihalogen-hydroxyphenyl)-, α-aryl-, α-aralkyl-, α-phenoxy- and α-phenylmercaptoacrylic acids, β-(diiodo-hydroxyphenyl)-α-phenoxy- and α-phenylmercaptopropionic acids and diiodo-amino-diaryl- propionic and acrylic acids have been synthesized and examined pharmacologically for cholecystographic properties.

BLOOMFIELD, N. J. RECEIVED APRIL 10, 1950

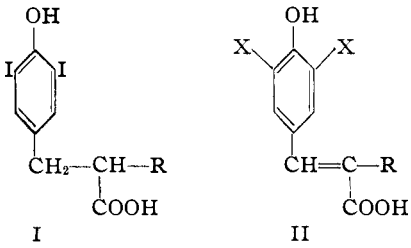
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

X-Ray Diagnostics. V. Halogenated Polycyclic Compounds[1]

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

Of the numerous compounds which have been suggested or used clinically as gall bladder contrast agents, only the halogenated phenolphthaleins[2] and the iodinated cinchopen derivatives[3] have more than two six-membered rings. Notwithstanding the known clinical toxicity of these two types of compounds, it was of interest to establish whether α-naphthyl, α-tetralyl and α-diphenyl derivatives of β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid would be suitable for gall bladder visualization. Although it has been shown that the 3,5-diiodo-4-hydroxyphenyl moiety is not essential for cholecystographic property, we have retained this grouping in the polycyclic compounds because of the ease of preparation of such compounds and the clinical efficacy and safety of this configuration.

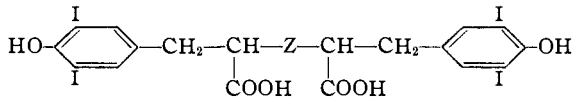
The halogenated polycyclic compounds prepared in this study are of general formulas I and II wherein X is halogen and R is a naphthyl, tetralyl or diphenyl radical. In addition, the



I

II

compounds III and IV were also prepared, the phenyl and diphenyl radicals being substituted in the para positions.



III, Z = $-C_6H_5-$ IV, Z = $-C_6H_4-C_6H_4-$

The diiodo acids of formula I, wherein R is naphthyl or tetralyl, were secured from the known appropriately substituted propionic acids[4] by iodination with potassium triiodide in alkaline solution. The diphenyl compound of formula I was prepared in the conventional manner. The Perkin condensation of diphenyl-4-acetic acid with *p*-hydroxybenzaldehyde gave α-diphenyl-4-hydroxycinnamic acid, which on reduction with Raney alloy and subsequent iodination yielded the α-diphenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid in good yield.

The tetraiodo acids III and IV were obtained by the same sequence of reactions from *p*-phenylene diacetic acid and *p,p'*-diphenyldiacetic acid, respectively. The intermediate products, bis-α,α'-(*p*-hydroxybenzal)-*p*-phenylenediacetic acid, bis - α,α' - (*p* - hydroxybenzal) - *p,p'* - diphenyldiacetic acid and the corresponding benzyl derivatives were high melting compounds and although analytically pure samples were obtained, the melting points could not be used as a criterion of purity. Iodination of the two benzyl derivatives yielded tan to brown crystalline products which could not be recrystallized to constant melting point. In fact, repeated recrystallization of the tetraiodo acids resulted in decomposition with the liberation of iodine.

The acrylic acid derivatives of formula II were secured readily by the condensation of the anhydrous potassium salt of the arylacetic acid and the halogenated *p*-hydroxybenzaldehyde. In addition to the iodo compounds of Formula

(1) For the previous papers in this series see THIS JOURNAL, **72**, 4906 (1950), ref. 1.

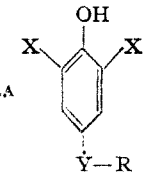
(2) Graham and Cole, *J. Am. Med. Assoc.*, **82**, 613 (1924).

(3) Dohrn and Diedrich, U. S. Patent 2,220,086, Nov. 5, 1940; Orator and Walchshofer, *Deut. Z. Chir.*, **205**, 86 (1927).

(4) Papa, Breiger and Peterson, *J. Org. Chem.*, **14**, 362 (1949).

TABLE I

COMPOUNDS OF FORMULA



No.	X	Y[a]	R	Yield, %	M. p.,[b] °C.	Recryst. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	I	A	α-$C_{10}H_7$-	44	232–233	Acetone–H_2O	$C_{19}H_{12}O_3I_2$[c]				
2	Br	A	α-$C_{10}H_7$-	50	255–256	C_2H_5OH–H_2O	$C_{19}H_{12}O_3Br_2$	50.90	51.50	2.70	3.01
3	Cl	A	α-$C_{10}H_7$-	62	253–254	C_2H_5OH–H_2O	$C_{19}H_{12}O_3Cl_2$	63.51	63.70	3.37	3.40
4	Br	A	β-$C_{10}H_7$-	48	234–236	C_2H_5OH–H_2O	$C_{19}H_{12}O_3Br_2$	50.90	50.90	2.70	3.10
5	[d]	A	α-$C_{10}H_7$-	22	224–226[e]	Acetone–H_2O	$C_{19}H_{11}O_3I_3$[f]				
6	I	B	α-$C_{10}H_7$-	52	178.5–180	$CHCl_3$	$C_{19}H_{14}O_3I_2$[g]				
7	I	B	α-$C_{10}H_{11}$[h]	56	178–179	Ether–P. E.[i]	$C_{19}H_{18}O_3I_2$	41.59	41.76	3.31	3.42
8	I	B	α-$C_{10}H_{11}$[j]	46	169.5–170.5	$CHCl_3$–P. E.[i]	$C_{19}H_{18}O_3I_2$	41.59	42.15	3.31	3.48
9	Br	A	α-$C_{10}H_{11}$[h]	44	251[e]	C_2H_5OH–H_2O	$C_{19}H_{16}O_3Br_2$	50.47	50.68	3.57	3.88

[a] A is the radical —CH=C(COOH)— and B is —CH_2—CH(COOH)—; [b] The melting points are for analytically pure samples; [c] I, 46.7. Found: I, 46.9. [d] This is the 2,4,6-triiodo-3-hydroxy substituted compound. [e] Melted with decomposition with liberation of iodine. [f] I, 57.0. Found: I, 56.2. [g] I, 46.7. Found: I, 47.0. [h] α-(5,6,7,8-tetrahydronaphthyl). [i] Petroleum ether, b. p. 35–60°. [j] α-(1,2,3,4-tetrahydronaphthyl).

II, the chloro and bromo analogs were also prepared. None of the compounds described in this paper gave gall bladder visualization when tested in dogs by the previously outlined procedure.[1]

Experimental

The compounds 1–5 and 9 were prepared as follows: The condensations were carried out in three-necked flasks provided with stirrer, thermometer and condenser carrying a calcium chloride drying tube. Unless otherwise specified, a mixture of 0.1 mole of the anhydrous potassium salt of the arylacetic acid, 0.1 mole of the aromatic aldehyde and 150 cc. of acetic anhydride was heated at 110° for 10–12 hours. After cooling the reaction mixture to about 60°, the excess acetic anhydride was cautiously decomposed with water. The crude condensation product was taken up in 1 l. of 5% sodium hydroxide solution, heated for about one hour on the steam-bath, filtered and acidified with hydrochloric acid. The resulting product was then recrystallized. The compounds 6–8 were prepared by the potassium triiodide iodination procedure previously described.[5]

The requisite intermediates, diphenyl-4-acetic acid,[6] *p,p'*-diphenyldiacetic acid,[6] *p*-phenylenediacetic acid,[7] 5,6,7,8-tetrahydro-β-naphthylacetic acid,[4] α-(1,2,3,4-tetrahydro-1-naphthyl)-β-(4-hydroxyphenyl)-propionic acid,[4] α-(1-naphthyl)-β-(4-hydroxyphenyl)-propionic acid,[4] α-(5,6,7,8-tetrahydro-2-naphthyl)-β-(4-hydroxyphenyl)-propionic acid,[4] 3,5-diiodo-, 3,5-dibromo-, 3,5-dichloro-4-hydroxybenzaldehydes and 2,4,6-triiodo-3-hydroxybenzaldehyde were prepared in accordance with published methods.

α-Diphenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic Acid.—The requisite intermediate, α-diphenyl-4-hydroxycinnamic acid, was prepared by the condensation of diphenyl-4-acetic acid and *p*-hydroxybenzaldehyde; yield 62%, m. p. 225.5–226.6° after recrystallization from acetic acid. *Anal.* Calcd. for $C_{21}H_{16}O_3$: C, 79.71; H, 5.10. Found: C, 79.84; H, 5.35.

Reduction to the propionic acid proceeded in 86% yield, m. p. 230–235°. Purification of this compound was carried out as follows: To 160 g. (0.5 mole) of the acid dissolved in 500 cc. of 10% sodium hydroxide solution, there was added in portions with stirring 150 g. of sodium chloride. After stirring for an additional hour, the precipitated sodium salt was filtered and then dissolved in 1 l. of water. The somewhat cloudy solution was heated on a steam-bath (70–80°), Norite added and, after stirring for one-half hour, it was filtered. The filtrate was acidified and washed with water; yield 88%, m. p. 242–244°; recrystallized from alcohol–water for analysis, m. p. 245.5–246.5°. *Anal.* Calcd. for $C_{21}H_{18}O_3$: C, 79.21; H, 5.70. Found: C, 78.95; H, 5.86.

Iodination of the purified propionic acid yielded the diiodo compound; yield 48%, m. p. 203–206° after recrystallization from chloroform–petroleum ether. A further recrystallization from aqueous alcohol raised the melting point to 209.5–211°. *Anal.* Calcd. for $C_{21}H_{16}O_3I_2$: C, 44.20; H, 2.83. Found: C, 44.36; H, 3.00.

Bis-α,α'-(3,5-diiodo-4-hydroxybenzyl)-*p*-phenylenediacetic Acid.—The condensation of 0.1 mole of anhydrous potassium *p*-phenylenediacetate and 0.22 mole of *p*-hydroxybenzaldehyde gave bis-α,α'-(*p*-hydroxybenzal)-*p*-phenylenediacetic acid; yield 46%, m. p. 292–295° after recrystallization from acetic acid. *Anal.* Calcd. for $C_{24}H_{18}O_6$: C, 71.62; H, 4.51. Found: C, 71.71, H, 4.37. Reduction to the corresponding benzyl compound proceeded smoothly with Raney alloy; yield 78%, m. p. 282–285° after recrystallization from aqueous ethanol. *Anal.* Calcd. for $C_{24}H_{22}O_6$: C, 70.90; H, 5.46. Found: C, 71.25; H, 5.63. Iodination with potassium triiodide gave the tetraiodo acid; yield 58%, m. p. 220–228°. Purification by solution in sodium carbonate and precipitation with acetic acid followed by recrystallization from ethanol gave a tan product, m. p. 247–250°. The iodine analysis (calcd. for $C_{24}H_{18}O_6I_4$: I, 55.8. Found: I, 54.2) indicated the presence of impurities and further attempts at purification resulted in a product with a lower iodine value and m. p. 230–238°. The ethanol filtrate from the latter recrystallization contained free iodine arising from the decomposition of the iodo acid.

Bis-α,α'-(3,5-diiodo-4-hydroxybenzyl)-*p,p'*-diphenyldiacetic Acid.—Bis-α,α'-(4-hydroxybenzal)-*p,p'*-diphenyldiacetic acid was secured from 0.1 mole of anhydrous potassium *p,p'*-diphenyldiacetic acid and 0.22 mole of *p*-hydroxybenzaldehyde in 42% yield, m. p. above 300° after purification by solution in sodium carbonate and precipitation with acetic acid. The product so purified was reduced with Raney alloy to give bis-α,α'-(4-hydroxybenzyl)-*p,p'*-

(5) Papa, Schwenk, Breiger and Peterson, THIS JOURNAL, **72**, 4906 (1950).

(6) Schwenk and Papa, *J. Org. Chem.*, **11**, 798 (1946).

(7) Papa, Schwenk and Klingsberg, THIS JOURNAL, **68**, 2133 (1946).

diphenyldiacetic acid, m. p. above 300°. Recrystallized for analysis from aqueous ethanol. *Anal.* Calcd. for $C_{30}H_{36}O_6$: C, 74.76; H, 5.43. Found: C, 74.82; H, 5.78. Iodination with potassium triiodide in alkaline solution yielded a brown crystalline substance which could not be purified either by the use of sodium carbonate solution or organic solvents. The product gave a positive test for halogen and was for the most part alkali soluble. Iodination with iodine chloride in acetic acid also gave a dark crystalline product which could not be purified.

Summary

A series of α-naphthyl and α-tetralyl derivatives of halogenated arylpropionic and acrylic acids have been prepared. Preliminary pharmacological study in animals indicates that these compounds do not possess cholecystographic properties.

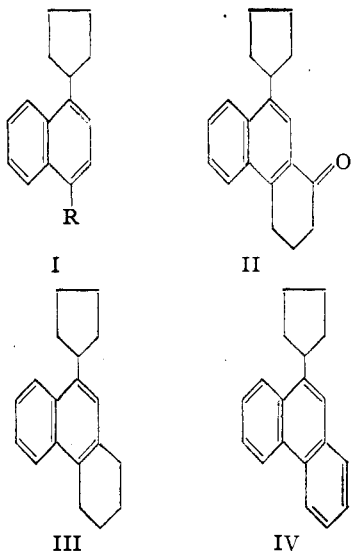
BLOOMFIELD, N. J. RECEIVED APRIL 10, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Preparation and Reactions of 1-Cyclopentylnaphthalene

BY W. E. BACHMANN AND L. H. KLEMM[1]

In a study of antimalarials carried out during the war years in coöperation with the Committee on Medical Research we prepared 1-cyclopentylnaphthalene (I, R = H) and studied some of its reactions. No mention of the hydrocarbon or its derivatives was found in the literature other than the report of Pokrovskaya and Sushchik[2] that a "monocyclopentylnaphthalene" fraction of unknown structure was isolated from the Friedel–Crafts condensation of cyclopentene with naphthalene.



I II

III IV

We prepared 1-cyclopentylnaphthalene by hydrogenation of the known 1-(1′-naphthyl)-1-cyclopentene, which results from the reaction between 1-naphthylmagnesium bromide and cyclopentanone followed by dehydration of the intermediate tertiary alcohol. The addition of hydrogen to the olefin occurred readily and almost quantitatively at low pressure and room temperature in acetic acid solution in the presence of Adams catalyst. This behavior is in sharp contrast to that of the homologous compound 1-(1′-naphthyl)-1-cyclohexene, which, as reported by Cook and Lawrence,[3] strongly resisted the addition of hydrogen under the same conditions.

Sulfonation, acetylation and succinoylation of 1-cyclopentylnaphthalene were effected by means of chlorosulfonic acid in carbon tetrachloride, acetyl chloride and aluminum chloride in carbon disulfide, and succinic anhydride and aluminum chloride in nitrobenzene, respectively. The substituents introduced by these reactions were all shown to occupy the 4-position of the naphthalene nucleus by means of a series of four separate steps: (1) proof of the equivalence of the positions occupied by the sulfonic acid and the acetyl groups; (2) a similar proof for the acetyl and succinoyl groups; (3) proof that the succinoyl group occupied either the 3- or the 4-position; (4) proof that the acetyl group occupied an alpha position.

For the first part of this proof the sulfonic acid group was replaced successively by a bromo and a cyano group. By a Grignard reaction with methylmagnesium iodide the cyano derivative was converted into the acetyl compound which was identical with that obtained by acetylation. The production of the same acid by hydrolysis of the cyano compound and by hypochlorite oxidation of the acetyl derivative confirmed the previous result.

For the second part the acetyl compound (I, R = $COOH_3$) was brominated in ether to the ω-bromoacetyl derivative, which on reaction with sodio-malonic ester, hydrolysis, and decarboxylation gave the succinoyl derivative.

In the third part of the proof the succinoyl

(1) From the Ph.D. dissertation of L. H. Klemm, 1945.

(2) Pokrovskaya and Sushchik, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 2291 (1939); [*C. A.*, **34**, 5433 (1940)].

(3) (a) Cook and Lawrence, *J. Chem. Soc.*, 1431 (1936). Compare (b) Bachmann and Kloetzel, THIS JOURNAL, **60**, 2204 (1938); (c) Bergmann and Bergmann, *ibid.*, **62**, 1699 (1940); and (d) Bergmann and Szmuszkowicz, *ibid.*, **69**, 1367 (1947), for differences in the reactivities of these olefins to maleic anhydride in the Diels-Alder reaction, and (e) Bachmann and Deno, *ibid.*, **71**, 3062 (1949), for differences in the ultraviolet absorption spectra. See (h) Orchin and Reggel, *ibid.*, **69**, 505 (1947), for the reduction of 1-(1′-naphthyl)-1-cyclohexene. Further investigations on the addition of hydrogen to these and other 1-aryl-1-cycloalkenes are being carried out by L. H. K.