tion of 18.0 g. (0.04 mole) of 21-bromo-3α,17α-dihydroxypregnane-11,20-dione[9] and 1.685 g. (0.015 mole) of triethylenediamine in 200 ml. of dry ethyl methyl ketone was heated at 50° for 4 days. The solution became cloudy and crystals separated. Filtration gave 10.3 g. of crystalline solid, m.p. 243–248° after sintering and darkening from 210°. Dilution of the filtrate to 1 l. with absolute ether gave 1.9 g. of additional compound. A sample dried at 100° in a high vacuum overnight was found by Karl Fischer analysis to be anhydrous. However, it was hygroscopic and was difficult to analyze.

Anal. Calcd. for $C_{48}H_{74}Br_2N_2O_8$: C, 59.62; H, 7.71; Br, 16.53; N, 2.90; O, 13.24. Found: C, 58.01; H, 8.29; Br, 16.52; N, 3.22; O, 13.59.

A sample of this material was boiled with about 2 l. of water. The cloudy solution was filtered through Supercel and the warm solution was decanted from a little gum which immediately separated. On cooling a flocculent gelatinous precipitate separated and after standing overnight in the refrigerator it was collected, washed with water, and dried giving 3.7 g. of near white solid, m.p. 242-246° dec. Samples allowed to equilibrate in air at 50% humidity were found by analysis to contain 2.5 molecules of water (Table I). The nuclear magnetic resonance spectrum supported the proposed structure.

Triethylenediamine Mono-N-oxide Dihydrochloride (17).—To a solution of 22.4 g. (0.2 mole) of triethylenediamine in 400 ml. of absolute ethanol was added during 15 min. with stirring at 20° 100 ml. of 30% aqueous hydrogen peroxide. After standing at room temperature for 4 days the excess hydrogen peroxide was destroyed by cautiously adding an aqueous slurry of 0.5 g. of 30% platinum on charcoal. After stirring vigorously for 4 hr. the mixture was filtered through Supercel and the colorless solution was evaporated below 80° giving the free N-oxide base as a clear colorless oil.

The oil was dissolved in 300 ml. of absolute ethanol and acidified with 75 ml. of 6 *N* ethanolic hydrogen chloride. The resulting white precipitate was collected and dried giving 37.4 g. of white solid. In the melting point bath it darkened at 200–220° but was not all decomposed at 310°. This was dissolved in about 1.4 l. of methanol and concentrated on a steam bath by a stream of nitrogen to 800 ml. After cooling, the crystals were collected and dried giving 23.5 g. of white solid with melting behavior the same as above. An additional 8.9 g. was obtained from the methanol filtrate. The infrared spectrum was very different from that of triethylenediamine dihydrochloride and the potentiometric titration showed two breaks in the curve; neut. equiv. calcd: 100.6; found: 101.3.

1-Phenacyl-4-aza-1-azoniabicyclo[2.2.2]octane Bromide 4-Oxide Hydrate (18).—Mono-N-oxide free base was prepared as above from 22.4 g. (0.2 mole) of triethylenediamine. The solution, after filtration from the platinum on charcoal, was cooled to 3° and a solution of 41 g. (0.21 mole) of phenacyl bromide was added. After standing overnight the solution was concentrated to 500 ml. The resulting crystals were collected, boiled with methanol, and cooled. After filtration from a small amount of white solid, the two filtrates were diluted with ether giving white solids which were combined and dissolved in 1.1 l. of 90% ethanol by warming. After filtration this was diluted with 2 l. of absolute ether giving 54.2 g. of white solid, m.p. 165–166° dec. (with some darkening from 145°). The infrared spectrum showed this to be a hydrate.

3α,17α-Dihydroxy-11,20-diketopregnene-21-trimethylammonium Bromide.—To a cold solution of 25.6 g. (0.06 mole) of 21-bromo-3α,17α-dihydroxypregnane-11,20-dione[9] in 330 ml. of ethyl methyl ketone was added 6.2 g. (0.1 mole) of cold trimethylamine. The flask was stoppered, clamped, and allowed to stand at room temperature for 3 days. A tan gummy solid separated and then white crystals separated from the supernatant solution. These crystals were twice recrystallized from a mixture of ethanol and ethyl methyl ketone giving 5.49 g. of white solid, m.p. 200–204°. The crystallized gummy solid proved hard to purify.

Anal. Calcd. for $C_{24}H_{33}BrNO_4$: C, 59.25; H, 8.29; N, 2.88; Br, 16.43. Found: C, 59.23; H, 8.76; N, 2.79; Br, 16.37.

Acknowledgment.—The author wishes to thank the following people who contributed to this work: Dr. Hugh H. Keasling, Mr. William Veldkamp, and Mr. Kurt F. Stern for the biological data, our Department of Physical and Analytical Chemistry for the spectral and analytical data, and Mr. R. F. Tripp for technical assistance.

Antihypertensive Agents. III.[1] 3-Hydroxy-3-phenylphthalimidines

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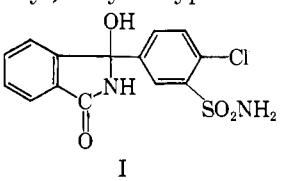
3-Hydroxy-3-phenylphthalimidines, related structurally to the diuretic agent chlorphthalidone but lacking a sulfamoyl substituent, showed antihypertensive but not diuretic activity when administered intravenously to anesthetized dogs. Structure–activity relationships in the series were explored.

In 1961, a preliminary account was given[2] of investigations concerned with the antihypertensive activity of compounds related to certain known diuretic sulfonamides, but lacking the free sulfamoyl group. Subsequently detailed accounts of work in the 1,2,4-benzothiadiazine series were published.[3] We would now like to report results obtained with some substituted phthalimidines.

A noteworthy feature of chlorphthalidone[4] (I) is its close similarity in diuretic and antihypertensive effects with chlorothiazide (and related thiazides)[5] in spite of major structural differences between the compounds. In view of the enhancement of the antihypertensive effect and elimination or reversal of the diuretic effect obtained on removal of the sulfamoyl group in the thiazide series,[2,3] we were prompted to examine the biological properties of 3-(*p*-chlorophenyl)-3-hydroxyphthalimidine (II).



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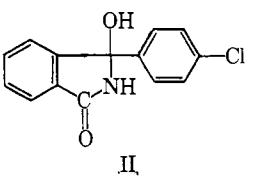

II

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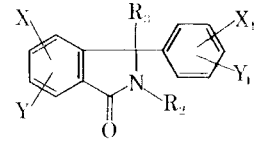
Table I

3-Hydroxy-3-phenylphthalimidines

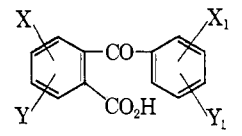


No.	X	Y	X_1	Y_1	R_2	R_3	M.p., °C.	Recrystn. solvent[a]	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity
1[b]	H	H	3′-SO_2NH_2	4′-Cl	H	OH			$C_{14}H_{11}ClN_2O_4S$							−
2[b]	H	H	H	4′-Cl	H	OH			$C_{14}H_{10}ClNO_2$							++++
3[b]	H	H	H	H	H	OH			$C_{14}H_{11}NO_2$							++
4	H	H	3′-Cl	H	H	OH	174–175	E–B–H	$C_{14}H_{10}ClNO_2$	64.75	64.57	3.88	3.67	13.65	13.74	++
5	H	H	2′-Cl	H	H	OH	174–175	E–B–H	$C_{14}H_{10}ClNO_2$	64.75	64.38	3.88	3.92	13.65	13.11	++
6	H	H	H	4′-CF_3	H	OH	239–241	E–B	$C_{15}H_{10}F_3NO_2$	61.43	61.28	3.44	3.25	19.44[c]	19.75[c]	+++
7	H	H	H	4′-CH_3	H	OH	173–175	E–B–H	$C_{15}H_{13}NO_2$	75.29	75.20	5.48	5.17			±
8	H	H	H	4′-OCH_3	H	OH	171–173	E–B–H	$C_{15}H_{13}NO_3$	70.58	70.49	5.13	5.39			−
9	H	H	3′-Cl	4′-Cl	H	OH	200–202	E–B–H	$C_{14}H_9Cl_2NO_2$	57.17	57.07	3.08	3.25	24.11	24.30	+++
10	H	H	2′-Cl	4′-Cl	H	OH	180–182	E–B–H	$C_{14}H_9Cl_2NO_2$	57.17	56.93	3.08	3.10	24.11	23.82	+++
11	4-Cl	H	H	H	H	OH	209–211	E–B–H	$C_{14}H_{10}ClNO_2$	64.75	64.89	3.88	4.14	13.65	13.51	++
12	4-Cl	H	H	4′-Cl	H	OH	251–252	E–B–H	$C_{14}H_9Cl_2NO_2$	57.17	56.85	3.08	3.10			+++
13	4-Cl	H	2′-CH_3	4′-CH_3	H	OH	206–208	E–B–H	$C_{16}H_{14}ClNO_2$	66.78	66.73	4.90	4.89	12.32	12.28	++
14	5-OCH_3	6-OCH_3	H	4′-Cl	H	OH	230–231	E–B–H	$C_{16}H_{14}ClNO_4$	60.10	60.22	4.41	4.58	11.09	11.12	++
15[b]	H	H	H	4′-Cl	CH_3	OH			$C_{15}H_{12}ClNO_2$							+++
16[b]	H	H	H	4′-Cl	H	OCH_3			$C_{15}H_{12}ClNO_2$							++
17[b]	H	H	H	4′-Cl	H	$-NC_5H_{10}$			$C_{19}H_{19}ClN_2O$							+++
18	H	H	H	4′-Cl	H	H	210–211	C–H	$C_{13}H_{10}ClNO$	69.00	69.30	4.46	4.39	5.75[d]	5.71[d]	++

[a] E = ethanol, B = benzene, H = hexane, C = chloroform. [b] See ref. 7. [c] Fluorine. [d] Nitrogen.

TABLE II

2-BENZOYLBENZOIC ACIDS

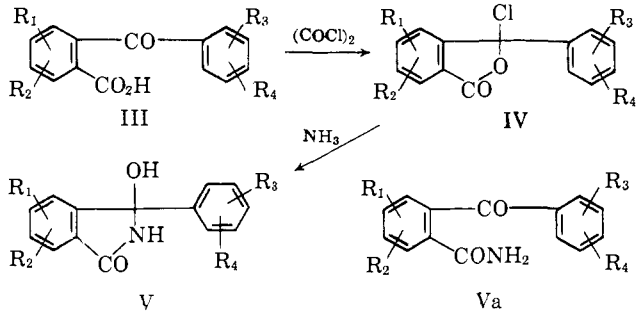


No.	X	Y	X_1	Y_1	M.p., °C.	Recrystn. solvent[a]	Empirical formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Chlorine, %— Calcd.	Found
19[b]	H	H	3′-Cl	H			$C_{14}H_9ClO_3$						
20[b]	H	H	2′-Cl	H			$C_{14}H_9ClO_3$						
21	H	H	H	4′-CF_3	176–178	B–H	$C_{15}H_9F_3O_3$	61.23	61.41	3.08	3.30	19.37[c]	19.30[b]
22	H	H	H	4′-OCH_3	145–147	Et–H	$C_{15}H_{12}O_4$	70.30	70.46	4.72	4.90		
23[d]	H	H	3′-Cl	4′-Cl			$C_{14}H_8Cl_2O_3$						
24[e]	H	H	2′-Cl	4′-Cl			$C_{14}H_8Cl_2O_3$						
25[f]	3-Cl	H	H	H			$C_{14}H_9ClO_3$						
26	3-Cl	H	H	4′-Cl	182–183	C–H	$C_{14}H_8Cl_2O_3$	56.97	56.81	2.73	2.90	24.03	24.45
27[f]	3-Cl	H	2′-CH_3	4′-CH_3			$C_{16}H_{13}ClO_3$						
28	4-OCH_3	5-OCH_3	H	4′-Cl	227–228	Et–H	$C_{16}H_{13}ClO_5$	59.91	59.84	4.09	4.20	11.06	11.22

[a] B = benzene, C = chloroform, Et = ether, H = hexane. [b] M. S. Newman, *J. Am. Chem. Soc.*, **60**, 1368 (1938). [c] Fluorine. [d] See ref 10b. [e] See ref. 10a. [f] See ref. 10d.

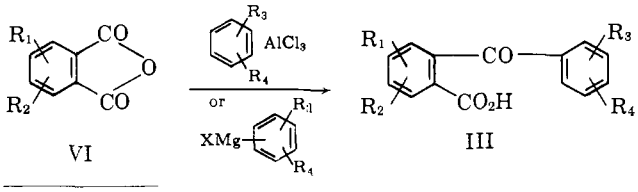
This compound, when administered intravenously to anesthetized dogs at doses of 10 mg./kg., produced a fall in blood pressure of extent and duration similar to that brought about by diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide).[3] Also, on oral administration of the phthalimidine (II) to saline-loaded rats, an antidiuretic effect was observed of the same order as that produced by diazoxide.[6]

Accordingly, other related phthalimidines were prepared and evaluated biologically. These are listed in Table I. A number of them were known compounds and were prepared according to procedures described in the literature. The new compounds were synthesized from the corresponding 2-benzoylbenzoic acids (III) by conversion to the pseudo acid chloride (IV) followed by treatment with ammonia to give the phthalimidine (V). The phthalimidine structure (V) was established from a consideration of the infrared

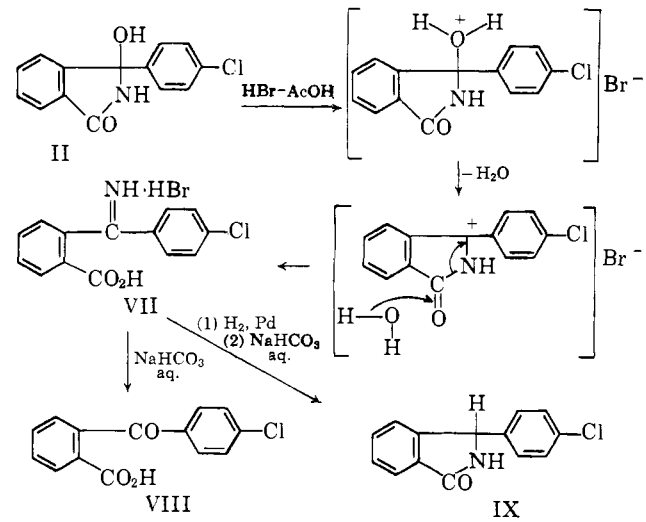


spectra of the products determined in pyridine solution. These show a single sharp carbonyl absorption band in the 5.8 μ region indicative of the phthalimidine structure (V) as opposed to the open-chain form Va which requires two carbonyl absorptions.[7]

The benzoylbenzoic acids (III) (Table II) were obtained from the phthalic anhydride (VI) *via* a Friedel–Crafts reaction or by reaction with an appropriate Grignard reagent. The structure of the benzoylbenzoic acid **26** (Table II) was established by decarboxylation with copper powder in quinoline affording 2,4′-dichlorobenzophenone.



In connection with some projected demethylation experiments on methoxyl-substituted 3-hydroxy-3-phenylphthalimidines we were led to investigate the reactivity of 3-(*p*-chlorophenyl)-3-hydroxyphthalimidine (II) towards refluxing 50% hydrogen bromide–acetic acid. The crystalline product which separated from the reaction mixture had the elemental composition $C_{14}H_{11}BrClNO_2$ and appeared to be a hydrobromide salt since an immediate, copious precipitate formed with silver nitrate solution. The empirical formula of the product corresponds to the hydrobromide of the starting phthalimidine (II); however, treatment with hot sodium bicarbonate solution gave 2-(*p*-chlorobenzoyl)benzoic acid (VIII), whereas II was stable under these conditions. Catalytic reduction of the compound in methanol solution in the presence of platinum oxide and treatment of the reduction product with sodium bicarbonate solution furnished 3-(*p*-chlorophenyl)phthalimidine (IX) identified by comparison with an authentic sample.[8] These transformations established the structure of the initial reaction product from II as VII. A probable pathway for the formation of VII is shown in the accompanying reaction scheme.



(6) R. M. Taylor, *Angiology*, **14**, 79 (1963).

(7) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

(8) Synthesized by M. H. Sherlock and N. Muller-Kulenkampff, Schering Corporation.

Pharmacological Methods.[9]—The test procedure has been described in part I.[3b] The activities of the compounds are given in Table I and are rated according to categories defined in part II.[1]

Structure–Activity Relationships.—With the exception of **7** and **8** all of the compounds show significantly greater antihypertensive activity than chlorphthalidone (**1**). 3-Hydroxy-3-phenylphthalimidine (**3**) exhibits moderate antihypertensive activity. Introduction of a chlorine atom in the 4′-position (**2**) results in a marked increase in activity, but in other positions this substituent does not significantly change activity (**4**, **5**, and **11**). Dichloro compounds (**9**, **10**, and **12**) are moderately active but not as active as the 4′-monochloro compound (**2**). More highly substituted compounds (**13** and **14**) are no more active than **3** which has no aromatic ring substituents. Some loss of activity is evident when the chlorine atom in **2** is replaced by a trifluoromethyl group and activity is practically abolished when the replacing group is methyl or methoxyl. Replacement of the hydroxyl group of **2** by methoxyl, piperidyl, or hydrogen lowers activity. None of the compounds tested shows significant diuretic activity; some exhibit antidiuretic properties.

Experimental

3-Hydroxy-3-phenylphthalimidines.—These were prepared by a modification of the method of Graf.[7] The requisite benzoylbenzoic acid (40.0 g.) in benzene (150 ml.) was mixed with oxalyl chloride (20% excess) and, after the initial reaction had subsided, the reaction mixture was refluxed for 1 hr. Benzene and excess of oxalyl chloride were removed by distillation, the residue was cautiously added to a solution of 28% ammonium hydroxide (200 ml.) and ethanol (100 ml.), kept at room temperature for 16 hr., and the crude product was collected by filtration. Recrystallization was effected best by dissolving the crude dry product in the minimum volume of a 1:1 mixture of benzene and alcohol, concentrating the solution to about half the original volume, and adding hot hexane until crystallization began. Yields of crude product were 50–90% and yields of the purified compounds 25–78%.

2-Benzoylbenzoic Acids.—The benzoylbenzoic acids were prepared either by a Friedel–Crafts reaction between a substituted phthalic anhydride and the appropriately substituted benzene or by reaction of the phthalic anhydride with a Grignard reagent from a substituted benzene.[10]

2-(*p*-Trifluoromethylbenzoyl)benzoic Acid (21).—This was prepared in 68% yield from *p*-trifluoromethylphenylmagnesium bromide[11] and phthalic anhydride.

2-(*p*-Anisoyl)benzoic Acid (22).—Compound **22** was obtained in 57% yield from the reaction of *p*-anisoylmagnesium bromide and phthalic anhydride.

2-(*p*-Chlorobenzoyl)-3-chlorobenzoic Acid (26).—This compound was prepared in 77% yield from the Friedel–Crafts reaction of 3-chlorophthalic anhydride[10d] and chlorobenzene.

A mixture of the acid (2.0 g.) and copper powder (0.2 g.) in quinoline (15 ml.) was refluxed for 1 hr., cooled, and the solution was decanted from the copper and diluted with ether (100 ml.). The ether solution was washed with three 50-ml. portions of 10% hydrochloric acid followed by 10% sodium carbonate solution (100 ml.), and then dried over anhydrous sodium sulfate. Concentration of the dried ether solution and addition of hexane gave 2,4′-dichlorobenzophenone (0.8 g.), m.p. 64–65° (lit.[12] m.p. 66.5–67°). 3,4′-Dichlorobenzophenone[13] melts at 113°.

2-(*p*-Chlorobenzoyl)-4,5-dimethoxybenzoic Acid (28).—This was prepared in 46% yield from *m*-hemipinic anhydride[14] and *p*-chlorophenylmagnesium bromide.

1-(*o*-Carboxyphenyl)-1-(*p*-chlorophenyl)methyleneimine Hydrobromide (VII).—A mixture of 3-(*p*-chlorophenyl)-3-hydroxyphthalimidine (II) (40.0 g.) and a 50% solution of hydrogen bromide in acetic acid (150 ml.) was refluxed for 1 hr., cooled, and the separated solid was collected by filtration, washed thoroughly with anhydrous ether (total 400 ml.), and dried giving the product (46.2 g., 89%), m.p. 233° dec. Recrystallization was effected from methanol–chloroform–ether mixtures, but the melting point did not change; λ_{max}^{MeOH} 231 mμ (ε 18,600), 294 (13,400).

Anal. Calcd. for $C_{14}H_{11}BrClNO_2$: C, 49.36; H, 3.26; Br, 23.46; Cl, 10.41. Found: C, 48.90; H, 3.60; Br, 23.81; Cl, 10.48.

Hydrolysis of VII.—A solution of VII (0.3 g.) in 10% sodium bicarbonate solution (10 ml.) was refluxed for 1 hr. and then acidified with concentrated hydrochloric acid. The reaction mixture was chilled and filtered yielding 2-(*p*-chlorobenzoyl)-benzoic acid (VIII), m.p. 152–154°, identified by a mixture melting point determination and comparison of infrared spectra with an authentic sample.

3-(*p*-Chlorophenyl)phthalimidine (IX). A.—Compound VII (4.0 g.) in methanol (125 ml.) was reduced in the presence of platinum oxide (0.1 g.) at room temperature on a Parr hydrogenator for 2 hr. The catalyst was filtered and the solvent evaporated affording an orange gum which was dissolved in methanol containing an excess of hydrogen bromide. Evaporation of the solvent again gave a gum, presumable crude α-(*o*-carboxyphenyl)-*p*-chlorobenzylamine hydrobromide, which did not solidify. This gum was dissolved in methanol (50 ml.) and the pH adjusted to *ca.* 8 with 5% sodium bicarbonate solution. The resultant solution was concentrated in an air current giving a solid (0.4 g.), m.p. 198–200°. Recrystallization from chloroform–hexane gave IX (0.2 g.), m.p. 210–212°, identified by mixture melting point and comparison of infrared spectra with an authentic sample (synthesized as described in B).

B.—A mixture of 3-*p*-chlorophenylphthalide[15] (25.0 g.) and 28% ammonium hydroxide solution saturated with ammonia at 0° (150 ml.) was heated in an autoclave at 150–160° for 10 hr. A solid was filtered from the cooled reaction mixture, washed with water, and dried to give the crude product (23.2 g.), m.p. 205–208°. Recrystallization from chloroform–hexane furnished 3-(*p*-chlorophenyl)phthalimidine (18.0 g.), m.p. 207–208°. The analytical sample, m.p. 210–211°, was obtained by recrystallizing from the same solvent mixture.

Acknowledgment.—The authors are indebted to Mr. E. Conner for the microanalyses.

(9) These studies were carried out by Drs. F. E. Roth, A. A. Rubin, and R. M. Taylor of the Department of General Pharmacology, Biological Research Division, Schering Corporation.

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