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AMINO ALCOHOLS. XVI.[1] PHENYL HALOGENATED PROPADRINES

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INTRODUCTION

The effect of nuclear substituents such as OH, CH_3, OCH_3, etc. on the sympathomimetic properties of propadrine, $C_6H_5CH(OH)CH(NH_2)CH_3$, has been studied (1, 2, 3, 4, 5, 6). However, reports of the effect of nuclear halogen substitution in this series are still meager. Only *p*-chloropropadrine has been studied and reported as possessing three times the toxicity and one twenty-fifth the pressor activity of the unsubstituted amine (2).

Reported studies of the effect of halogens in related amines are also limited (7, 8, 9, 10, 11). Consequently, adequate correlation of the effect of the presence of a halogen atom in the phenyl nucleus on physiological activity is difficult.

This investigation was undertaken to make available for pharmacological study a series of propadrines containing halogens substituted in various positions of the aromatic nucleus in order to make possible a more complete correlation of the physiological effect of halogen substitution with the effect produced by other nuclear substituents already studied in this series.

The synthesis of *o*-, *m*-, and *p*-fluoro-; *o*-, *m*-, and *p*-chloro; and *o*-, *m*-, and *p*-bromopropadrine, $XC_6H_4CH(OH)CH(NH_2)CH_3$, was undertaken. *p*-Chloropropadrine, though previously reported, was included for comparison.

The synthesis depended, first, on the preparation of the appropriately substituted propiophenones. The *p*-halogen ketones were prepared by the Friedel-Crafts reaction from the appropriate phenyl halide and propionyl chloride. The *o*- and *m*-halogen ketones were obtained by replacing the amino group of *o*- and *m*-aminopropiophenones, respectively, with the desired halogen atom.

Nitration of propiophenone produced both the *o*-and *m*-mononitro derivatives. Since large amounts of these intermediates were required, a study of the optimum conditions for their preparation was made. Their reduction to the aminopropiophenones was conveniently accomplished by catalytic hydrogenation in benzene. The water formed in the reaction was drawn off, and the amine hydrochloride was precipitated in good yield by passing hydrogen chloride into the benzene solution. This method gave improved yields over those reported using tin and hydrochloric acid (3, 12, 13), iron and acetic acid (12), or stannous chloride and hydrochloric acid (14). The ketone group was unaffected under the conditions used.

Attempts to replace the amino group with fluorine by heating the dry dia-

[1] For Amino Alcohols XV, see Hartung and Foster, *J. Am. Pharm. Assoc., Scientific Ed.*, **35**, 15 (1946).

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zonium fluoroborates, according to the procedure of Schiemann and Winkelmüller (15), gave poor yields and formed large amounts of tar. However, it was found during this investigation that if the diazonium fluoborates were dropped into a stirred inert liquid hydrocarbon (toluene for the *m*-compound or heptane for the *o*-isomer) maintained at a temperature above the decomposition point of salt, satisfactory yields of the fluoropropiophenones were obtained.

The halogenated ketones were next converted into their corresponding isonitroso derivatives by a general reaction (1, 2, 3, 16) using butyl nitrite and hydrogen chloride in ether,

$$XC_6H_4COCH_2CH_3 \xrightarrow[HCl]{CH_3(CH_2)_2CH_2ONO} XC_6H_4COCCH_3 \quad (\text{NOH})$$

It has well been established that isonitroso ketones of this type can be hydrogenated in good yields to the corresponding amino alcohols with a palladium-charcoal catalyst in ethanolic hydrogen chloride (1, 2, 3, 4). However reports in the literature indicated that difficulty in preventing the loss of halogen from the ring during hydrogenation might be encountered.

Edkins and Linnell (9), in an attempt to prepare *p*-chloro- and *p*-bromopropadrine by the hydrogenation of the corresponding *p*-halogen aminopropiophenone, $XC_6H_4COCH(NH_2)CH_3$, with a palladium-charcoal catalyst in acid aqueous medium, obtained only propadrine, the halogen being removed from the ring. They further found that hydrogenation in an acidified ethanolic solution gave, instead of the desired products, the corresponding *p*-halogen benzoic acid in almost theoretical yield. The formation of these acids was explained by a hydrolysis involving a break of the carbon chain at the carbonyl group,

$$XC_6H_4CCH(NH_2)CH_3 \longrightarrow XC_6H_4C{=}C(NH_2)CH_3 \longrightarrow$$

(O above the first C; OH below the second C)

$$XC_6H_4COOH + CH_3CH_2NH_2$$

In our work no formation of halogen benzoic acids was observed.

Hartung, Munch, and Crossley (2) observed, in the hydrogenation of *p*-chloroisonitrosopropiophenone, that in the presence of water the aromatic chlorine atom was removed, but they were able to obtain the desired *p*-chloropropadrine by avoiding the use of water in the hydrogenation solvent.

In this work the isonitroso ketones were hydrogenated until three equivalents of hydrogen had been taken up. The fluorine atom did not possess the reported lability of chlorine and bromine in the presence of water, and the desired *o*-, *m*-, and *p*-fluoropropadrines were obtained as their hydrochloride salts. By the use of anhydrous conditions, it was also possible to obtain *m*- and *p*-chloropropadrine hydrochloride. However the *o*-chloro isomer was not successfully isolated in pure form; the hydrogenation product appeared to be a mixture of the hydrochlorides of the dehalogenated amino ketone, C_6H_5COCH-

$(NH_2)CH_3 \cdot HCl$, and *o*-chloropropadrine whose separation by recrystallization was not successful.

Hydrogenation of the *m*-bromoisonitroso ketone resulted in the loss of bromine from the ring, the product isolated being the dehalogenated amino ketone salt. The reduction of *o*- and *p*-bromoisonitroso ketones was not tried in this investigation.

The authors are indebted to Dr. Karl H. Beyer of Sharp and Dohme for a physiological evaluation of the halogenated propadrines. Compared to *l*-epinephrine as unity the observed potencies were: propadrine 1/185, *o*-fluoropropadrine 1/80, *m*-fluoropropadrine 1/102, *p*-fluoropropadrine 1/275, *m*-chloropropadrine 1/133, *p*-chloropropadrine 1/550. It is of particular interest to note that a fluorine atom introduced into the ortho position of the parent molecule doubles the pressor activity, but introduced into the para position it decreases the activity.

EXPERIMENTAL

All melting points recorded were taken with an Anschütz thermometer; all boiling points are uncorrected.

Synthesis of Phenyl Halogenated Propiophenones

A summary of the data for all the phenyl substituted propiophenones is given in Table I.

p-Halogen propiophenones. Propionyl chloride (92.5 g., 1 mole) was allowed to react with a stirred mixture of anhydrous aluminum chloride (147 g., 1.1 mole) and the phenyl halide (1 mole) in 400 cc. of dry carbon disulfide by the usual Friedel-Crafts procedure. After refluxing for 2 to 3 hours, the complex (surrounded by a cold water-bath) was decomposed in the presence of the solvent by the dropwise addition of water with stirring. Any suspended aluminum salts were dissolved by the addition of hydrochloric acid. The reaction mixture was filtered, the carbon disulfide layer was separated, and the aqueous layer was extracted with carbon disulfide. The combined carbon disulfide solutions were washed, dried over anhydrous calcium chloride, and the solvent was distilled off through a short column. The residue was distilled *in vacuo* in a Claisen flask.

Nitration of propiophenone. After investigating a number of nitrating mixtures, the best results were obtained by the addition of propiophenone to fuming nitric acid according to the method described by Hartung *et al.* (3, 17).

In order to determine the effect of temperature on the course of the reaction, a series of runs was carried out in which the temperature was varied. The results are summarized in Table II. At each temperature studied, two ½-mole portions of propiophenone were nitrated in two separate batches, the products of the two runs being combined and purified together. This procedure decreased the time during which the initial portions of the ketone remained in contact with the acid, thereby reducing the possibility of oxidation.

The general nitration procedure was as follows: Into 425 cc. of stirred fuming nitric acid (*d.* 1.5, straw colored), previously cooled to the desired temperature by an ice-bath, was dropped 67 g. (0.5 mole) of propiophenone. The temperature of the reaction was controlled by the rate of the addition of the ketone and by external cooling. Temperatures of $-10°$ to $-5°$ were obtained by the addition of solid carbon dioxide chips to the reaction mixture. Stirring was continued for 5 to 10 minutes after all the ketone had been added. The reaction mixture was then poured into 2 liters of ice and water and the product which separated was filtered off with suction. The filtrate was extracted with benzene and the benzene was warmed and used to dissolve the product on the filter. The benzene solution was washed with water, then with 10% sodium hydroxide until the washings were practically colorless, and finally with water. After drying over anhydrous calcium chloride, the ben-

zene was distilled off through a short column. The residue, consisting of the *o*- and *m*-nitropropiophenones, was washed with cold 95% ethanol to remove the soluble *o*-isomer. The insoluble *m*-isomer was recrystallized from 95% ethanol.

TABLE I

PHENYL SUBSTITUTED PROPIOPHENONES

$XC_6H_4COCH_2CH_3$ X =	M.P., °C.	B.P.		YIELD %	SEMICARBAZONE
		°C.	Mm.		M.P., °C.
p-F		215–217[j]	atm.	86	196–197
m-F[a]		94–96	4–5	68	187–188
o-F		87–91[k]	12–13	47	143–144
p-Cl	34–35[e]	114–118[l]	2	76	176–177[p]
m-Cl[a]	45–46			73	179–180
o-Cl[a]		105–106	12	85	172–173
p-Br	45–46[f]	137–140[m]	2	58	170–171
m-Br	37.5–40[g]			44	182–183[q]
o-Br		116–118[n]	10–11	77	178–179[r]
m-NO_2	98–99[h]			*	188–189
o-NO_2[b]		152–155[o]	2–3	*	183–184[s]
m-$NH_2 \cdot HCl$[c]	198–199[i]			83–88	
o-$NH_2 \cdot HCl$[d]	184–185			73–79	

[a] Not previously reported.

[b] Commanducci and Pescitelli (24) reported *o*-nitropropiophenone, which they claimed to have obtained by the addition of propiophenone to "136%" nitric acid at 40°, to be a crystalline compound, m.p. 85°. However subsequent workers (3, 13, 14), as well as the present work, have shown it to be an oil. From our experiments, as well as those of other colleagues, it develops that if the temperature of the nitration is allowed to rise above 25–35°, the reaction becomes vigorous and difficult to control, brown fumes are evolved, and a large amount of oxidation takes place.

[c] Melts with decomposition. Oxime, m.p. 112–113°. *p*-Toluenesulfonamide, m.p. 102–103°; reported m.p. 97° (12).

[d] Melts with decomposition. Free amine, m.p. 44–45°; reported m.p. 45–46° (13), 46–47° (14), 46° (12). Oxime, m.p. 87–88°; reported m.p. 88–89° (14). Commanducci and Pescitelli (24) reduced their purported *o*-nitropropiophenone and obtained an amine whose hydrochloride decomposed at 200°. However since they probably did not have *o*-nitropropiophenone, they probably did not have *o*-aminopropiophenone.

Reported melting points: [e]35–36° (25), 35.8° (9); [f]44–45° (25), 47° (9); [g]36° (12); [h]97° (3) 100° (26), 98–100° (12), 98° (24); [i]202.5 (3); [p]175–176° (27); [q]180° (12); [r]182° (12) [s]182–183° (14).

Reporting boiling points: [j]105–107° at 22 mm. (28); [k]95–99° at 19 mm. (29); [l]115° at 3 mm. (2), 152° at 30 mm. (9); [m]167° at 30 mm. (9); [n]125° at 12 mm. (12), 135–140° at 16 mm. (30); [o]153–160° at 7–10 mm. (3), 161° at 10–11 mm. (14), 175° at 25 mm. (13).

* See Table II.

Distillation of the solvent from the alcohol washings left the *o*-isomer as a brown oil which was placed in the refrigerator for several days to allow the separation of any dissolved *m*-isomer. On distillation *in vacuo*, *o*-nitropropiophenone was obtained as a yellow oil which darkened on standing.

Upon acidification, the sodium hydroxide washings gave a yellow crystalline precipitate which was soluble in sodium bicarbonate solution and which probably consisted of the nitrobenzoic acids, though its identity was not further investigated.

m-Aminopropiophenone hydrochloride. A solution of 53.7 g. (0.3 mole) of *m*-nitropropiophenone in 300 cc. of thiophene-free benzene was hydrogenated with 3 g. of a palladium-charcoal catalyst at room temperature and at approximately atmospheric pressure in an apparatus similar to that described by Hartung (18). The theoretical amount of hydrogen required to reduce the nitro group was absorbed in 13 hours, after which the uptake of hydrogen ceased. The catalyst was filtered off, and the benzene solution was dried over anhydrous sodium sulfate. Upon saturation of the dried solution with hydrogen chloride, the amine hydrochloride precipitated. It was filtered off, washed with benzene, and then with acetone until practically colorless. The compound was used without further purification.

When the hydrogenation was carried out in a glass container under an initial pressure of 300 pounds, the reaction required only $\frac{1}{4}$ to $\frac{1}{5}$ of the time needed under atmospheric pressure.

o-Aminopropiophenone hydrochloride. *o*-Nitropropiophenone (53.7 g., 0.3 mole) was hydrogenated in 100 cc. of benzene with 5 g. of catalyst at an initial pressure of 300 pounds, and the product was isolated as described for the *m*-isomer. It was necessary to heat the reduction mixture to start the uptake of hydrogen. The theoretical amount of hydrogen

TABLE II

EFFECT OF TEMPERATURE ON THE NITRATION OF PROPIOPHENONE

NITRATION TEMPERATURE, °C	YIELD (FROM 1 MOLE OF PROPIOPHENONE)		
	Nitropropiophenone		NaOH Extractive[a] g.
	Meta %	Ortho %	
−10 to −5	60	30	2
10	51.4	37.4	4
15	47.5	36.8	7
20	41.3	35.2	9
25	35.8	34.0	16

[a] Crude acidic material obtained upon acidification of the NaOH washings. Soluble in $NaHCO_3$ solution.

was absorbed in approximately 7 hours. *o*-Aminopropiophenone hydrochloride was obtained as a pinkish powder which darkened on standing.

m-Fluoropropiophenone. The amino group was replaced with fluorine by a modification of the method of Schiemann and Winkelmüller (15).

A mixture of 83.5 g. (0.45 mole) of *m*-aminopropiophenone hydrochloride, 45 cc. of concentrated hydrochloric acid, and 200 cc. of water was diazotized with a solution of 34.5 g. (0.5 mole) of sodium nitrite in 60 cc. of water. Then 120 cc. of cold commercial 48% fluoboric acid was rapidly added with vigorous stirring. The diazonium fluoborate which separated as a thick suspension was collected on a filter, washed with cold ethanol, then with ether, and dried in a vacuum desiccator over concentrated sulfuric acid. The diazonium fluoborate was obtained as a pinkish powder in a yield of 88%, decomposition point 97-98°. It was converted into *m*-fluoropropiophenone by the following procedure:

In a 1-liter, 3-neck flask fitted with a sealed stirrer and a reflux condenser connected to a gas absorption trap for the evolved boron trifluoride, was placed 300 cc. of dry toluene. To the stirred and boiling toluene was added in small portions 98 g. (0.39 mole) of the dry diazonium fluoborate, each portion being added after the initial evolution of gas from the previous portion had subsided. The toluene solution was decanted from a small amount of tar which separated during the reaction, cooled, and washed with water, 5% sodium

hydroxide, and again with water. After drying over calcium chloride, the toluene was distilled off and the residual oil was distilled *in vacuo*. *m*-Fluoropropiophenone was obtained as a light yellow oil which formed colorless crystals on cooling in an ice-bath.

o-Fluoropropiophenone. *o*-Aminopropiophenone hydrochloride was converted into its diazonium fluoborate by the method used for the *m*-isomer. After the addition of the fluoboric acid to the diazotized amine, it was necessary to stir the mixture in the ice-bath for about 10 minutes before the diazonium salt precipitated. After filtration, a second crop was obtained by saturating the filtrate with sodium fluoborate. The total yield was washed with cold alcohol, then with ether, and dried in a vacuum desiccator over sulfuric acid; yield 79%, decomposition point 81–82°.

The diazonium fluoborate was converted to *o*-fluoropropiophenone as described for the *m*-isomer, substituting dry heptane for the toluene. The *o*-fluoropropiophenone was obtained as a light yellow oil which did not solidify on cooling in an ice-bath.

m-Chloropropiophenone. This ketone was prepared by the Sandmeyer reaction by a procedure similar to that described by Marvel and McElvain for *o*-chlorotoluene (19).

A mixture of 92.7 g. (0.5 mole) of *m*-aminopropiophenone hydrochloride, 300 cc. of water, and 200 cc. of concentrated hydrochloric acid was diazotized at 0° to 5° by the addition of a solution of 34.5 g. (0.5 mole) of sodium nitrite in 75 cc. of water. The cold diazonium solution was then poured into a well stirred cold cuprous chloride solution previously prepared in the following manner:

An alkaline solution of sodium meta sulfite (33.3 g., 0.175 mole) and 40 g. (1 mole) of sodium hydroxide in 300 cc. of water was added over a 10-minute period to a stirred hot solution of 162.3 g. (0.65 mole) of crystallized copper sulfate and 76 g. (1.3 mole) of sodium chloride in 500 cc. of water. The mixture was allowed to cool to room temperature. The cuprous chloride which precipitated as a white powder was washed with water by decantation and dissolved in a mixture of 200 cc. of concentrated hydrochloric acid and 150 cc. of water.

The reaction mixture, containing a solid addition compound, was allowed to warm up to room temperature and then was heated at 70° with stirring until the evolution of nitrogen ceased (½ to 1 hour). The crude *m*-chloropropiophenone was distilled with steam from the reaction mixture and extracted from the distillate with benzene. The benzene solution was washed with water, then with 5% sodium hydroxide, again with water and dried over calcium chloride. After distilling off the benzene, *m*-chloropropiophenone was obtained as colorless crystals by recrystallization of the crude product from dilute alcohol (charcoal).

o-Chloropropiophenone. This ketone was prepared by the method used for the *m*-isomer from *o*-aminopropiophenone hydrochloride. The crude product obtained was distilled *in vacuo* and yielded the *o*-chloro ketone as a light yellow oil.

m- and o-Bromopropiophenone. These ketones were also obtained by the Sandmeyer reaction from *m*- and *o*-aminopropiophenone hydrochloride.

The aminopropiophenone hydrochloride (92.7 g., 0.5 mole) was neutralized with 20% sodium hydroxide and the free amine which separated from the aqueous portion was removed, washed with water, and added to a mixture of 84 cc. of concentrated sulfuric acid and 350 cc. of water. This mixture was diazotized, and the diazonium compound was converted to the corresponding bromopropiophenone with a cuprous bromide-hydrobromic acid solution by the procedure used for the preparation of the *m*-chloropropiophenone.

The cuprous bromide used was obtained by replacing the sodium chloride in the procedure described for the preparation of cuprous chloride with 72 g., (0.7 mole) of sodium bromide. After washing with water by decantation, the cuprous bromide was dissolved in a mixture of 200 cc. of 48% hydrobromic acid and 100 cc. of water.

m-Bromopropiophenone was obtained as colorless crystals by recrystallization of the crude product from dilute alcohol (charcoal).

o-Bromopropiophenone was obtained as a light yellow oil by distillation of the crude product *in vacuo*.

Oxidation of the halogenated propiophenones. The position of the halogen in the ring in the nine halogenated propiophenones was verified by permanganate oxidation of the ketones to the corresponding halogenated benzoic acids.

Synthesis of Isonitroso Ketones

Nitrosation of ketones. The halogenated propiophenones were nitrosated by the general procedure described by Levin and Hartung (16), using *n*-butyl nitrite as the nitrosating

TABLE III
ISONITROSO KETONES

$XC_6H_4COCCH_3$ ‖ NOH, X =	RECRYSTALLIZATION SOLVENT	M.P., °C	YIELD, %	FORMULA	NITROGEN %	
					Calc'd	Found
p-F	Toluene	106.5–107.5	88.4	$C_9H_8FNO_2$	7.73	7.73
m-F	Dilute Alcohol	109–110	85.6	$C_9H_8FNO_2$	7.73	7.50
o-F	Heptane	82–82.5	73.6	$C_9H_8FNO_2$	7.73	7.62
p-Cl[a]	Toluene	119–120	89.4	$C_9H_8ClNO_2$	7.09	7.06
m-Cl	Toluene	94–95	82.7	$C_9H_8ClNO_2$	7.09	6.94
o-Cl	Heptane	102.5–103	76.0	$C_9H_8ClNO_2$	7.09	6.96
p-Br[b]	Toluene	132–133	86.8	$C_9H_8BrNO_2$	5.79	5.75
m-Br	Toluene	104.5–105	76.4	$C_9H_8BrNO_2$	5.79	5.74
o-Br	Heptane	101–101.5	71.1	$C_9H_8BrNO_2$	5.79	5.72

[a] Reported m.p. 114° (9), 122–123° (2).
[b] Reported m.p. 113.6° (9).

TABLE IV
HYDROGENATION OF ISONITROSO KETONES

$XC_6H_4COCCH_3$ ‖ NOH, X =	KETONE MOLES	HYDROGENATION SOLVENT CC.	CATALYST[a] G.	HYDROGEN UPTAKE, EQUIV.	
				1st + 2nd eq. hrs.	3rd eq. hrs.
p-F	0.05	200	2	1.7	16
m-F	0.05	200	2	1.6	6
o-F	0.03	150	2	1.7	4
p-Cl	0.085	500	3	3	17.5
m-Cl	0.05	500	2	2	8
o-Cl	0.05	400	2	2.5	17.5
m-Br	0.05	400	2	3	6

[a] Initial amount; additional catalyst added after the 1st 2 equivalents of hydrogen had been taken up.

agent. After completion of the reaction, the ether was removed by distillation from a steam-bath, the distillation then being continued under reduced pressure to remove the butyl alcohol formed in the reaction. The residue was allowed to stand overnight in a vacuum desiccator over sulfuric acid, and was recrystallized from a suitable solvent. The experimental data on the various isonitroso ketones are given in Table III.

Synthesis of Amino Alcohols

Catalytic hydrogenations. The isonitroso ketones were hydrogenated in 2 *N* absolute ethanolic hydrogen chloride at approximately atmospheric pressure using an active[3] palladium charcoal catalyst, in a manner described elsewhere (1, 2, 22). The first two equivalents of hydrogen were taken up rapidly and the absorption of hydrogen ceased with the appearance of a precipitate of the amino ketone hydrochloride. In the case of the three fluorine compounds, fresh catalyst and sufficient water to dissolve the precipitate was added, and hydrogenation was continued until the third equivalent of hydrogen had been taken up. In the case of the three chlorine compounds and the *m*-bromo compound, fresh catalyst but no water was added at the two-thirds stage, and the precipitate was dissolved by blowing steam over the agitated reduction flask. In all cases the third equivalent of hydrogen was taken up much more slowly than the first two, and it was necessary to heat the reduction flask with steam from time to time to complete the absorption of the third equivalent of hydrogen. The reduction data are given in Table IV.

After filtering off the catalyst, the solvent was removed by distillation under reduced pressure. The crude hydrochloride was dried over sulfuric acid in a vacuum desiccator and washed with ether to remove most of the color. Recrystallization from absolute alcohol gave colorless crystals. Second crops of crystals were obtained by the addition of ether to the mother liquors.

TABLE V

NUCLEAR HALOGENATED PROPADRINE HYDROCHLORIDES

$XC_6H_4CH(OH)CH(NH_2)CH_2 \cdot HCl$ X =	M.P., °C	YIELD, %	FORMULA	CHLORINE[b] %	
				Calc'd	Found
p-F	225–226	78	$C_9H_{13}ClFNO$	17.24	17.27
m-F	210–211	68	$C_9H_{13}ClFNO$	17.24	17.38
o-F	231–232	65	$C_9H_{13}ClFNO$	17.24	17.39
p-Cl	244–245[a]	69	$C_9H_{13}Cl_2NO$	15.96	16.17
m-Cl	183–184	63	$C_9H_{13}Cl_2NO$	15.96	16.17

[a] Reported m.p. 245° (2).

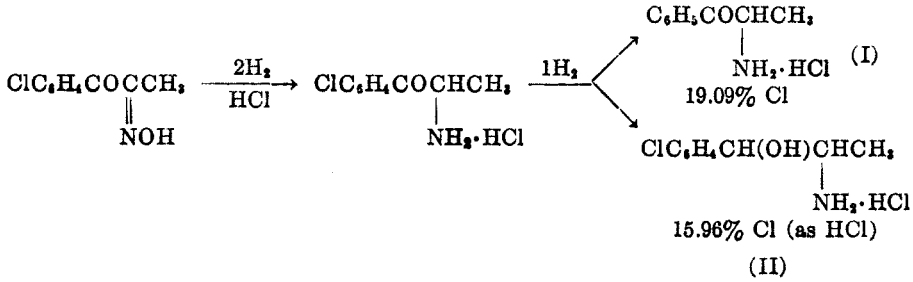
[b] Determined (as Cl^-) by the Volhard method.

When hydrogenation is incomplete, intermediate amino ketone hydrochlorides are produced; and they may be characterized by their reduction of Fehling's solution, by their melting with decomposition or effervescence, and by their undergoing spontaneous condensation in alkaline solution to dihydropyrazines which are readily oxidized to the more stable pyrazine derivatives (1, 2, 3, 23). Since these tests are not given by pure amino alcohols, they were used to determine whether the compounds isolated from the hydrogenations were the desired amino alcohols. In addition, permanganate oxidation to the corresponding halogenated benzoic acid was used to verify the presence and position of the halogen in the ring.

Hydrogenation of o-, m- and p-fluoroisonitrosopropiophenone; and m- and p-chloroisonitrosopropiophenone. By the hydrogenation of these compounds as described under *catalytic hydrogenations*, the corresponding halogenated propadrines were obtained as their hydrochlorides. Tests for the presence of amino ketone were negative, and permanganate oxidation produced the corresponding halogenated benzoic acids.

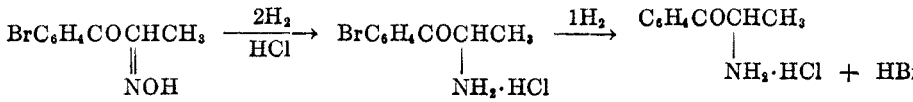
[3] The preparation of an active palladium catalyst with the aid of sodium acetate has been previously described (20, 21).

Hydrogenation of o-chloroisonitrosopropiophenone. The hydrogenated product, after several recrystallizations from absolute alcohol, melted at 182–183°, and further recrystallization produced no significant rise in melting point. It reduced Fehling's solution, gave ray pazine test, gave only a small yield of *o*-chlorobenzoic acid on permanganate oxidation, and contained 17.20% of chlorine (as HCl). Since the absorption of 3 equivalents of hydrogen could proceed in several directions,



the above evidence suggested that the product was a mixture of compounds I and II.

Hydrogenation of m-bromoisonitrosopropiophenone. The hydrogenated product, after several recrystallizations from sec.-butyl alcohol, gave colorless crystals, m.p. 164–165°. On permanganate oxidation it produced benzoic acid, indicating that the bromine had been removed. It gave tests for an amino ketone, reduced Fehling's solution, and formed a dihydropyrazine, m.p. 94–96°. Gabriel (23) reported the m.p. 99–100° for the dihydropyrazine obtained from $C_6H_5COCH(NH_2)CH_3$. Quantitative analysis for halogen (as HX) indicated the product to be a mixture of the hydrochloride and hydrobromide salts of α-aminopropiophenone; and qualitative analysis verified the presence of bromide ion. This evidence seemed to indicate that the hydrogenation apparently had taken the course:



SUMMARY

1. In order to study the physiological effect of nuclear halogen substitution in propadrine (phenylpropanolamine), the synthesis of a series of monohalogenated propadrines was undertaken.

2. For this purpose, nine halogenated propiophenones containing F, Cl, or Br in the *o*-, *m*-, and *p*-positions were prepared.

3. These ketones were then nitrosated to obtain their isonitroso derivatives.

4. Catalytic hydrogenation of the *o*-, *m*-, and *p*-fluoro, and the *m*- and *p*-chloro isonitroso ketones produced the desired corresponding halogenated propadrines. Hydrogenation of the *o*-chloro and *m*-bromo intermediates resulted in the removal of the halogen from the ring.

5. A study was made of the effect of temperature on the nitration of propiophenone.

6. A preliminary pharmacological examination of the five halogenated propadrines obtained indicated that only fluorine in the ortho position produces any appreciable increase in the pressor activity of the parent molecule.

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