[CONTRIBUTION FROM SAHYUN LABORATORIES]

Antihypertensive Agents: Derivatives of 2-Imidazoline and 1,4,5,6-Tetrahydropyrimidine[1a]

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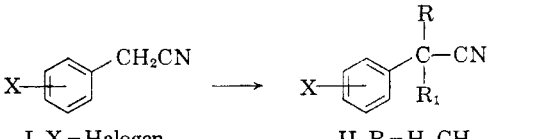
A series of twenty-eight halobenzyl-2-imidazolines and 1,4,5,6-tetrahydropyrimidines was prepared and studied pharmacologically in the experimental dog. Several of these compounds induced a pressor response while others exhibited strong adrenolytic and sympatholytic activity. One compound, 2-(*o*-chlorobenzyl)-2-imidazoline, was of particular interest for the management of essential hypertension in man.

Certain derivatives of 2-imidazoline, especially aralkyl-substituted 2-imidazolines, exhibit sympathomimetic activity while others cause an initial pressor or depressor response followed by an adrenolytic action both in the experimental animal and in man. Many structural variations of this type of compound have been examined for possible effect on blood pressure,[1b] but, as far as we are aware, only one halogenated aryl 2-imidazoline has been reported.[2] We, therefore, undertook the preparation of this series of halogenated compounds which included 1,4,5,6-tetrahydropyrimidines as well as 2-imidazolines for evaluation of their effect on blood pressure.

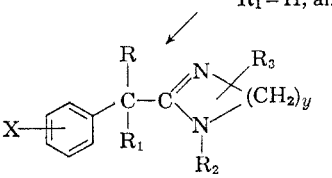
During the course of this investigation, Cavallini and co-workers[3] reported on a group of pharmacologically active substituted 2-benzyl-2-imidazolines which included two compounds that we had synthesized and studied: 2-(*m*-chlorobenzyl)-2-imidazoline and 2-(*p*-chlorobenzyl)-2-imidazoline. They reported that the introduction of a chlorine atom on the aryl ring can enhance the specific activity of a pharmacologically active molecule and cited, as an example, that 2-(*p*-chlorobenzyl)-2-imidazoline is a more powerful antiadrenergic agent than 2-benzyl-2-imidazoline itself. Our results were in general accord with their findings. However, we found that the optimum adrenolytic activity of this group of compounds was exhibited by the corresponding *o*-chloro derivative.

The compounds prepared for this study are listed in Table II, and, with two exceptions, were synthesized according to the scheme:



I. X = Halogen

II. R = H, CH_3
R_1 = H, alkyl, etc.



III. R_2 = H, CH_3
R_3 = H, OH, CH_3
y = 2, 3

The nitriles (I) were obtained by the interaction of potassium cyanide and the corresponding α-halotoluenes which were prepared by the bromination of the corresponding halogenated toluenes. The step-wise alkylation of I with various alkyl halides and sodium amide in the conventional procedure provided good yields of the substituted nitriles (II).

o-Chlorodiphenylacetonitrile (II. R = C_6H_5) was made from *o*-chlorobenzyl cyanide by the method used[4] for the *p*-chloro compound. One nitrile (II. R = OH) is actually a cyanohydrin and was obtained from *o*-chlorobenzaldehyde and hydrogen cyanide as previously described.[5] The constants of those nitriles (I and II), hitherto unreported, are presented in Table I.

The nitriles (II) were converted into the heterocycles (III) by two different methods. The more direct method, and the one used in all but two instances, involved the reaction between the nitrile and a diamine monotosylate at temperatures up to 210°, a procedure first reported by Oxley and Short.[6] The second method, applicable to the cyanohydrins (II. R = OH), involved the conversion of the cyanohydrins to imidate esters which in turn were condensed with diamines at low temperature to form the heterocycles (III).

Pharmacology. An investigation of the pharmacology of these compounds was carried out in the Department of Pharmacology, University of Texas, under the direction of Professors G. A. Emerson and J. B. Nash. The compounds were tested in the anesthesized dog for their effect on blood pressure and adrenolytic and/or sympatholytic properties. Pressor activity was found in several members of

(1)(a) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960. (b) C. R. Scholz, *Ind & Eng. Chem.*, **37**, 120 (1945).

(2) M. Hartmann and H. Isler, *Arch. expil. Path. Pharmacol.*, **192**, 141 (1939).

(3) G. Cavallini, E. Milla, E. Grumelli, E. Massarini, and D. Nardi, *Il. Farmaco*, **XI**, 634 (1956).

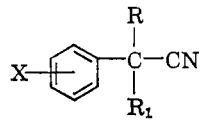
(4) M. E. Specter, L. C. Cheney, and S. B. Binkley, *J. Am. Chem. Soc.*, **72**, 1659 (1952).

(5) J. S. Buck, *J. Am. Chem. Soc.*, **55**, 2593 (1933).

(6) P. Oxley and W. F. Short, *J. Chem. Soc.*, 497 (1947).

TABLE I

SUBSTITUTED NITRILES (II)



X	R	R_1	Yield, %	B.p. (Mm.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
o-Cl	H	CH_3	60	79–81 (1.2)	C_9H_8ClN	8.46	8.62
o-Cl	CH_3	CH_3	71	92–93 (1.2)	$C_{10}H_{10}ClN$	7.81	8.03
o-Cl	H	C_3H_7	84	103–104 (1.3)	$C_{12}H_{14}ClN$	6.74	6.69
o-Cl	H	C_5H_9	71	129–130 (1)	$C_{13}H_{14}ClN$	6.38	6.28
o-Cl	H	C_6H_{11}	56	153–155 (1.6)	$C_{14}H_{16}ClN$	6.00	6.01
o-Cl	H	C_6H_5	79	148–150 (0.9)	$C_{14}H_{10}ClN$	6.15	6.24
o-Cl	H	$CH_2CH_2N(C_2H_5)_2$	80	131–133 (0.8)	$C_{14}H_{19}ClN_2$	11.17	11.99
o-I	H	H	37	119–121 (1)	C_8H_6IN	5.76	5.61
m-Br	H	C_6H_{11}	29	169–171 (2)	$C_{14}H_{16}BrN$	5.04	5.09
p-Cl	H	C_4H_9	47	126–129 (1.1)	$C_{12}H_{14}ClN$	6.75	6.71
p-Cl	H	C_6H_{11}	38	71–73[a]	$C_{14}H_{16}ClN$	6.00	5.91
o,o-diCl	H	H	65	75–76[a]	$C_8H_5Cl_2N$	7.53	7.45

[a] M.p.

this series, but the most interesting physiologic response noted was the prolonged adrenolytic activity of a few compounds, notably compound 2, the *o*-chloro derivative. Replacement of the chlorine atom in the aryl moiety by the other halogens in the same position altered the physiologic response so that these derivatives were predominantly pressor, although they did antagonize the effect of epinephrine and arterenol, but to a much lesser extent.

Compound 2 was studied extensively in the experimental animal. Upon the intravenous administration of 2.5 mg./kg., it produced an initial transient (two to four minutes) pressor response which was followed by an adrenolytic action lasting for as long as eighteen hours. During this time it abolished completely the effect of repeated injections of epinephrine and, to a considerable degree, the repeated injections of norepinephrine. The initial pressor response noted upon intravenous administration was not observed when the drug was given intraduodenally in amounts of 2.5 to 30 mg./kg. In view of its prolonged adrenolytic action, its low toxicity, and relative freedom from side effects, this compound was selected as a candidate for preliminary clinical trial. A report of this trial has been published.[7]

EXPERIMENTAL[8]

2-Imidazolines and 1,4,5,6-tetrahydropyrimidines (III). The general procedure was as follows: A mixture of 0.05 mole of the nitrile (II) and 0.06 mole of the diamine monotosylate[9] was heated at 200–210° until the evolution of ammonia had practically ceased (1–2 hr.). The cooled residue[10] was dissolved in water or dilute hydrochloric acid, and the solution was clarified by filtration or by ether extraction. The aqueous solution was then rendered alkaline with sodium hydroxide to precipitate the bases of the heterocycles (III). Solid bases were isolated by filtration and recrystallized, usually from heptane. Oily or semisolid bases were extracted with ether, the ether solutions were washed, dried, and treated with hydrogen chloride to form the hydrochloride salts which were purified by recrystallization from a suitable solvent, usually alcohol-ether. Certain of the bases were purified by distillation.

The following diamine tosylates were employed: monoethylenediamine,[6] bis-*N*-methylethylenediamine,[11] bis-1,3-diaminopropane[6]; bis-*N*-methyldiaminopropane, bis-1,3-diaminopropanol-2, and bis-1,3-diaminobutane.

1,3-Diaminobutane bistosylate. A solution of 26 g. (0.3 mole) of 1,3-diaminobutane in 40 ml. of isopropyl alcohol was combined with a solution of 114 g. (0.3 mole) of *p*-toluenesulfonic acid in 80 ml. of water and distilled to dryness. The solid salt was recrystallized from isopropyl alcohol, m.p. 190–191°.

Anal. Calcd. for $C_{18}H_{28}N_2O_6S_2$: N, 6.48. Found: N, 6.72.

1,3-Diaminopropanol-2 bistosylate was prepared from 1,3-diaminopropanol-2 in the manner described above; m.p. 272–273°.

Anal. Calcd. for $C_{17}H_{26}N_2O_7S_2$: N, 6.47. Found: N, 6.46.

N-Methyl-1,3-diaminopropane bistosylate was prepared from *N*-methyl-1,3-diaminopropane in the manner described above; m.p. 160–161°.

Anal. Calcd. for $C_{18}H_{28}N_2O_6S_2$: N, 6.48. Found: N, 6.36.

Ethyl p-chlorophenyl-α-hydroxyacetimidate hydrochloride. An ethereal solution containing 26 g. (0.155 mole) of the cyanohydrin[5] of *o*-chlorobenzaldehyde and 9.4 ml. of ethanol was treated with excess hydrogen chloride, and the mixture was allowed to remain at 25° overnight. The solid was isolated, washed with ether and dried; yield, 20 g. (51%); m.p. 130° dec.

Anal. Calcd. for $C_{10}H_{12}ClNO_2 \cdot HCl$: Cl^-, 14.17. Found: Cl^-, 14.16.

2-(p-Chloro-α-hydroxybenzyl)-1-methyl-1,4,5,6-tetrahydro-

(7) D. Rochelle and R. V. Ford, *Amer. Heart Jour.*, 56, 463 (1958).

(8) All melting points are corrected.

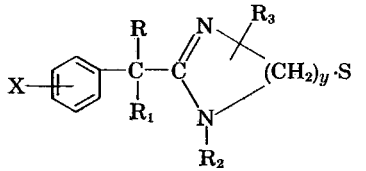
(9) In some instances the monotosylates were prepared *in situ* by combining equimolar quantities of the crystalline diamine bistosylate and diamine.

(10) This residue consisted largely of the heterocycle tosylate which in certain instances was isolated as a crystalline material and purified.

(11) P. Oxley and W. F. Short, *J. Chem. Soc.*, 8, 59 (1950).

TABLE II

2-IMIDAZOLINES AND 2-(1,4,5,6-TETRAHYDROPYRIMIDINES) (III)



No.	X	R	R_1	R_2	R_3	y	S	M.P.	Formula	Neut. Equiv.[a] Calcd.	Neut. Equiv.[a] Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	*o*-F	H	H	H	H	2	HCl[b]	194–195	$C_{10}H_{11}FN_2$·HCl	178	174	13.06	12.92	16.52	16.80
2	*o*-Cl	H	H	H	H	2	HCl[c]	235–236	$C_{10}H_{11}ClN_2$·HCl	195	198	12.12	12.33	15.34	15.39
3	*o*-Cl	H	H	H	H	3	HCl	214–215	$C_{11}H_{13}ClN_2$·HCl	—	—	11.43	11.40	14.46	14.33
4	*o*-Cl	H	H	CH_3	H	3	HCl	209–210	$C_{12}H_{15}ClN_2$·HCl	—	—	10.81	10.79	13.68	13.78
5	*o*-Cl	H	CH_3	H	H	2	HCl[d]	222–223	$C_{11}H_{13}ClN_2$·HCl	209	202	11.43	11.28	14.46	14.46
6	*o*-Cl	H	H	CH_3	H	2	HCl[e]	185–186	$C_{11}H_{13}ClN_2$·HCl	209	204	11.43	11.24	14.46	14.37
7	*o*-Cl	H	$CH_2CH_2N(Et)_2$	H	H	2	Base	57–58[f]	$C_{16}H_{24}ClN_3$	—	—	14.3	13.9	—	—
8	*o*-Cl	CH_3	CH_3	H	H	2	HCl[g]	224–225	$C_{12}H_{15}ClN_2$·HCl	223	225	10.81	10.95	13.67	13.65
9	*o*-Cl	CH_3	CH_3	CH_3	H	2	Base	62–64	$C_{13}H_{17}ClN_2$	237	238	11.84	12.03	—	—
10	*o*-Cl	OH	H	H	H	2	HCl	249–251	$C_{10}H_{11}ClN_2O$·HCl	—	—	11.34	11.30	14.35	14.21
11	*o*-Cl	OH	H	CH_3	H	3	H_2SO_4	183–184	$C_{12}H_{15}ClN_2O$·H_2SO_4	—	—	8.32	8.20	28.64	28.54[h]
12	*o*-Cl	CH_3	C_3H_7	H	H	2	Base	101–102	$C_{14}H_{19}ClN_2$	250	251	11.17	11.19	—	—
13	*o*-Cl	H	H	H	5-OH	3	HCl[i]	212–214	$C_{11}H_{13}ClN_2O$·HCl	225	225	10.73	10.65	13.58	13.61
14	*o*-Cl	H	H	H	4-CH_3	3	HCl	173–174	$C_{12}H_{15}ClN_2$·HCl	—	—	10.81	10.64	13.68	13.64
15	*o*-Cl	H	C_6H_5	H	H	2	Base	163–165	$C_{16}H_{15}ClN_2$	271	269	10.35	10.25	—	—
16	*o*-Cl	H	C_6H_{11}	H	H	2	Base	148.4–149.5	$C_{16}H_{21}ClN_2$	—	—	10.13	10.17	—	—
17	*o*-Cl	H	C_5H_9	H	H	2	Base	124–125	$C_{15}H_{19}ClN_2$	—	—	10.67	10.58	—	—
18	*o*-Br	H	H	H	H	2	HCl	246–247	$C_{10}H_{11}BrN_2$·HCl	—	—	10.17	10.14	12.86	12.80
19	*o*-I	H	H	H	H	2	HCl[j]	272–273 dec.	$C_{10}H_{11}IN_2$·HCl	2896	283	8.68	8.80	10.99	11.21
20	*m*-Cl	H	H	H	H	2	HCl	181–182[k]	$C_{10}H_{11}ClN_2$·HCl	—	—	12.12	12.26	15.34	15.34
21	*m*-Br	H	H	H	H	2	HCl	180–181	$C_{10}H_{11}BrN_2$·HCl	—	—	10.17	10.07	12.86	12.97
22	*m*-Br	H	C_6H_{11}	H	H	2	Base	155.5–157	$C_{16}H_{21}BrN_2$	—	—	8.72	8.61	—	—
23	*p*-Cl	H	C_5H_9	H	H	2	HCl[l]	188–189	$C_{14}H_{19}ClN_2$·HCl	—	—	9.77	9.55	12.36	12.37
24	*p*-Cl	H	H	H	H	2	HCl[m]	200–201[n]	$C_{10}H_{11}ClN_2$·HCl	195	195	—	—	15.34	15.36
25	*p*-Cl	H	C_6H_5	H	H	2	Base	132–134	$C_{16}H_{15}ClN_2$	—	—	10.35	10.19	—	—
26	*p*-Cl	H	C_6H_{11}	H	H	2	Base	184–185.5	$C_{16}H_{21}ClN_2$	—	—	10.13	9.85	—	—
27	*o*,*o*-diCl	H	H	H	H	2	HCl[o]	257–258	$C_{10}H_{11}Cl_3N_2$	229	234	—	—	13.35	13.57
28	*o*,*p*-diCl	H	H	H	H	2	HCl	197–198	$C_{10}H_{10}Cl_2N_2$·HCl	—	—	10.55	10.31	13.35	13.47

[a] Of bases. [b] Base, m.p. 90–91°. [c] Base, m.p. 116–118°. [d] Base, m.p. 104–105°. [e] Base, b.p. 122–124° (1 mm.). [f] B.p. 164–167° (1 mm.). [g] Base, m.p. 122–123°. [h] SO_4=. [i] Base, m.p. 157–158°. [j] Base, m.p. 100–101°. [k] Reported m.p. 180°. Ref. 3. [l] Base, m.p. 90–91°. [m] Base, m.p. 148–150°. [n] Reported m.p. 193–195°. Ref. 3. [o] Base, m.p. 185–186° (methanol).

pyrimidine sulfate (Compound 11). The acetimidate ester (20 g.; 0.8 mole) was added in portions to a stirred solution of 7 g. (0.08 mole) of *N*-methyl-1,3-diaminopropane in 100 ml. of ethanol at 5°. The mixture was stirred at 5° for 1 hr. and at 25° for 1 hr., after which it was vacuum-distilled to an oil. The oil was dissolved in a small volume of dilute hydrochloric acid, clarified by an ether extraction, and made alkaline. The base was extracted with ether, the ether solution was dried and stripped to an oil which solidified; yield, 11 g. (57%); m.p. 69–70° after recrystallization from heptane. The sulfate salt melted at 183–184° after recrystallization from isopropyl alcohol.

2-(p-Chloro-α-hydroxybenzyl)-2-imidazoline hydrochloride (Compound 10). This compound was prepared by essentially the same procedure used for compound 11, using ethylene diamine in place of *N*-methyl-1,3-diaminopropane.

SANTA BARBARA, CALIF.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE ORGANIC CHEMICALS DIVISION, MONSANTO CHEMICAL CO.]

The Synthesis of Organic Trithiocarbonates[1]

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Because of the interest of organic trithiocarbonates as biological toxicants and also as oil additives, fifty-five compounds of this class were synthesized which included symmetrical and unsymmetrical dialkyl, symmetrical diaryl, aryl alkyl, and aralkyl alkyl trithiocarbonates. Various synthetic routes for the preparation of these compounds were investigated.

Several members of the class of organic trithiocarbonates, particularly the symmetrical types, have been known for many years and various synthetic routes have been employed for their synthesis; however, no concentrated preparative study has been reported in the literature. Because of this fact and because of certain indications of biological activity[2-4] as well as utility as oil additives,[5] this work was undertaken.

Four methods for the preparation of trithiocarbonates were investigated. A synthetic route, which proved to be of great utility, involved the reaction of an aryl- or alkylthiol in the presence of base with an alkyl (Method A1) or aryl chlorodithioformate (Method A2). Forty-seven compounds were prepared by this general method. Thirty-five

$$\text{Method A } R_1SH + ClCSSR_2 \xrightarrow{NaOH} R_1SCSSR_2$$

$$\text{Method B } R_2SH + CS_2 \xrightarrow{KOH} KSCSSR_2 \xrightarrow{R,Br} R_1SCSSR_2$$

$$\text{Method C } 2RSH + CSCl_2 \xrightarrow{NaOH} RSCSSR$$

$$\text{Method D } R_1N_2^+Cl^- + KSCSSR_2 \longrightarrow R_1SCSSR_2$$

aryl alkyl trithiocarbonates, two aralkyl alkyl trithiocarbonates, and four unsymmetrical dialkyl trithiocarbonates were made by Method A1, and six aryl alkyl trithiocarbonates were made by Method A2.

Another route, which gave very good results, was the reaction of an alkylthiol with carbon disulfide in the presence of potassium hydroxide to form the potassium alkyl trithiocarbonate which subsequently reacted with an alkyl or aralkyl bromide to form the desired trithiocarbonate (Method B). Three aralkyl alkyl trithiocarbonates and two symmetrical dialkyl trithiocarbonates were prepared in this manner. In the case of diethyl trithiocarbonate (Table I, No. 13), the latter method gave a higher yield than when Method A1 was employed (75%, compared to 50%).

Three symmetrical diaryl trithiocarbonates were prepared by the reaction of thiophosgene with an aryl thiol (Method C) in the presence of base.

Only six of the trithiocarbonates reported in this paper have been previously described. Only diphenyl trithiocarbonate was prepared by the same method indicated in the literature. The dimethyl, diethyl, dibutyl, and diallyl trithiocarbonates were previously prepared by reaction of sodium trithiocarbonate, potassium trithiocarbonate or ammonium trithiocarbonate with an appropriate alkyl halide.

In an attempt to prepare ethyl *o*-nitrophenyl trithiocarbonate from *o*-nitrochlorobenzene and potassium ethyl trithiocarbonate by Method B, only bis(*o*-nitrophenyl) disulfide was obtained as determined by infrared analysis and melting point. Also an attempt was made to prepare methyl *p*-nitrophenyl trithiocarbonate by Method A1 using *p* - nitrobenzenethiol and methyl chlorodithioformate. Only bis(*p*-nitrophenyl) disulfide could

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(1) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(2) J. T. Bashour, U. S. Patent, **2,676,129** (1954); *Chem. Abstr.* **48**, 8472i (1954); Symmetrical dialkyl trithiocarbonates as nematocides.

(3) J. T. Bashour, U. S. Patent, **2,731,487** (1956); *Chem. Abstr.* **50**, 15583h (1956); Asymmetrical *t*-alkyl trithiocarbonates as insecticides and miticides.

(4) H. J. Renner, G. Schneider, and J. Weissflog, East Ger. Patent **15,431** (1958); *Chem. Abstr.* **54**, 2650f (1960). Symmetrical alkyl- or arylthiomethyl trithiocarbonates as insecticides.

(5) E. S. Blake, U. S. Patent, **2,396,487** (1946); *Chem. Abstr.* **40**, 2974[4] (1946).