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SOME DERIVATIVES OF CHLORAL WITH AROMATIC AMINES[1]

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INTRODUCTION

The superiority of the chloral derivatives which have been introduced into medicine as substitutes for chloral hydrate is supposed to lie in their enhanced activity, lack of irritant properties, and improved taste. As a class, however, they are sometimes dismissed with the statement that their activity depends solely on the chloral which they liberate more or less rapidly after ingestion (1).

Although several derivatives of chloral with amides have found some use as hypnotics and sedatives (2, 3, 4), chloral has been combined with amines to give only three compounds for which therapeutic merit is claimed, namely: Hypnal, the addition compound of antipyrine and chloral (5), and the products of the reaction of chloral with Orthoform (6) and with Orthoform New (6), respectively. These three compounds represent in each instance the addition or "aldehyde ammonia" type of compound which results when an amine adds to chloral through its carbonyl group.

In addition to the "chloral amines", two other possible series of compounds from chloral and primary amines are the Schiff bases, $RN{=}CHCCl_3$, obtained by condensing a primary amine with chloral through the elimination of water; and the bis(arylamino)trichloromethylmethanes, $CCl_3CH(NHAr)_2$, obtained by condensing two molecules of an aromatic primary amine with one molecule of chloral through the elimination of one molecule of water.

The bis(arylamino)trichloromethylmethanes, commonly called condensation compounds, are of pharmacological interest for three reasons. (a) The introduction of halogen atoms in an organic molecule may enhance or even confer physiological activity by increasing its solubility in fats (7, 8). (b) The condensation compound of chloral and *p*-phenetidine is analogous to the local anesthetic, Phenacaine (9). (c) It has been reported that the accidental swallowing of a small amount of the derivative from chloral and *o*-toluidine produced a feeling of numbness over the entire body (10).

In view of the above, a series of the addition compounds, 2-trichloro-1-hydroxyethylarylamines, $CCl_3CH(OH)NHAr$, and a series of the condensation compounds, bis(arylamino)trichloromethylmethanes, $CCl_3CH(NHAr)_2$, have been prepared from chloral and some selected aromatic primary amines to be tested as analgesics and anesthetics.

Previous workers, notably Wheeler and his students (11), usually obtained the addition compounds by allowing equal molecular quantities of chloral and

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the amine stand in inert solvents at temperatures ranging from 0 to 40°. Although the condensation compounds could sometimes be obtained under these mild conditions, they were usually prepared by refluxing chloral with the amine for several hours in benzene or toluene.

One Schiff base of chloral, that of chloral with *o*-aminobenzoic acid, is mentioned in the literature (12), but apparently this type of compound is rarely formed from the reaction of chloral with amines.

TABLE I

CONDENSATION COMPOUNDS $CCl_3CH(NHAr)_2$

Ar	FORMULA	YIELD, %	M.P., °C. (corr.)	NITROGEN, %	
				Calc'd	Found
o-C_6H_4COEt[a]	$C_{20}H_{21}Cl_3N_2O_2$	77	160	6.54	6.49
p-$C_6H_4CO_2Et$[b]	$C_{20}H_{21}Cl_3N_2O_4$	97	91.5	6.09	6.04
p-$C_6H_4CO_2Me$[c]	$C_{18}H_{17}Cl_3N_2O_4$	95	104	6.48	6.45
2-Naphthyl[d]	$C_{22}H_{17}Cl_3N_2$	88	116–118	6.73	6.60
m-$C_6H_4CH_3$[e]	$C_{16}H_{17}Cl_3N_2$	95	103.5	8.15	8.00
o-C_6H_4Cl[f]	$C_{14}H_{11}Cl_5N_2$	90	104	7.28	7.20
p-C_6H_4OEt[g]	$C_{18}H_{21}Cl_3N_2O_2$	65	91	6.93	6.86
C_6H_5CO-[h]	$C_{16}H_{13}Cl_3N_2O_2$	95	116	7.53	7.55

[a] From an equal mixture of toluene and ligroin. [b] From ligroin. [c] From an equal mixture of benzene and ligroin. [d] From heptane. [e] From isopropanol. [f] From an equal mixture of ligroin and cyclohexane. [g] From cyclohexane. [h] From benzene.

TABLE II

ADDITION COMPOUNDS $CCl_3CHOHNHAr$

Ar	FORMULA	YIELD %	M.P., °C. (corr.)	NITROGEN, %	
				Calc'd	Found
o-$C_6H_4CO_2Me$[a]	$C_{10}H_{10}Cl_3NO_3$	86	105	4.69	4.52
o-HOC_6H_3-*p*-CO_2Me[b]	$C_{10}H_{10}Cl_3NO_4$	93	155	4.45	4.40
p-C_6H_4COMe[c]	$C_{10}H_{10}Cl_3NO_2$	93	104.5	4.95	4.88

[a] From ligroin. [b] From glacial acetic acid. [c] From a mixture of 8 parts of heptane and 2 parts of benzene. Compound No. 2 has been prepared earlier in an impure state (6).

In contrast to most previous methods, it was found that the condensation compounds, and in a few instances the addition compounds, could be prepared in excellent yields directly from chloral hydrate and the amine, thus avoiding the use of the unstable chloral and the severe conditions which are usually employed for these reactions.

EXPERIMENTAL

One-tenth mole of the amine or its salt was added to 0.1 mole of glacial acetic acid contained in a 500-ml. Erlenmeyer flask. To this was added 0.1 mole of chloral hydrate previously dissolved in 100 ml. of distilled water containing 0.01 mole of sodium acetate. The mixture was mechanically shaken for 72 hours or less depending on the length of time re-

quired for the reaction. The crystalline product, which formed, was filtered off, washed by suction with distilled water and then recrystallized from the appropriate solvent.

The method was checked by treatment of chloral hydrate with *o*-toluidine (10), *p*-aminoacetophenone (13), ethylurethan (14) and several other amines and amides, the chloral addition compounds and/or the chloral condensation compounds of which are known, and in each instance the constants of the particular compound obtained were identical with those reported.

The method was then used to combine chloral hydrate with the following: (a) *o*-aminopropiophenone, (b) ethyl *p*-aminobenzoate, (c) methyl *p*-aminobenzoate, (d) β-naphthylamine, (e) *m*-toluidine, (f) *o*-chloroaniline, (g) *p*-phenetidine, and (h) benzamide. In each case the condensation compound was obtained, and these new compounds are listed in Table I.

Under identical conditions chloral hydrate reacted with the following amines: (a) methyl anthranilate, (b) Orthoform, and (c) *p*-aminoacetophenone respectively to yield the addition compound. These new compounds are listed in Table II.

DISCUSSION

Most of the aromatic amines and the amides, both aliphatic and aromatic, which have been tried with the method gave excellent yields of either the addition compound or the condensation compound with the latter predominating. The compounds can be isolated in a relatively pure state.

The somewhat anomalous reaction of chloral hydrate, which lacks unsaturation, with amines to give these addition and condensation compounds becomes more acceptable in view of the fact that the ammonia addition compound of acetaldehyde readily reacts with semicarbazide to give the same semicarbazide addition compound of acetaldehyde which is obtained when acetaldehyde reacts with semicarbazide (15).

In general it was found that equal molecular quantities of chloral hydrate and the amines reacted more readily and gave better yields regardless of whether the addition or condensation compound was obtained. It would appear, therefore, that the reaction always goes through the addition or "aldehyde ammonia" stage (11), and that the proportion of the reactants has little if any influence on the type of compound produced. Removal of one molecule of chloral hydrate from two molecules of the addition compound should give one molecule of the corresponding condensation compound; and, in fact, this was accomplished with the addition compounds listed in Table II by heating them at 75° in an oven.

The compounds listed in Tables I and II are fairly stable, easily-purified chloral derivatives, some of which can be dissolved in diluted acids.

In no instance was it possible to cause the addition compound to lose the elements of water to produce the —HC=N— linkage which characterizes Schiff bases. This is in agreement with the findings of others.

Some of the compounds described here have been turned over to Dr. Eugene L. Jackson of the Department of Pharmacology of the Medical School of Emory University for pharmacological testing.

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SUMMARY

1. A method has been described for preparing a series of addition compounds and a series of condensation compounds of chloral with amines by the use of chloral hydrate.

2. Three new addition compounds of chloral with amines and eight new condensation compounds of chloral with amines have been prepared and purified for pharmacological testing.

3. The three new addition compounds have been converted to the corresponding condensation compounds by means of heat.

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REFERENCES

(1) MAY AND DYSON, "May's Chemistry of Synthetic Drugs," Longmans, Green and Co., New York, N. Y., **1939**, p. 52.
(2) VON MERING, U. S. Patents 425,039 and 425,040.
(3) RICHTER, German Patent 234,741.
(4) GODECKE Co., German Patent 498,432.
(5) GLEY, *Compt. rend. soc. biol.*, **2**, 371 (1890).
(6) KALLE AND Co., German Patent 112,216.
(7) ABEL AND ALDRICH, *Science*, new series, **1**, 113 (1895).
(8) BERGMANN AND HASKELBERG, *J. Am. Chem. Soc.*, **63**, 1437 (1941).
(9) "United States Pharmacopoeia," twelfth decennial revision, Mack Printing Co., Easton, Pa., **1942**, pp. 354–55.
(10) WHEELER, *J. Am. Chem. Soc.*, **30**, 136 (1908).
(11) SPRUNG, *Chem. Rev.*, **26**, 297 (1940).
(12) NIEMENTOWSKI, *Ber.*, **35**, 3898 (1902).
(13) WHEELER AND JORDAN, *J. Am. Chem. Soc.*, **31**, 937 (1909).
(14) DIELS AND SEIB, *Ber.*, **42**, 4062 (1909).
(15) HILL AND KELLEY, "Organic Chemistry", The Blakiston Co., Philadelphia, Pa., **1943**, pp. 199–200.