Quaternary Salts of Triethylenediamine

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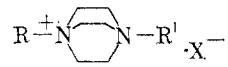
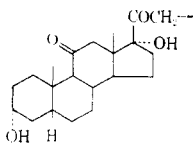
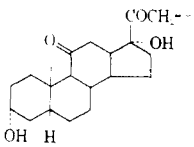
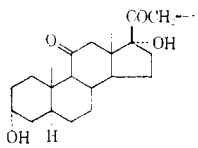
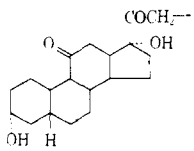
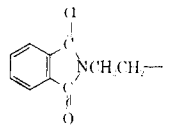
Thirteen monoquaternary (II) and diquaternary (III) salts were made from triethylenediamine (I) and various substituted alkyl halides (mostly α-halo ketones). The mono-N-oxide and its phenacyl derivative were also prepared. Although these showed some scattered pharmacological activities, the most interesting was the antibacterial activity of a disteroid quaternary salt.

Triethylenediamine (I)[1] has been known since 1858[2] but except for very simple quaternary salts (such as those from ethyl and methyl halides) few such salts have been reported.[3,4]

TABLE I

CHEMICAL DATA



No.	R	R′	X	Yield,[a] %	Dec. pt., °C.	Recrystallizing solvent
1	CH_3COCH_2—	None	$Cl^- \cdot 0.5H_2O$	87[c]	282	MeOH–MeEtCO–hexane
2	CH_3COCH_2—	·HCl	$Cl^- \cdot H_2O$	85[d]	250	Abs. MeOH then 90% MeOH
3	CH_3COCH_2—	CH_3COCH_2—	$2\,Cl^- \cdot H_2O$	31[e]	285[e]	90% EtOH
4	$C_6H_5COCH_2$—	None	Br^-	100[d]	273	MeOH
5	$C_6H_5COCH_2$—	$C_6H_5COCH_2$—	$2\,Br^- \cdot 0.25H_2O$	95[d]	283	MeOH
6	*p*-$NO_2C_6H_4$-$COCH_2$—	None	Br^-	81	190[h]	MeOH
7	*p*-$NO_2C_6H_4$-$COCH_2$—	·HBr	$Br^- \cdot 0.5H_2O$	91[g]	>300	MeOH + H_2O
8	*p*-$NO_2C_6H_4$-$COCH_2$—	*p*-NO_2-C_6H_4-$COCH_2$—	$2\,Br^-$	98	>300[i]	H_2O
9	3,4-$(OH)_2$-$C_6H_3COCH_2$—	None	Cl^-	45	268	80% MeOH
10	3,4-$(OH)_2$-$C_6H_3COCH_2$—	3,4-$(OH)_2$-$C_6H_3COCH_2$—	$2\,Cl^- \cdot H_2O$	8.1[e]	260	H_2O
			$Br^- \cdot H_2O$	[d]	263–266	MeOH + Et_2O
11		None	$Br^- \cdot 3H_2O$	[d]	245–265[k]	H_2O
12		·HBr	$2Br^- \cdot 2.5H_2O$	60[d]	243–248	H_2O
13			$Br^- \cdot H_2O$	56[f]	306[e]	MeOH
14		None				
15	*p*-(H_2NSO_2)-$C_6H_4CH_2$—	None	Br^-	100	240–245	80% MeOH
16	*p*-(H_2NSO_2)-$C_6H_4CH_2$—	*p*-(H_2NCO_2)-$C_6H_4CH_2$—	$2Br^-$	91[a]	266	H_2O
17	O·HCl	·HCl		93[d]		MeOH
18	$C_6H_5COCH_2$—	→ O	$Br^- \cdot H_2O$	78[d]	165–166	90% EtOH + Et_2O

[a] The yields of the monoquaternary salts are based on the alkyl halide used (RX). Those of the diquaternary salts are based on the trithylenediamine used. The yields of the acid additions salts are based on the corresponding monoquaternary salt bases. Unless otherwise specified the yields are based on materials whose decomposition points are not more than 2° below those of the analyzed samples. [b] Water was determined by the Karl Fisher method. [c] The product which crystallized from the reaction mixture had m.p. 168–175° and an infrared spectrum practically identical with that of the recrystallized (analytical) sample. The large difference in melting points may be due to different degrees of hydration or to dimorphic forms. [d] See Experimental section for specific preparation of this compound. [e] Analysis by Huffman Microanalytical Laboratories. [f] This product was precipitated from the reaction mixture by the addition of 400 ml. of methyl ethyl ketone. [g] The decomposition point was not sharp. There was some sintering from 220°. [h] The

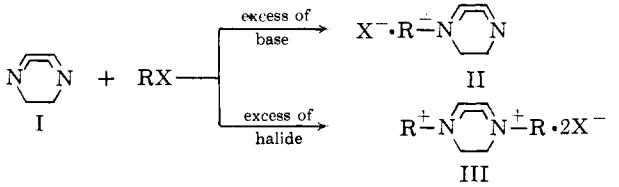
(1) Systematically named 1,4-diazabicyclo[2.2.2]octane.

(2) A. W. Hofmann, *Jahresber. Fortschr. Chem.*, 343 (1858); *Proc. Roy. Soc.* (London), **9**, 153 (1859).

(3) F. G. Mann and D. B. Mukherjee, *J. Chem. Soc.*, 2298 (1949); F. G. Mann and A. Senior, *ibid.*, 4476 (1954); F. G. Mann and F. C. Baker, *ibid.*, 1881 (1957).

We were interested in the preparation of different types of quaternary salts in order to study their pharmacological properties. For this purpose a series of substituted alkyl halides (mostly α-halo ketones) was allowed to react with the base to give the salts listed in Table I.

It was usually possible to obtain either the monoquaternary salt (II) or the diquaternary salt (III), depending on the ratio of reactants and on the solvent. A solvent such as ethyl methyl ketone in which the mono- salts (II) were insoluble favored these whereas methanol in which they were more soluble favored the di-salts (III). The general methods for preparing these salts are illustrated in the Experimental section by the preparation of the mono- and diphenacyl salts, and their chemical properties are listed in Table I. Since the mono-salts (II) still contained a basic nitrogen, acid addition salts could be made from them.



Treatment of triethylenediamine in ethanol with an excess of hydrogen peroxide surprisingly gave an excellent yield of the mono-N-oxide and little if any of the di-N-oxide. This structure was established by conversion to the dihydrochloride (**17**) which gave a

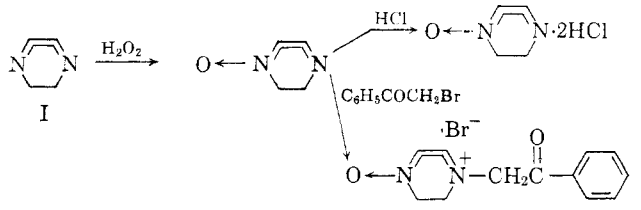
Molecular formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Halogen Calcd.	Halogen Found	O Calcd.	O Found	H_2O[b] Calcd.	H_2O[b] Found
$C_9H_{17}ClN_2O \cdot 0.5H_2O$	50.58	50.23	8.49	8.58	13.11	13.24	Cl, 16.59	Cl, 17.09	...	...	...	...
$C_9H_{18}Cl_2N_2O \cdot H_2O$	41.70	42.08	7.78	7.61	10.81	10.58	Cl, 27.36	Cl, 27.63	12.35	12.02[e]	6.95	7.05
$C_{12}H_{22}Cl_2N_2O_2 \cdot H_2O$	45.72	45.61	7.67	7.54	8.89	8.72	Cl, 22.49	Cl, 22.20	15.23	15.48	5.72	5.77
$C_{14}H_{19}BrN_2O$	54.03	54.21	6.15	5.86	9.00	8.77	Br, 25.68	Br, 25.62	5.14	5.07	...	...
$C_{22}H_{26}Br_2N_2O_2 \cdot 0.25H_2O$	51.33	51.61	5.19	5.13	5.44	5.32	Br, 31.05	Br, 31.04	7.00	7.87	0.88	0.91
$C_{14}H_{18}BrN_3O_3$									...	...	...	...
$C_{18}H_{19}Br_2N_3O_3 \cdot 0.5H_2O$	37.69	37.82	4.52	4.70	9.42	9.23	Br, 35.82	Br, 35.50	12.55	11.84[e]	2.02	2.51
$C_{22}H_{24}Br_2N_4O_6$	44.02	43.74	4.03	3.75	9.33	9.31	Br, 26.63	Br, 26.24	15.99	16.35[e]	...	...
$C_{14}H_{19}ClN_2O_3$	56.28	56.04	6.41	6.21	9.38	9.16	Cl, 11.87	Cl, 11.40	...	...	0.00	0.00
$C_{22}H_{26}Cl_2N_2O_6 \cdot H_2O$	52.49	52.09	5.61	5.25	5.57	5.34	Cl, 14.09	Cl, 13.99	22.25	22.60[e]	3.58	3.65
$C_{27}H_{43}BrN_2O_4 \cdot H_2O$	...	...	...	...	5.02	4.93	Br, 14.33	Br, 14.67	...	...	...	...
$C_{27}H_{44}Br_2N_2O_4 \cdot 3H_2O$	48.07	47.90	7.47	7.29	4.15	3.86	Br, 23.70	Br, 23.03	...	...	8.01	8.23
$C_{48}H_{74}Br_2N_2O_8 \cdot 2.5H_2O$	56.97	56.88	7.82	7.97	2.77	2.72	Br, 15.79	Br, 15.66	...	...	4.45	4.53
$C_{16}H_{20}BrN_3O_2 \cdot H_2O$	50.01	50.07	5.77	5.88	10.94	10.85	Br, 20.80	Br, 20.83	...	...	4.69	4.84
$C_{13}H_{20}BrN_3O_2S$[n]	43.10	42.96	5.56	5.70	11.59	11.27	Br, 22.06	Br, 21.57	8.83	9.17	0.00	0.00
$C_{20}H_{28}Br_2N_4O_4S_2$[p]	39.22	39.50	4.61	4.52	9.15	8.77	Br, 26.10	Br, 25.87	...	...	0.00	0.00
$C_6H_{14}Cl_2N_2O$	35.83	36.18	7.02	6.82	13.93	13.86	Cl, 35.26	Cl, 35.28	7.96	7.87	...	...
$C_{14}H_{19}BrN_2O_2 \cdot H_2O$	48.70	48.92	6.13	6.02	8.12	7.82	Br, 23.15	Br, 23.25	13.90	13.45	...	...

decomposition point was not sharp. There was some darkening from 174°. Although this was converted to the hydrobromide (**7**) in excellent yield, analysis indicates it may not be of high purity. [i] With darkening from 235°. [j] A large amount of insoluble black solid separated from the reaction mixture. The product was obtained from the filtrate by treatment with decolorizing charcoal, filtering, and evaporating to dryness. The residue was recrystallized from 50% 2-propanol and twice from water. [k] With darkening from 210°. [l] The reaction was run in 25% methanol and 75% methyl ethyl ketone. An attempt was made to prepare the diquaternary salt, using an excess of N-(2-bromoethyl)phthalimide. However, only the monoquaternary salt was obtained. [m] With darkening from 269°. [n] *Anal.* Calcd.: S, 8.83. Found: S, 8.75. [o] Methanol (800 ml.) was used as solvent for a 0.1-mole run. [p] *Anal.* Calcd.: S, 10.47. Found: S, 10.61.

(4) S. Oae, B. Hovarth, C. Zalut, and R. Harris, *J. Org. Chem.*, **24**, 1348 (1959); W. E. Earner, U. S. Patent 3,010,963; *Chem. Abstr.*, **56**, P 10167*g* (1962); S. D. Ross and M. Finkelstein, *J. Am. Chem. Soc.*, **85**, 2603 (1963).

good analysis. Potentiometric titration showed two breaks in the curve (indication that the nitrogens are different) and gave a good neutral equivalent value. Furthermore the N-oxide reacted with phenacyl bromide to give the quaternary salt N-oxide (Table I, **18**).

Since the completion of this work, two reports[5] have appeared in which the di-N-oxide of triethylenediamine was obtained with an excess of hydrogen peroxide. This was not obtained under our conditions.



I

Pharmacology.—These salts were tested widely for various pharmacological properties. They are surprisingly nontoxic and, although several showed interesting properties, no general activity was found. Compounds **2, 8, 10, 12, 13,** and **14** showed some central nervous system depression while **7** and **15** showed central nervous system stimulation in intact mice.[6] Compounds **4, 5, 12,** and **13** were anorexigenic[7] but were only about one-fiftieth as active as amphetamine. Compound **12** seemed to have some anticholinergic properties as shown by pupil dilation in mice injected intraperitoneally at 10% of the LD_{50}.

The most interesting activity was found for the steroid diquaternary salt **13**. It is an active antibacterial agent *in vivo* in mice against a number of organisms (especially Gram-positives). Table II shows this activity by the intraperitoneal and subcutaneous routes. It was virtually inactive orally. The tolerated dose in mice is about 30 mg./kg. i.p. and about 200 mg./kg. s.c.

TABLE II

ANTIBACTERIAL ACTIVITY OF COMPOUND **13**

Organism	CD_{50} (mg./kg.)[a] i.p.	CD_{50} (mg./kg.)[a] s.c.
Streptococcus hemolyticus	sl <2.5	65.5 ± 13
Staphylococcus aureus	<5	50 ± 18
Klebsiella pneumoniae I	>40	172 ± 55
Streptococcus viridans	18 ± 4	>200
Escherichia coli	>40	>200
Proteus vulgaris	>40	>200

[a] CD_{50} is the dose that will cure one-half of the animals given 100 lethal doses of the bacterium.

All the other quaternary salts of this series, even the monosteroid salt (**12**), had no antibacterial activity at the doses tested. For comparison the trimethylamine quaternary salt of this same steroid [(3α,17α-dihydroxy-11,20-dioxo-5β-pregnan-21-yl)trimethylammonium bromide] was prepared, but this too was inactive.

Experimental[8]

General Method for the Preparation of the Monoquaternary Salts. 1-Phenacyl-4-aza-1-azoniabicyclo[2.2.2]octane Bromide (4).—To a solution of 44.8 g. (0.4 mole) of triethylenediamine in 400 ml. of ethyl methyl ketone was slowly added with stirring during 2.5 hr. a solution of 39.8 g. (0.2 mole) of α-bromoacetophenone in 250 ml. of ethyl methyl ketone. A white precipitate separated and after stirring for 1.5 hr. more it was collected, washed with ethyl methyl ketone, and dried giving 64.2 g. of white solid, m.p. 272° dec. (after darkening from 240°). This was recrystallized from 300 ml. of methanol giving 42 g. of white solid, m.p. 273° dec. (after darkening from 240°).

General Method for the Preparation of the Diquaternary Salts. 1,4-Diphenacyl-1,4-diazoniabicyclo[2.2.2]octane Dibromide Hydrate (5).—To a solution of 11.2 g. (0.1 mole) of triethylenediamine in 50 ml. of methanol was added 60.0 g. (0.3 mole) of α-bromoacetophenone. The temperature reached reflux and then subsided and a white solid separated in about 30 min. After standing for 2.5 days the solid was collected, washed with methanol, and dried giving 48.9 g. of solid, m.p. 285° dec. (after darkening from 242°). This was recrystallized from 600 ml. of 50% methanol giving 37.9 g. of white crystals with the same melting characteristics. After drying at 100° under high vacuum, it analyzed for about 0.25 molecule of water.

1-Acetonyl-4-aza-1-azoniabicyclo[2.2.2]octane Chloride Hydrochloride Hydrate (2).—The unrecrystallized monoquaternary salt (**1**) (m.p. 168–175°) was dissolved in 500 ml. of absolute methanol and the solution was acidified with methanolic hydrogen chloride. After cooling, the white crystalline salt was collected and dried in a vacuum desiccator giving 43.13 g. of white solid, m.p. 250° dec. This was recrystallized first from absolute methanol and then from 90% methanol giving 22.7 g. of white crystals, m.p. 250° dec.

1-(*p*-Nitrophenacyl)-4-aza-1-azoniabicyclo[2.2.2]octane Bromide Hydrobromide Hemihydrate (7).—A solution of 52.6 g. (0.148 mole) of the base (**6**) in 550 ml. of methanol was acidified with 40 ml. of 48% aqueous hydrobromic acid. The mixture was heated to boiling and just sufficient water was added to dissolve the solid. On cooling, crystals separated. The crystals were collected, washed with methanol, and dried giving 55.8 g. of yellow crystals, m.p. >300° (with darkening from 232°). Analysis showed this to be the hemihydrate.

(3α,17α-Dihydroxy-11,20-dioxo-5β-pregnan-21-yl)-4-aza-1-azoniabicyclo[2.2.2]octane Bromide Hydrate (11).—To a solution of 11.2 g. (0.1 mole) of triethylenediamine in 50 ml. of dry ethyl methyl ketone was added slowly during 1.5 hr. at room temperature with stirring a solution of 13.5 g. (0.03 mole) of 21-bromo-3α-dihydroxypregnane-11,20-dione[9] in 150 ml. of dry ethyl methyl ketone. After standing at room temperature for 4 days and warming for a few minutes, the solution was cooled and filtered from a gummy precipitate. The precipitate was dried giving 15 g. of solid, m.p. 250° dec. with sintering from 100°. An additional 4.7 g. was obtained by dilution of the filtrate with absolute ether. A sample which was dissolved in methanol and diluted with absolute ether gave a nearly white solid, m.p. 263–266° dec. (with sintering from 150°). The nuclear magnetic resonance spectrum supported the proposed structure.

Hydrobromide (12).—A solution of 19 g. of the above salt in 180 ml. of water was acidified with 5 ml. of 48% hydrobromic acid. On standing in the refrigerator crystals slowly separated. The solid was collected, washed with water and ethanol, and dried giving 13.3 g. of light tan solid, m.p. 227–240°, with sintering from 210°. Concentration of the filtrate and dilution with ethanol gave an additional 2.2 g. of white crystalline hydrobromide, m.p. 245–265° dec., with darkening from 210°. Samples dried for various lengths of time and at various temperatures were found by Karl Fischer analysis to contain from 0–3 molecules of water. A sample dried at 25° in a vacuum desiccator for several days contained about 1.3 molecules of water. A sample of dried material allowed to equilibrate in air at 50% humidity contained about 3 molecules of water and had the analysis given in Table I. A sample dried overnight at 100° under high vacuum analyzed as anhydrous material.

Anal.[10] Calcd. for $C_{32}H_{44}Br_2N_2O_4$: C, 52.26; H, 7.15; Br, 25.76; N, 4.52. Found: C, 52.63; H, 7.15, Br, 24.65, N, 4.54.

1,4-Bis(3α,17α-dihydroxy-11,20-dioxo-5β-pregnan-21-yl)-1,4-diazoniabicyclo[2.2.2]octane Dibromide Hydrate (13).—A soln-

(5) A. Farkas and E. C. Herrick, U. S. Patent 3,038,903 (1962); *Chem. Abstr.*, **57**, 13776*d* (1962); A. A. Oswald and D. L. Guertin, *J. Org. Chem.*, **28**, 651 (1963).

(6) R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964), footnotes *a* and *b* to Table I.

(7) E. L. Schumann and R. V. Heinzelman, *ibid*, **7**, 329 (1964).

(8) Melting points were taken in capillary tubes with Thomas-Hoover apparatus using a partial immersion thermometer. Calibration against standards showed that no correction was necessary within an accuracy of about ±1°. Infrared spectra were taken on all pure products and in all cases were in accordance with the assigned structures.

(9) T. H. Kritchevsky, D. L. Garmaise, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 483 (1952).

(10) The carbon, hydrogen, and bromine analysis by Huffman Microanalytical Laboratories.

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.

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

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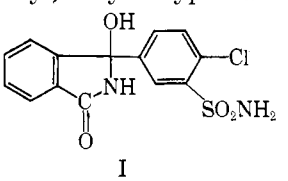
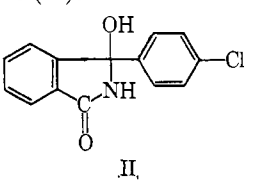
3-Hydroxy-3-phenylphthalimidines, related structurally to the diuretic agent chlorphthalidone but lacking a sulfamoyl substituent, showed antihypertensive but not diuretic activity when administered intravenously to anesthetized dogs. Structure–activity relationships in the series were explored.

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).



I



II

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