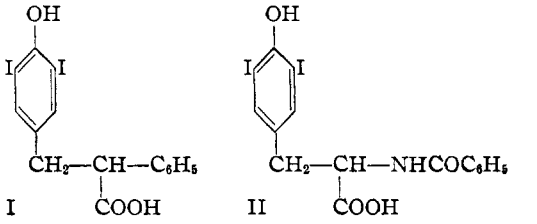
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

X-Ray Diagnostics. VI. Diiodohydroxydihydrostilbazoles and Related Compounds

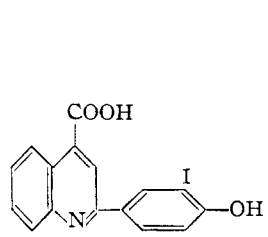
BY DOMENICK PAPA, ERWIN SCHWENK AND ERWIN KLINGSBERG[1]

In previous reports[2] on the correlation of structure and cholecystographic properties, a number of modifications in the structure of the known clinically efficacious cholecystographic agent, α-phenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid[3] I,



I

II



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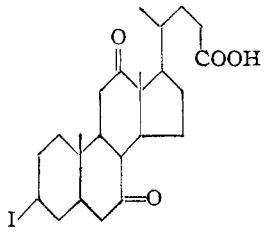
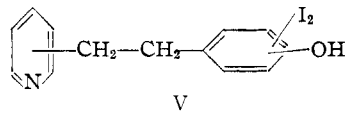


IV

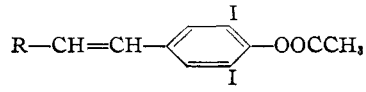
revealed that neither the 3,5-diiodo-4-hydroxyphenyl moiety, saturation in the aliphatic chain, nor the unsubstituted phenyl group of this configuration is essential for this type of property. In addition, the N-benzoyl derivative of 3,5-diiodotyrosine[4] (II), heterocyclic compounds such as atophan derivatives[5] of type III and iodinated bile acids[6] of type IV have been tested or proposed for gall bladder visualization. Notwithstanding the diversity of structures which have been suggested or studied as cholecystographic agents, it is to be noted that, almost without exception, all of these variations have retained the carboxyl group, be it aliphatic, alicylic or aromatic.

In continuation of our studies on the minimum structural requirements for cholecystographic properties, it appeared of interest to prepare for pharmacological examination diiodo compounds of the general types previously described lacking the carboxyl group. Since the presence of two iodine atoms ortho to the hydroxyl group greatly enhances the acidic character of this group, we have retained the 3,5-diiodo-4-hydroxyphenyl configuration in the carboxyl-free compounds. This paper describes the synthesis and pharmacological properties of the first series of these compounds, namely, the diiodohydroxydihydrostilbazoles of general formula V and two related compounds of formulas VI and VII.

The hydroxystilbazoles, intermediates for the di-



V

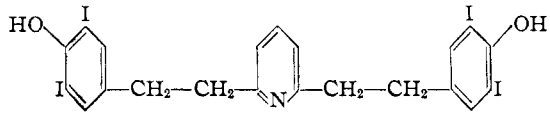


VI, R = 6-Me-2-pyridyl
VII, R = 2-Quinolyl

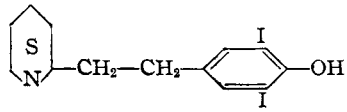
iodo compounds V (Table I), were prepared from α- and γ-picoline and *o*- and *p*-hydroxybenzaldehydes by condensation in acetic anhydride, essentially as previously described.[7] Reduction to the dihydro derivatives was effected by sodium amalgam, Raney alloy in aqueous alkali[8] and Raney catalyst at 80–90° and an initial hydrogen pressure of about 1500 p.s.i. The latter procedure gave yields exceeding 95%, whereas the sodium amalgam and Raney alloy methods gave between 55–88% of the dihydro compounds. Iodination proceeded smoothly with potassium triiodide in very dilute alkaline solution.

The unsaturated compounds VI and VII were prepared by refluxing, in acetic anhydride, a mixture of 3,5-diiodo-4-hydroxybenzaldehyde with 2,6-lutidine and quinaldine, respectively. In the case of the acetoxy compound VI, hydrolysis with alcoholic alkali yielded the hydroxy compound as a brick-red solid.

The synthesis of two other pyridine derivatives, namely, 2,6-di-(3,5-diiodo-4-hydroxy-β-phenethyl)-pyridine (VIII) and 2-(3,5-diiodo-4-hydroxy-β-phenethyl)-piperidine (IX) was studied. The intermediate, 2,6-di-(*p*-hydroxy-β-phenethyl)-pyridine (X), for the tetraiodo compound VIII, was ob-



VIII



IX

tained by the condensation of *p*-hydroxybenzaldehyde and 2,6-lutidine, followed by reduction of the distyryl derivative. The requisite intermediate for IX, 2-(*p*-hydroxy-β-phenethyl)-piperidine, was secured by sodium and butyl alcohol reduction or catalytic hydrogenation of 4′-hydroxy-2-stilbazole. The latter procedure also yielded the perhydro derivative, 2-[β-(4-hydroxycyclohexyl)-ethyl]-piperidine. However, iodination of X or XI by either potassium triiodide or iodine chloride yielded products which could not be purified.

(1) American Cyanamid Co., Calco Chemical Division, Bound Brook, N. J.

(2) For paper V in this series, see THIS JOURNAL, **72**, 4909 (1950).

(3) See ref. 3 in *ibid.*, **72**, 2619 (1950).

(4) Fox, *ibid.*, **68**, 194 (1946).

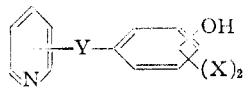
(5) Dohrn and Diedrich, U. S. Patent 2,220,086, Nov. 5, 1940.

(6) Jacobsen, Picha, Weinstein and Romanoff, *J. Biol. Chem.*, **171**, 87 (1947).

(7) Chiang and Hartung, *J. Org. Chem.*, **10**, 21 (1945).

(8) Papa, Schwenk and Whitman, *ibid.*, **7**, 586 (1942).

TABLE I

COMPOUNDS OF FORMULA 

No.	Y[a]	OH[b]	$(X)_2$	Yield, %	M.p., °C.	Recrys. solvent	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	2-CH=CH—	2	H	68	142-143[c]	C_2H_5OH	$C_{13}H_{11}NO$	79.16	78.85	5.62	5.76
2	2-CH_2—CH_2—	2	H	70, 65, 98[d]	93-94[e]	$C_2H_5OH \cdot H_2O$					
3	2-CH_2—CH_2—	2	3,5-I_2	83	126-128	C_2H_5OH	$C_{13}H_{11}NOI_2$	34.60	34.92	2.46	2.72
4	2-CH_2—CH_2—	2	3,5-Br_2[f]	56	116-117	$C_2H_5OH \cdot H_2O$	$C_{13}H_{11}NOBr_2$	43.73	43.92	3.11	3.58
5	2-CH=CH—	4	H	78	219-220[g]	C_2H_5OH					
6	2-CH_2—CH_2—	4	H	74, 55[d]	154-155[h]	$C_2H_5OH \cdot H_2O$					
7	2-CH_2—CH_2—	4	3,5-I_2	76	170-171	$C_2H_5OH \cdot H_2O$	$C_{13}H_{11}NOI_2$	34.60	34.93	2.46	2.69
8	4-CH=CH—	2	H	70	192-194[i]	C_2H_5OH	$C_{13}H_{11}NO$	79.16	79.03	5.62	5.87
9	4-CH_2—CH_2—	2	H	88, 74, 100[d]	163-164	$C_2H_5OH \cdot H_2O$	$C_{13}H_{13}NO$	78.35	78.04	6.58	6.61
10	4-CH_2—CH_2	2	3,5-I_2[j]	88	145-146	$C_2H_5OH \cdot H_2O$	$C_{13}H_{11}NOI_2$	34.60	34.96	2.46	2.73
11	4-CH=CH—	4	H	57	280-282	$C_5H_5N \cdot H_2O$[k]	$C_{13}H_{11}NO$	79.16	79.38	5.62	5.93
12	4-CH_2—CH_2	4	H	63, —, 95[d]	169-170	H_2O[l]	$C_{13}H_{13}NO$	78.35	78.64	6.58	6.83
13	4-CH_2—CH_2	4	3,5-I_2	94	161-162	$C_2H_5OH \cdot H_2O$	$C_{13}H_{11}NOI_2$	34.60	34.93	2.46	2.69

[a] The numeral preceding the carbon atom refers to the point of attachment on the pyridine ring. [b] The numeral refers to the position of the hydroxyl group. [c] Previously reported,[7] m.p. 130–132°. [d] The three yields reported are those obtained by reduction methods a, b, and c, respectively. [e] Lit.,[7] m.p. 92–93°. [f] To 10 g. of compound 4 in 100 cc. of acetic acid added in one hour 16.3 g. of bromine in 30 cc. of acetic acid. The mixture was then diluted with 500 cc. of water, buffered with sodium acetate and the white dibromo compound filtered. [g] Lit.,[7] m.p. 215–217°. [h] Lit[7], m.p. 152–153°. [i] Previously reported[7] as a liquid. [j] This compound is light sensitive and darkens and decomposes on exposure to sunlight. [k] The crude condensation product from 1 mole of reactants is purified by digestion in 2–2.5 l. of hot pyridine, filtration of the insolubles and addition of 3 l. of boiling water. On cooling the stilbazole crystallizes out. [l] Although excessively large volumes of water were required for recrystallization, it was the solvent of choice in securing a white product of m.p. 169–170°.

Pharmacological examination of these compounds by the method previously described showed that these substances do not concentrate in the gall bladder in the experimental animal. For the most part, the pyridyl compounds remained in the gastrointestinal tract and were excreted by the colon.

Experimental

All melting points are corrected. The alkyl pyridines were commercial products and were used without purification.

The stilbazoles 1, 5, 8 and 11 of Table I were prepared by the following procedure which is a modification of that previously described. A mixture of 1 mole of the alkyl pyridine, 1 mole of the aromatic aldehyde and 2 moles of acetic anhydride is refluxed for 17 hours. The cooled reaction mixture is then poured into a mixture of methanol and hydrochloric acid and digested on the steam-bath for 3 hours. Neutralization of the acid solution with ammonium hydroxide or buffering with sodium acetate precipitated the crude stilbazoles. Purification was effected by recrystallization using Norite.

Reduction of the stilbazoles to the dihydro compounds 2, 6, 9 and 12 (Table I) was carried out as follows:

Method (a).—To a solution of 0.05 mole of the hydroxystilbazole in 0.2 mole of sodium hydroxide in sufficient water for complete solution, there was added 250 g. of 5% sodium amalgam in five portions. After about 24 hours, the solution was decanted from the mercury, acidified to litmus paper with acetic acid and the precipitated dihydro compound filtered and then recrystallized.

Method (b).—Ten grams of the stilbazole was dissolved in 250 cc. of 10% sodium hydroxide, the solution heated to 75° and 20 g. of Raney alloy added in the course of about two hours. The alkaline solution, after filtering, was acidified with hydrochloric acid, buffered with sodium acetate and cooled. The precipitated dihydro compound was filtered, washed with water and recrystallized.

Method (c).—A mixture of 0.1 mole of stilbazole, 250 cc. of methanol and about 5 g. of Raney catalyst was hydrogenated at 80–90° at an initial pressure of 1400 p.s.i. The hydrogenation proceeded rapidly and, after filtering off the catalyst, the methanol was evaporated and the residue recrystallized.

The diiodo compounds 3, 7, 10 and 13 of Table I were prepared by the potassium triiodide procedure previously described except that the volumes o fwater used were sufficient to retain the dihydro and diiodo compounds in solution throughout the iodination.

(14) α-(3,5-Diiodo-4-acetoxystyryl)-α′-methylpyridine.—A solution of 187 cc. of 2,6-lutidine and 187 g. of 3,5-diiodo-4-hydroxybenzaldehyde in 175 cc. of acetic anhydride is refluxed for 24 hours. The mixture is then thoroughly cooled (0–5°) and the precipitated acetoxy product filtered; yield 185 g. (80%), m.p. 177–180°. Recrystallized from ethanol, it is a white to gray tinted product, m.p. 188–189°. *Anal.* Calcd. for $C_{16}H_{13}NO_2I_2$: C, 38.04; H, 2.59. Found: C, 38.33; H, 2.83.

(15) α-(3,5-Diiodo-4-hydroxystyryl)-α′-methylpyridine.—A mixture of 164.9 g. of α-(3,5-diiodo-4-acetoxystyryl)-α′-methylpyridine, 31.4 g. of sodium hydroxide and 1.5 l. of 80% ethanol is refluxed for three hours. The red alcoholic solution is concentrated to about 400 cc., diluted with water and acidified with acetic acid. The brick-red solid is filtered, washed with water and dried; yield 150 g., m.p. 182–183.5°. Recrystallized from a large volume of benzene for analysis, m.p. 185–187° dec. *Anal.* Calcd. for $C_{14}H_{11}NOI_2$: C, 36.41; H, 2.39. Found: C, 36.47; H, 2.73.

(16) α-(3,5-Diiodo-4-acetoxystyryl)-quinoline.—A solution of 7.7 g. (0.054 mole) of quinaldine and 18.7 g. (0.05 mole) of 3,5-diiodo-4-hydroxybenzaldehyde and 75 cc. of acetic anhydride was refluxed for 19 hours, then thoroughly chilled. The precipitated quinoline compound was filtered and washed with cold methanol; yield 17 g. (63%), m.p. 184–185°. Recrystallization from ethanol raised the melting point to 186.5–187.5°. *Anal.* Calcd. for $C_{19}H_{13}NO_2I_2$: C, 42.17; H, 2.42. Found: C, 42.34; H, 2.59.

(17) 2,6-Di-(3,5-diiodo-4-hydroxy-β-phenethyl)-pyridine.—The intermediate 2,6-di-(*p*-acetoxystyryl)-pyridine was prepared as follows: A solution of 46 g. (0.43 mole) of 2,6-lutidine and 140 g. (1.15 moles) of *p*-hydroxybenzaldehyde in 425 ml. of acetic anhydride is refluxed for 66 hours. (Shorter reaction periods give lower yields and it is possible that a longer reaction time would give a higher yield.) The reaction mixture is then worked up in the usual manner with methanol to destroy excess acetic anhydride. The yield of the crude condensation product, m.p. 182.5–183.5°, is 70 g. (41%). Recrystallization from ethanol or dilute pyridine raises the m.p. to 184.5–185°. *Anal.* Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30. Found: C, 75.44; H, 5.51.

A mixture of 10 g. of the acetoxy compound, 10 cc. of concentrated sulfuric acid, 50 cc. of acetic acid and 25 cc. of water was refluxed for 6 hours. The solution was made

just alkaline with sodium hydroxide, a slight precipitate filtered off and the filtrate hydrogenated in a Parr apparatus with Raney catalyst. After 4 hours the calculated amount of hydrogen was absorbed, the catalyst was filtered and the filtrate acidified with acetic acid. The crude yield of 2,6-di-(*p*-hydroxy-*β*-phenethyl)-pyridine was 10 g., m.p. 171–174°; recrystallized twice from dilute ethanol for analysis, m.p. 180–181°. *Anal.* Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63. Found: C, 78.78; H, 6.56.

To a solution of 3.19 g. (0.01 mole) of the hydroxy compound dissolved in 320 cc. of 1% sodium hydroxide solution, there was added dropwise with stirring a solution of 10.2 g. of iodine and 10.2 g. of potassium iodide in 100 cc. of water. The solution was stirred for an additional hour, filtered and then acidified with sulfur dioxide. The precipitated tetraiodo compound was filtered and air-dried; yield 7.2 g., m.p. 150–157°. Attempts to recrystallize the product from dilute ethanol, dilute acetic acid or alcohol–ether resulted in liberation of iodine with the formation of tarry products.

(18) **2-(*p*-Hydroxy-*β*-phenethyl)-piperidine and 2-[*β*-(4-hydroxycyclohexyl)-ethyl]-piperidine.**—A solution of 7.5 g. (0.04 mole) of 4′-hydroxy-*α*-dihydrostilbazole in 150 cc. of dry *n*-butanol was refluxed in an oil-bath at approximately 180° and treated rather rapidly with 14 g. (0.6 mole) of sodium. After 1.5 hours, an additional 50 cc. of butanol was added. After 3 hours at 175–180°, the sodium had been consumed. The solvent was removed by steam distillation and a small amount of solid filtered from the steam distillation residue. The 2-(*p*-hydroxy-*β*-phenethyl)-piperidine was precipitated by careful acidification with acetic acid; yield 6.6 g. (85%), m.p. 197–198°. Recrystallization from toluene raised the m.p. to 198.5–199.5°. *Anal.* Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.13; H, 9.26.

Twenty grams (0.1 mole) of 4′-hydroxy-*α*-stilbazole was hydrogenated in 250 cc. of ethanol for 9 hours at 80° at an initial pressure of 1,200 p.s.i. The catalyst was then filtered and the solvent evaporated. Leaching the residue with hot dilute sodium hydroxide solution left, as an insoluble residue, 4.0 g. (18%) of substantially pure perhydro compound, 2-[*β*-(4-hydroxycyclohexyl)-ethyl]-piperidine, m.p. 174–175.5. Recrystallization from dilute ethanol raised the m.p. to 176–177.5° using Raney nickel catalyst. *Anal.* Calcd. for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 74.21; H, 11.87; N, 6.51.

The alkali soluble fraction was precipitated by careful acidification with acetic acid, yielding 8.0 g. (38%), of 2-(*p*-hydroxy-*β*-phenethyl)-piperidine, m.p. 195.5–196.5°. Recrystallization from toluene raised the m.p. to 198.5–199.5°, not depressed by admixture with a sample prepared by sodium–butanol reduction.

Summary

A series of diiodohydroxydihydrostilbazoles and *α*-(3,5-diiodo-4-hydroxy-styryl)-*α*′-methyl pyridine and *α*-quinoline compounds have been prepared for pharmacological examination as X-ray diagnostic agents. None of the compounds showed cholecystographic properties in dogs.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

The Photochemical Decomposition of Gaseous Di-*t*-butyl Peroxide[1]

BY LEON M. DORFMAN[2] AND Z. W. SALSBURG[3]

The extensive investigations of Vaughan and his co-workers[4,5,6,7] on the thermal decomposition of the alkyl peroxides have led to considerable interest in di-*t*-butyl peroxide. As a result of this work the mechanism of the pyrolysis of this compound is reasonably well understood.

Very little is recorded in the chemical literature, on the photolysis of alkyl peroxides. The above authors[6] have reported one run on the photolysis of liquid di-*t*-butyl peroxide but no investigations of the photochemical decomposition of this compound in the gaseous phase have yet been reported.

Di-*t*-butyl peroxide, because of its relatively high stability at temperatures below 80°, lends itself to a study of the reactions of the methyl radical, which are currently of much interest, as well as those of the butoxy radical. Its use as a radical source in reaction initiation is well established[8] at temperatures above 100°. It may also be used for this purpose at room temperature since the photolysis will provide radicals.

The present investigation has been carried out over a temperature range from 25 to 75° using both filtered light and the full light of the mercury arc where necessary in order to obtain sufficient quantities of liquid products for accurate analysis.

Experimental Details

Di-*t*-butyl peroxide, obtained from the Shell Development Company, was purified by distillation at reduced pressure using a column packed with glass beads. The liquid was distilled at a temperature of 40–45° over the pressure range 55–70 mm. The middle third of the distillate was retained, then dried over anhydrous copper sulfate and subsequently bulb-to-bulb distilled in the vacuum system before being stored over a mercury cut-off in a storage bulb painted black. Prior to each run the peroxide was degassed for at least one hour at Dry Ice temperature. The refractive index of the purified liquid was found to be $n^{20}D$ 1.3889. This compares with previously listed values[4,9] of 1.3890 and 1.3872. After the liquid had been stored for over two months the refractive index was found to be unchanged.

A Hanovia Alpine burner type S-100 was used as the light source in all runs. For the low intensity runs in which only gaseous products were analyzed, this mercury arc was used in conjunction with a chlorine gas filter (460 mm. pressure, 50-mm. path length) and a Corning No. 9863 filter of standard thickness. These filters provided light consisting chiefly of 2537 and 2650 Å. The intensity was further reduced, when desired, by interposing a neutral density filter in the beam. For these runs with the filtered light the reaction vessel consisted of a cylindrical quartz cell, 200 mm. in length and 22 mm. inside diameter. The light beam had an incident diameter of 14.1 mm. and an emergent diameter of 14.3 mm. The absorbed light intensity was determined with the use of a photocell, and the necessary corrections[10,11] for multiple reflections were made.

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(2) General Electric Company, Knolls Atomic Power Laboratory, Schenectady, N. Y.

(3) Department of Chemistry, California Institute of Technology, Pasadena, Calif.

(4) J. H. Raley, F. F. Rust and W. E. Vaughan, THIS JOURNAL, **70**, 88 (1948).

(5) J. H. Raley, F. F. Rust and W. E. Vaughan, *ibid.*, **70**, 1336 (1948).

(6) E. R. Bell, F. F. Rust and W. E. Vaughan, *ibid.*, **72**, 337 (1950).

(7) F. F. Rust, F. H. Seubold, Jr., and W. E. Vaughan, *ibid.*, **72**, 338 (1950).

(8) F. F. Rust, F. H. Seubold, Jr., and W. E. Vaughan, *ibid.*, **70**, 95 (1948).

(9) N. A. Milas and D. M. Surgenor, *ibid.*, **68**, 205 (1946).

(10) R. E. Hunt and T. L. Hill, *J. Chem. Phys.*, **15**, 111 (1947).

(11) W. Davis, Jr., and W. A. Noyes, Jr., THIS JOURNAL, **69**, 2153 (1947).