$1/t$ (q = reacting area) at different temperatures are collected in Table II.

These data could be plotted according to the Arrhenius equation, from which an activation energy of 50 kcal./mole was derived.

On the basis of these results it can be concluded that in the present case the solid state reaction between magnesium and chromium oxides occurred only at the contact area between the two specimens and not by means of material transport through the gas phase and that the rate of the process is determined by *the diffusion of chromium oxide particles through the spinel layer.* The nature of the diffusing particles however cannot be ascertained from the present data.

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The System Water–Dioxane–Hydrogen Chloride

BY R. A. ROBINSON

RECEIVED JULY 7, 1952

In a recent note Grubb and Osthoff[1] published a study of the separation of water–dioxane mixtures at 25° into two layers on the addition of hydrogen chloride. They stated that this behavior had not been reported previously. It was, however, given brief mention in a review article 14 years ago[2] and has since[3] been studied quantitatively.

Figure 1a shows the tie-lines and the area corresponding to two-phase systems as determined by direct analysis of the conjugate solutions.[3] The points correspond to the data of Grubb and Osthoff.[1] (A few points on the lower right-hand side have been omitted to avoid over-crowding the graph.) In general the agreement between the two determinations is good; Grubb and Osthoff find that the region of partial miscibility is somewhat more extensive in the region of the water-rich mixtures but, considering the analytical difficulties inherent in this investigation, I think the agreement is satisfactory.

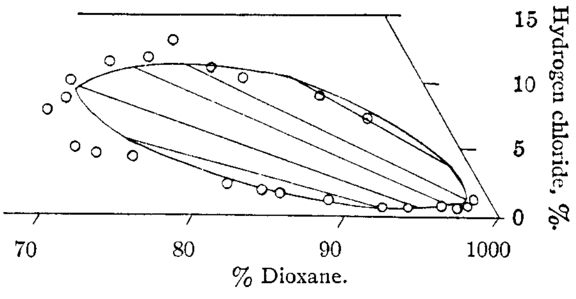

Fig. 1a.—Isotherm of the system water–dioxane–hydrogen chloride at 25°: O, data of Grubb and Osthoff; tie-lines from data of Robinson and Selkirk.

Some time ago, I made a few measurements on this system at 10° by the method I had used earlier at 25° and obtained the results given in Table I and Fig. 1b.

TABLE I

Upper layer			Lower layer		
HCl, %	H_2O, %	$C_4H_8O_2$, %	HCl, %	H_2O, %	$C_4H_8O_2$, %
4.68	3.8	91.5	9.56	9.6	80.8
2.84	2.5	94.7	10.02	14.5	75.5
1.49	1.4	97.1	9.50	18.0	72.5
0.76	2.0	97.2	8.33	21.8	69.9
.51	4.2	95.3	6.98	23.5	69.5
.57	5.6	93.8	5.03	23.8	71.2
.96	10.9	88.1	3.16	19.6	77.2

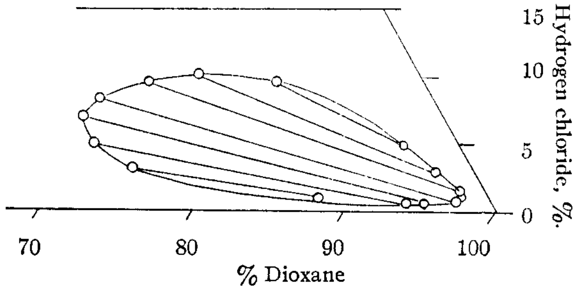

Fig. 1b.—Isotherm of the system water–dioxane–hydrogen chloride at 10°: O—O, tie-lines and composition of conjugate solution; present work.

Lowering the temperature by 15° causes the major axis of the (very approximately) elliptical curve to swing slightly in a counter-clockwise direction with, however, little change in composition of the conjugate solutions.

I have to thank Mr. Andrew Yeo Boon Hin and Mr. Oh Bak Kim for making some preliminary measurements on this system.

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[1] W. T. Grubb and R. C. Osthoff, THIS JOURNAL, **74**, 2108 (1952).

[2] H. S. Harned, *J. Franklin Institute*, **225**, 623 (1938).

[3] R. A. Robinson and R. C. Selkirk, *J. Chem. Soc.*, 1460 (1948).

Potential Antivirals. I. Simple Analogs of Chloramphenicol (Chloromycetin)

BY ARTHUR P. PHILLIPS

RECEIVED AUGUST 8, 1952

The simple chemical structure[1] and broad antibiotic spectrum[2] of chloramphenicol have made it an interesting model for other possible chemotherapeutic agents. While a variety of new synthetic and biologically produced drugs have become available in recent years for combating effectively many of the more common diseases of bacterial or protozoal origin, few if any of these are useful in the treatment of the important diseases attributed to a virus cause. Since chloramphenicol is somewhat effective against certain organisms believed to be viruses it seemed worthwhile to seek additional chemotherapeutic substances against important virus infections among various analogs of this useful antibiotic.

Two chemical units, the aromatic nitro and the dichloroacetyl, had been identified[1] as part of the chloramphenicol structure although these groupings had not been previously recognized in natural products, nor had they been thought desirable for incorporation into synthetic drugs. These two

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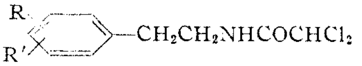
[1] M. C. Rebstock, *et al.*, THIS JOURNAL, **71**, 2458 (1949).

[2] I. W. McLean, Jr., *et al.*, *J. Clin. Investigation*, **28**, 953 (1949).

TABLE I

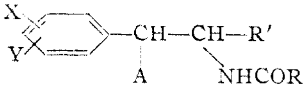


Compd. No.	R, R′	Cryst. solvent[a]	M.p., °C.[b] (uncor.)	Empirical formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
				A. Simple phenethyl dichloroacetamides				
I	H	Ea.H	80–81	$C_{10}H_{11}ONCl_2$	51.7	51.8	4.8	4.8
II	2-CH_3O	Ea.H	86–87	$C_{11}H_{13}O_2NCl_2$	50.4	50.7	5.0	4.9
					N 5.3	N 5.3		
III	3-CH_3O	E.H or B.H	72–73	$C_{11}H_{13}O_2NCl_2$	N 5.3	N 5.5		
IV	3-C_2H_5O	E.H	70–71	$C_{12}H_{15}O_2NCl_2$	52.2	52.6	5.5	5.3
V	4-CH_3O	Ea.H	90–92	$C_{11}H_{13}O_2NCl_2$	50.4	50.3	5.0	5.0
VI	3-CH_3-4-CH_3O	Ea.H	101–102	$C_{12}H_{15}O_2NCl_2$	52.1	52.1	5.4	5.4
VII	3,4-$(CH_3O)_2$	M	127–128	$C_{12}H_{15}O_3NCl_2$	49.3	49.7	5.2	5.1
VIII	2,5-$(CH_3O)_2$	B.H or E	83–84	$C_{12}H_{15}O_3NCl_2$	49.3	49.2	5.2	5.2
IX	2,5-$(CH_3O)_2$-4-Br	M	141–142	$C_{12}H_{14}O_3NBrCl_2$	38.8	38.6	3.8	3.7
				B. Simple nitro phenethyl dichloroacetamides				
X	4-NO_2	Ea.H	98–99	$C_{10}H_{10}O_3N_2Cl_2$	43.3	43.2	3.6	3.7
XI	3-NO_2-4-CH_3O	Ea.H	108–109	$C_{11}H_{12}O_4N_2Cl_2$	43.0	43.0	3.9	3.9
XII	2-NO_2-4,5-$(CH_3O)_2$	HOAc	194–195	$C_{12}H_{14}O_5N_2Cl_2$	42.7	42.7	4.2	3.9
XIII	2,5-$(CH_3O)_2$-4-NO_2	M	155–156	$C_{12}H_{14}O_5N_2Cl_2$	42.7	43.0	4.2	4.2

[a] B = benzene; E = ether; Ea = ethyl acetate; H = Skellysolve B; HOAc = acetic acid; M = methanol. [b] Yields were usually greater than 80%.

TABLE II

MISCELLANEOUS PHENETHYLAMIDES

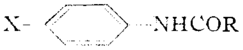


Compd. No.	X.Y.A.	R,R′	Cryst. solvent[a]	M.p., °C.[b] (uncor.)	Empirical formula	Carbon, %		Hydrogen, %	
						Calcd.	Found	Calcd.	Found
XIV	H	R = CH_2Cl R′ = H	Ea.H	67–68	$C_{10}H_{12}ONCl$	60.7	60.9	6.1	5.8
XV	X = 4-CH_3O	R = CH_2Cl R′ = CH_3	Ea.H	79–80	$C_{12}H_{16}O_2NCl$	59.6	60.1	6.7	6.7
XVI	X = 3,4-$(CH_3O)_2$	R = CCl_3 R′ = H	Ea.H	109–110	$C_{12}H_{14}O_3NCl_3$	44.1	44.3	4.3	4.5
XVII	X = 4,5-$(CH_3O)_2$ Y = 2-NO_2	R = CCl_3 R′ = H	M.Aq	137–138	$C_{12}H_{13}O_5N_2Cl_3$	38.7	38.7	3.5	3.5
XVIII	A = OH	R = $CHCl_2$ R′ = 4-$CH_3OC_6H_4$	M	178–179	$C_{17}H_{17}O_3NCl_2$	57.6	57.6	4.8	4.8
XIX	H	R = $CHCl_2$ R′ = 3,4-$(CH_3O)_2C_6H_3$	M	130–131	$C_{18}H_{19}O_3NCl_2$	58.7	58.7	5.2	5.2
XX	H	R = $CHCl_2$ R′-2-NO_2-4,5-$(CH_3O)_2$-C_6H_2	HOAc	242–243	$C_{18}H_{18}O_5N_2Cl_2$	52.3	51.9	4.4	4.4

[a] Aq = water; see footnote (*a*) Table I. [b] See footnote (*b*) Table I.

TABLE III

ANILINE DERIVATIVES



Compd. No.	X	R	Cryst. solvent[a]	M.p., °C.[b] (uncor.)	Empirical formula	Carbon, %		Hydrogen, %	
						Calcd.	Found	Calcd.	Found
XXI	COOH	$CHCl_2$	M	241–242	$C_9H_7O_3NCl_2$	43.5	44.0	2.9	3.0
XXII	$ClCH_2CONH$	CH_2Cl	HOAc or M	>315	$C_{10}H_{10}O_2N_2Cl_2$	45.9	45.8	3.9	4.2
XXIII	$Cl_2CHCONH$	$CHCl_2$	HOAc	252–253	$C_{10}H_8O_2N_2Cl_4$	36.4	36.4	2.4	2.4

[a] See footnote (*a*) Table I. [b] See footnote (*b*) Table I.

groups, either individually or together, have now been substituted in some simple phenethylamine derivatives (see Tables I and II). A few derivatives of aniline are shown in Table III.

The simple ring substituted phenethyl dichloroacetamides (Table IA) were prepared by warming of the appropriate amine with methyl dichloroacetate. The related nitro compounds (Table IB) from some of them were obtained by nitration of the dichloroacetamides with concentrated nitric acid in glacial acetic acid solution.

In Table II are shown a number of variations from the simpler substances of Table I. Included are some monochloroacetyl and trichloroacetyl amides as well as some variations on the phenethylamine skeleton. The trichloroacetyl amides were made from the methyl ester as were the dichloroacetyls. Use of the acid chloride or anhydride seemed to be necessary to introduce the monochloroacetyl group. The aniline derivatives shown in Table III were all made from the aniline and the corresponding acyl chloride.

Most of these compounds were examined for antiviral activity by Dr. D. J. Bauer of The Wellcome Laboratories of Tropical Medicine, Euston Road, London, England. Although several of the compounds showed some activity against one of the viruses used, that of Rift Valley Fever, on repetition of the experiments most of these proved to be inactive. Only one compound, N-(2,5-dimethoxy-4-nitrophenethyl)-dichloroacetamide (XIII of Table IB), gave a consistently positive result against Rift Valley Fever.

Acknowledgment.—The author is indebted to Samuel W. Blackman for the microanalyses included.

Experimental

A number of typical preparative procedures are outlined below.

N-(2,5-Dimethoxyphenethyl)-dichloroacetamide (VIII).—A mixture of 18 g. (0.1 mole) of 2,5-dimethoxyphenethylamine and 17 g. (0.12 mole) of methyl dichloroacetate was heated for two hours at 100°. The reaction mixture was cooled, 100 cc. of ether was added, and after scratching and chilling there was obtained 27 g. (93%) of white crystals. After recrystallization from benzene–hexane these melted at 83–84°.

N-(2,5-Dimethoxy-4-nitrophenethyl)-dichloroacetamide (XIII).—To 29 g. (0.1 mole) of the above amide (VIII) in 300 cc. of glacial acetic acid was added bit by bit with cooling and good stirring 15 cc. of concentrated nitric acid over a period of one hour. Yellow prisms start to precipitate near the end of the acid addition. After all acid had been added the mixture was left for two hours at room temperature, and then was diluted with 3 liters of cold water. The yellow crystalline product was collected and washed with water; yield 29 g. (87%); after recrystallization from methanol it melted at 155–156°.

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Spectrophotometric Study of the Tetrachloroiodide Complex in Acetonitrile

BY ALEXANDER I. POPOV AND JOHN N. JESSUP

RECEIVED JULY 7, 1952

In conjunction with a detailed investigation of the behavior of polyhalogen ions in solutions, it was found necessary to study the absorption spectrum of trimethylsulfonium tetrachloroiodide. While a large number of metallic salts of the tetrachlorohydroiodic acid have been reported in the literature,[1] these compounds were found unsuitable for this investigation since they are only soluble in water or aqueous alcohol, solvents which rapidly hydrolyze the polyhalogen complexes. In order to obtain compounds soluble in organic solvents, it was necessary to resort to the salts of large organic cations. Trialkyl sulfonium salts were chosen because of the ease with which they can be prepared.

Following the method given by Werner,[2] 2 g. of trimethylsulfonium iodide was dissolved in 200 ml. of glacial acetic acid containing about 8% of carbon tetrachloride, and a slow stream of dry chlorine was passed through the solution for several minutes. The solution was cooled to 0° and yellow crystals of the complex crystallized out. The product was filtered, washed with chloroform to remove excess chlorine, and dried in an oven at 50°. About 1.7 g. (50% yield) of the complex was obtained. The melting point of the final product was 180° which does not agree with the m.p. of 155° given by Werner. Analysis for chlorine gave 40.2% Cl, calculated for $(CH_3)_3SICl_4$, 41% Cl. The compound was quite stable when kept stoppered and out of contact with moisture. Odor of chlorine was noticeable, however, if it was exposed to humid air.

It was found impossible to recrystallize this compound even if the solvents were previously saturated with chlorine. Invariably a mixture of the tetrachloride and the dichloride complexes was obtained.

For comparison purposes it was necessary to prepare the analogous dichloroiodide complex. Method of preparation suggested by Dobbin and Mason[3] was used with some modifications. Dry trimethylsulfonium iodide was placed in an erlenmeyer flask and a current of chlorine was passed over it. A dark brown residue appeared in the first step of the reaction, being probably the iodine chloride formed: $(CH_3)_3SI + Cl_2 \rightarrow (CH_3)_3SCl + ICl$. After several minutes the dark color disappeared and a yellow crystalline product was obtained. Since in all cases the analysis showed an excess of chlorine present (due to the formation of some tetrachloroiodide complex), the complex was recrystallized from alcohol, dried in an oven at 50°, and analyzed. The amount of chlorine found was 25.2%, calculated for $(CH_3)_3SICl_2$, 25.8% Cl. The melting point was 103° which agreed with that given by Dobbin and Mason. The yield was 60%.

It was necessary to cool the erlenmeyer during the reaction, and to pass the chlorine only at a very slow rate; otherwise, iodine chloride formed in the first step of the reaction would be carried off with resulting poor yields.

Since the ultraviolet spectrum of these complexes was of particular interest, the choice of a suitable solvent was somewhat restricted. Alcohols could not be used for reasons already given, and the saturated aliphatic hydrocarbons did not possess sufficient polarity to dissolve appreciable amounts of the complex.

Acetonitrile solutions were found to be relatively stable for short periods of time and the solvent did possess the required transmittancy in the ultraviolet region. As in all previous work with the polyhalogen complexes,[4] the purity of the solvent was quite critical.

Acetonitrile was purified by shaking it for several hours with a concentrated solution of potassium hydroxide, drying over anhydrous sodium carbonate and then distilling from phosphorus pentoxide through a three-foot column. The b.p. was 81.0° at 760 mm. of pressure.

Solutions were prepared by dissolving the required amount of the complex in acetonitrile, just before the absorption measurements. Usually,

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(1) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. II, Oxford University Press, New York, N. Y., 1950, p. 1198 ff.

(2) E. A. Werner, *J. Chem. Soc.*, **89**, 1625 (1906).

(3) L. Dobbin and O. Mason, *ibid.*, **47**, 67 (1885).

(4) (a) R. E. Buckles, A. I. Popov, W. F. Zelezny and R. J. Smith, THIS JOURNAL, **73**, 4525 (1951); (b) R. E. Buckles, J. Yuk and A. I. Popov, *ibid.*, **74**, 4379 (1952); (c) A. I. Popov and E. H. Schmorr, *ibid.*, **74** 4672 (1952).