TABLE I

		M. p., °C.	B. p. (760 mm.), °C.	d^{20}_4	$n^{20}D$	MRD	A. RF	Analyses, % Found		Calcd.	Remarks
1	$CH_3CClFCH_3$		35.2	1.0072	1.35856	21.08	1.26	Cl	34.9	36.7	*d* and *n* at 10°
2	$CH_3CF_2CH_3$		−0.6 to −0.2	0.92				F	47.5	47.5	*d* at 0°
3	$CH_3CF_2CH_2Cl$		55.1	1.2023	1.3506	20.52	0.90	Cl	30.6	30.9	
4	$CH_3CF_2CHCl_2$		78.5–79.5	1.3666	1.38327	25.43	.92	Cl	47.6	47.6	
5	$CH_3CF_2CCl_3$	47–49	102					Cl	57.1	58.0	
6	$CH_2ClCF_2CCl_3$		151	1.7128	1.44421	33.94	.33	Cl		58.3	See analysis discussion
7	$CHCl_2CF_2CCl_3$		174	1.7557	1.46410	39.73	.84	Cl		70.3	See analysis discussion
8	$CCl_3CF_2CCl_3$	−15.8	194.0–194.4	1.8136	1.48064	44.98	.96	Cl	74.2	74.3	
9	$CH_3CFClCH_2Br$		110–112	1.6475	1.45503	28.90	1.32	Cl Br	65.3	65.8	
10	$CH_3CF_2CH_2Br$		76.2–76.3	1.6102	1.38860	23.34	0.86	Br	50.3	50.3	
11	$CH_3CF_2CCl_2F$		60.0–60.3	1.4215	1.35377	25.46	.99	Cl	41.9	42.5	
12	$CCl_3CF_2CCl_2F$		152–154	1.7607	1.43887	40.38	1.10	Cl	65.4	65.6	

Preparation of $CH_3CClBrCH_3$.—The ethylenic compound is added to a saturated solution of dry hydrobromic acid in acetic acid or acetic anhydride, at 0°. The bottle is stoppered and shaken mechanically at room temperature. Every twenty-four hours the unreacted ethylenic compound is separated from the addition product (about 50% yield) and added to a fresh solution of hydrobromic acid.

Preparation of $CH_3CF_2CH_3$.—$CH_3CCl_2CH_3$ cooled to 0° is added to a 25% excess of antimony trifluoride containing 5% of bromine by weight, also cooled to 0°. The reaction vessel is connected to a metal reflux condenser filled with ice. The reaction starts promptly and is regulated by means of an ice-bath intermittently applied. At the end of the operation, the reaction vessel is heated to about 70°. The vapors passing through the condenser are caught in a water gasometer, or in a receiver cooled with solid carbon dioxide. This operation, quickly performed, yields about 85% of difluoride, and 10 to 15% of $CH_3CClFCH_3$.

Analysis.—The fluorine and chlorine contents of the gaseous and highly volatile compounds can be analyzed by decomposition over white hot silica;[3] the chlorine and bromine of the more highly chlorinated substances can be analyzed only by the Carius method and this makes it impossible to titrate the fluorine, as the glass of the tube is badly affected. All other methods cause an incomplete decomposition, and the results are from 15 to 20% of what they should be. Even the Carius method requires a whole week of continuous heating at 250 to 300° to yield quantitative results. Results which were obtained by unsatisfactory methods are not reported.

Summary

A series of new fluorinated derivatives of propane has been presented, and the physical properties have been tabulated. The influence of a CF_2 group in the middle of the molecule has been examined and its stabilizing effect has been emphasized.

(3) Hubbard and Henne, THIS JOURNAL, **56**, 1078 (1934).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CLVII. The Action of Chlorine on 2,4-Diketotetrahydropyrimidines

BY TREAT B. JOHNSON AND JAMES M. SPRAGUE[1]

In connection with previous attempts to prepare 2-ethylsulfonyl-6-oxypyrimidines, the chlorination[2] of the corresponding 2-ethylmercapto compounds was carried out in methyl alcohol solution. The products formed were sulfur free, and were identified as methoxy chloropyrimidines represented by Formula IV. In the view of these results, a study has now been made of the action of chlorine upon some 2,4-diketotetrahydropyrimidines, I, in various solvents.

(1) Sterling Professorship of Chemistry Research Assistant, 1936–1937.

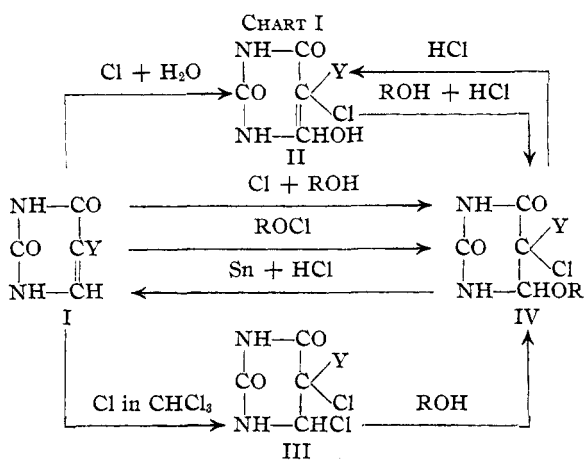
(2) Sprague and Johnson, THIS JOURNAL, **57**, 2252 (1935).

On treatment with chlorine in methyl alcohol suspension, the pyrimidines uracil, thymine, 4-methyluracil, 5-nitro-, 5-chloro-, and 5-bromouracil, I, were converted smoothly into the corresponding methoxychloropyrimidines, IV. When the 5-position of the diketopyrimidine I was unsubstituted (Y = H) the chlorination was accompanied by the substitution of a chlorine in this position (IV, Y = Cl). This was shown by the conversion of the methoxydichloro compounds to a 5-chloro-2,4-diketotetrahydropyrimidine (I, Y = Cl) by treatment with tin and

hydrochloric acid. In place of methyl alcohol, other alcohols as ethyl, and butyl alcohol or ethylene chlorohydrin worked equally well. The products formed were the corresponding alkoxyl derivatives.

The action of chlorine upon the diketotetrahydropyrimidines in the presence of alcohols is, therefore, perfectly analogous to its action in the presence of water. This latter reaction has been studied extensively and the structure of the products formed has been established with certainty.[3] In order to prove definitely the constitution of the alkoxychloro compounds, IV, it was desirable to convert the oxychlorohexahydropyrimidines, II, into the alkoxyl derivatives. This was accomplished by the action of alcohols in the presence of hydrochloric acid. These various transformations are expressed in Chart I.

CHART I



The structures of the different products indicate that the net result of the action of chlorine on 2,4-diketotetrahydropyrimidines in alcohol suspension may be explained by the addition of an alkyl hypochlorite to the 4,5-double bond of the pyrimidine ring. This behavior is in agreement with other observations on the action of chlorine and bromine on unsaturated compounds in alcohol solutions,[4] and on the addition of alkyl hypochlorites to ethylene compounds.[5] However, in view of the inability of ethyl hypochlorite to add to certain ethylene bonds,[6] and since there was no indication of the simultaneous formation of a dichloride in our reaction, as would be expected, a further study of the mechanism of the reaction was made.

It has now been found that chlorine acts upon chloroform suspensions of thymine (I, Y = CH_3) or uracil (I, Y = H) to form pyrimidine compounds which possess the properties of the corresponding dichlorides (III). The latter substances react instantaneously with alcohols to yield the corresponding alkoxychloropyrimidines (IV). It was also found that ethyl hypochlorite in chloroform solution reacts with thymine and 5-chlorouracil to form the corresponding ethoxychlorodiketohexahydropyrimidines (IV, R = C_2H_5, Y = CH_3 or Cl).

From these results it appears that the formation of the alkoxychloro compounds, IV, by chlorination in alcohols may proceed by three different paths: (1) direct addition of an alkyl hypochlorite to the 4,5-double bond of the pyrimidine cycle, (2) the action of the alcohol upon the 4,5-dichloride III which may be formed as an intermediate, and (3) the action of the alcohol on the oxychloropyrimidines II in the presence of hydrogen chloride. However, in the light of the recent study by Bartlett and Tarbell[7] of the mechanism of the action of bromine in methyl alcohol on stilbene it is probable that none of these routes presents a true picture of the mechanism of the various transformations.

The structure of the alkoxydichloropyrimidines derived from uracil (IV, Y = Cl) suggests that these compounds will give the characteristic Wheeler–Johnson pyrimidine color reaction.[8] When R was methyl or β-chloroethyl, an immediate, heavy, purple precipitate was formed with hot barium hydroxide; when R was ethyl the color was less intense; when R was *n*-butyl the precipitate was white or a faint pink. That this difference in behavior toward barium hydroxide is not due to any fundamental difference in structure was shown by the characteristic introconversion of the alkoxy compounds. In fact, these pyrimidine alkoxyl derivatives, IV, correspond in constitution to the acyclic ether-thioureas previously described in this Laboratory, $NH_2CSNHCH_2OC_2H_5$, and exhibit the same behavior by interaction with alcohols.[9] An alkoxy group of a given pyrimidine, IV, may be replaced or substituted by another alkoxyl by treatment with

(3) Johnson, *Am. Chem. J.*, **40**, 19 (1908); Behrend, *Ann.*, **336**, 61 (1886).

(4) Conant, Jackson, *et al.*, THIS JOURNAL, **46**, 1727 (1924); **48**, 2166 (1926); **49**, 2971 (1927); **56**, 977 (1934); Meinel, *Ann.*, **510**, 129 (1934); **516**, 231 (1935).

(5) Bloomfield and Farmer, *J. Chem. Soc.*, 2062 (1932); Sauknewitsch and Tschilingarjan, *Ber.*, **68**, 1210 (1935); Goldschmidt, *et al.*, *ibid.*, **58**, 572 (1925).

(6) Jackson and Pasiut, THIS JOURNAL, **49**, 2071 (1927).

(7) Bartlett and Tarbell, *ibid.*, **58**, 466 (1936).

(8) Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

(9) Johnson and Guest, THIS JOURNAL, **32**, 1279 (1910).

a different alcohol in the presence of hydrochloric acid. By this procedure it was possible to pass from one alkoxy compound to another, but the behavior toward barium hydroxide was unchanged. The manner by which the alkoxyl group effects the color reaction is not yet apparent.

Biltz and co-workers[10] have shown that characteristic acetoxychloro derivatives are produced by chlorinating certain uric acids in acetic anhydride solution. Similar results have been obtained with other olefinic compounds[11] when treated with acyl hypochlorites or with chlorine in acetic acid or acetic anhydride. A perfectly analogous reaction occurs when 2,4-diketotetrahydropyrimidines, I, are allowed to interact with chlorine in acetic anhydride. For example, 6-acetoxy-5-dichloro-2,4-diketohexahydropyrimidine (IV, Y = Cl, R = CH_3CO), was prepared in this manner from either uracil or 5-chlorouracil. It was also obtained from the oxydichloropyrimidine (II) or the methoxydichloropyrimidine (IV) by the action of acetic anhydride. In fact, we may now conclude from the results of our experiments that the ethylene grouping in the 4,5-positions of dioxypyrimidines of the uracil type and in uric acid function in the same manner.

Experimental Part

Preparation of 6-Alkoxy-5-chloro-2,4-diketohexahydropyrimidines, (IV).—**A.** The 2,4-diketotetrahydropyrimidine, I, was suspended in the alcohol (0.5 g. in 20–60 cc.) and a rapid stream of chlorine passed into the mixture until completely saturated. After standing for two to three hours, the solution was then allowed to evaporate on a watch glass at room conditions or under diminished pressure and the product recrystallized from water or dilute alcohol. All the tetrahydropyrimidines studied dissolved rapidly on chlorination, except in the experiment with uracil. In this case it was necessary to allow the chlorination mixture to stand for a longer time to complete the reaction. With larger quantities (2.0 g. in 80–100 cc.) it was found advisable to allow it to stand overnight. When *n*-butyl alcohol was used, the product was separated from the non-volatile chlorination products of the alcohol by washing with petroleum ether.

B. A solution of 5,5-dichloro-[3] or 5-methyl-5-chloro-6-hydroxy-2,4-diketohexahydropyrimidine[12] in the desired alcohol (0.3 g. in 10–50 cc.) was chilled in ice and treated with hydrogen chloride gas. After standing at room temperature for twelve to thirty-six hours, the alcohol was allowed to evaporate and the alkoxy compound recrystallized.

C. The crude reaction products III obtained by chlorinating thymine or uracil in chloroform were shaken with an alcohol and after standing for one to three hours the solution was evaporated.

D. A suspension of thymine or 5-chlorouracil (0.3 g.) in 10 cc. of a 10% solution of ethyl hypochlorite[13] in chloroform was chilled in ice. With frequent shaking, the solids dissolved in about two hours. Generally after standing overnight, the reaction product had separated as a voluminous precipitate. This was filtered off and recrystallized from water.

Except in the cases of derivatives of 5-nitro- or 6-methyluracil, the products of these reactions are very soluble in alcohols, acetone, ether, ethyl acetate and hot water. They are soluble in cold, dilute alkali solution, from which they are precipitated by addition of acids. The Wheeler–Johnson color reaction for detection of uracil derivatives (IV, Y = Cl) was carried out by the addition of a small sample (5–20 mg.) to a hot, saturated barium hydroxide solution (2–5 cc.). The reduction experiments with hydriodic acid,[14] or tin and hydrochloric acid were carried out as described for the oxychloro compounds,[3] and the thymine, 5-chlorouracil or 5-chloro-6-methyluracil identified by analysis. By evaporating to dryness with concentrated hydrochloric acid on a steam-bath, the alkoxyl was removed and the corresponding oxy compound II was formed.

Preparation of 5,6-Dichloro-2,4-diketohexahydropyrimidines, III.—A suspension of 0.5 g. of finely powdered thymine (I, Y = CH_3) in 25 cc. of dry chloroform was saturated, with dry chlorine gas, and allowed to stand for twenty to fifty hours. During this time, the mixture was kept saturated with chlorine. The voluminous solid was filtered off, washed thoroughly with chloroform and finally dried in vacuum over sulfuric acid and soda lime.

Anal. Calcd. for $C_5H_6O_2N_2Cl_2$: N, 14.21; Cl, 36.00. Found: N, 13.8–15.1; Cl, 32.0–33.3.

A similar reaction product was obtained with uracil (I, Y = H) except in this case substitution in the 5-position took place simultaneously, and the product formed was the 5,5-dichloro-6-chloro pyrimidine (III, Y = Cl). 5-Chlorouracil (I, Y = Cl) gave the same pyrimidine. With hot barium hydroxide solution this substance gave a heavy purple precipitate.

Anal. Calcd. for $C_4H_3O_2N_2Cl_3$: N, 12.88; Cl, 48.94. Found: N, 12.5–13.5; Cl, 43.5–46.5.

The melting points of these halogenated pyrimidines were indefinite (200–260° with effervescence), and varied with the sample and rate of heating. They are readily soluble in alcohol, ethyl acetate, acetone and ether. They are decomposed almost immediately by alcohol and water to give the corresponding alkoxy- or oxypyrimidines (IV, II).

Preparation of 5,5-Dichloro-2,4-diketohexahydropyrimidines (IV, R = CH_3, Y = Cl).—**A.** A suspension of 1 g. of uracil in 25 cc. of ice cooled acetic anhydride was saturated with chlorine gas, and allowed to stand at room temperature for five hours. The solution was then evaporated

(10) Biltz and Pardon, *Ann.*, **516**, 201 (1935).

(11) Bockemüller and Hoffmann, *ibid.*, **519**, 165 (1935).

(12) This second derivative was prepared by treating a suspension of thymine in water (1.5 g. in 8 cc.) with an excess of chlorine gas. The resulting solution was then allowed to evaporate at room temperature. The product melted at 193–197° with effervescence. *Anal.* Calculated for $C_5H_8ON_2Cl_2$: N, 15.68. Found: N, 15.65.

(13) Sandmeyer, *Ber.*, **18**, 1767 (1885); **19**, 857 (1886); Chattaway and Bäckeberg, *J. Chem. Soc.*, **125**, 1097 (1924); Taylor, MacMullen and Gamnal, THIS JOURNAL, **47**, 395 (1925).

(14) Baudisch and Davidson, *J. Biol. Chem.*, **64**, 234 (1925).

ANALYTICAL DATA

Compounds: 2,4-Diketohexahydropyrimidines	M. p., °C.	Nitrogen, % Calcd.	Found	Alkoxyl, % Calcd.	Found	Chlorine, % Calcd.	Found
5-Chloro-5-methyl-6-methoxy-	221–222	14.54	14.58	16.12	16.20	18.42	18.80
5-Chloro-5-methyl-6-β-chloroethoxy-	200–201	11.62	11.65	...	...	29.43	29.80
5-Chloro-5-methyl-6-ethoxy-	223–224	13.56	13.55	21.81	21.50	17.16	17.26
5-Chloro-5-methyl-6-*n*-butoxy-	193–194	11.94	11.92	...	...	15.12	15.12
5,5-Dichloro-6-methoxy-	225–226	13.09	13.16	14.50	14.53	33.30	33.34
5,5-Dichloro-6-ethoxy-	234–235	12.34	12.36	19.34	19.40	31.24	31.18
5,5-Dichloro-6-β-chloroethoxy-	195–196	10.71	10.78	...	...	40.70	40.73
5,5-Dichloro-6-*n*-butoxy-	172–173	10.98	11.04	...	...	27.81	27.65
5-Chloro-5-nitro-6-methoxy-	216–217(dec.)	18.79	18.60	13.88	13.83	...	...
5-Chloro-5-bromo-6-methoxy-	216–217	10.88	11.26	12.05	12.45	...	...
5,5-Dichloro-6-methyl-6-methoxy-	265–270(dec.)	12.33	12.30	13.67	13.63	31.24	31.15
5,5-Dichloro-6-acetoxy-	174–175	11.62	11.57	...	...	29.42	29.60

to dryness at ordinary temperature in a vacuum over sulfuric acid and soda lime. The chlorination product was best recrystallized by dissolving in a small amount of warm acetic anhydride and adding carbon tetrachloride to incipient crystallization; yield 1.25 g.; m. p. 174–175°. 5-Chlorouracil on similar treatment gave the same product.

B. A solution of 5,5-dichloro-6-hydroxy-2,4-diketohexahydropyrimidine (II, Y = Cl) in acetic anhydride was allowed to stand for thirty hours and the product isolated as described above; m. p. 174–175°.

C. A solution of 5,5-dichloro-6-methoxy-2,4-diketohexahydropyrimidine (IV, R = CH_3, Y = Cl) in equal volumes of acetic anhydride and acetic acid gave on standing two or three days, the same reaction product, melting at 174–175°.

With barium hydroxide, this compound gave a heavy purple precipitate. On standing for eighteen hours in a methanol–hydrogen chloride solution, the acetoxy group was replaced by a methoxy group, giving the 5,5-dichloro-6-methoxy compound (IV, R = CH_3, Y = Cl) melting after crystallizing from water at 226–227°.

Anal. Calcd. for $C_6H_8O_4N_2Cl_2$: N, 13.09; OCH_3, 14.50. Found: N, 13.07; OCH_3, 14.56.

Summary

1. 2,4-Diketotetrahydropyrimidines are attacked immediately by chlorine in different solvents, giving hexahydropyrimidines.

2. Chlorination of the 2,4-diketopyrimidines in alcohols leads to the formation of 6-alkoxyhexahydro derivatives.

3. Chlorination in acetic anhydride solution yields the corresponding 6-acetoxy-hexahydropyrimidines.

4. 6-Hydroxyhexahydropyrimidines are converted easily to the corresponding alkoxy derivatives by interaction with alcohols in the presence of hydrochloric acid.

5. The 6-alkoxyhexahydropyrimidines easily undergo introconversion reactions, when warmed with alcohols, with interchange of alkoxy groups.

6. The halogenated hexahydropyrimidines are converted easily to 2,4-diketotetrahydropyrimidines by reducing agents.

7. The study of hexahydropyrimidines will be continued in this Laboratory.

NEW HAVEN, CONN. RECEIVED SEPTEMBER 18, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Action of Chlorine on Isothioureas. III

BY JAMES M. SPRAGUE[1] AND TREAT B. JOHNSON

In this short paper the authors present further data obtained by chlorination of isothioureas. The results of our previous experiments on the chlorination of isothioureas[2] showed low yields of alkyl sulfonyl chlorides by the action of chlorine on isopropyl, isobutyl, *s*-butyl and cyclohexyl-isothioureas. In each of these cases, a large part of the sulfur of the respective isothiourea was split off during the chlorination process and was oxidized to sulfate ($-SO_4$). With *t*-butyl isothiourea this was the sole reaction; no sulfonyl chloride was obtained. These results indicate that branched aliphatic groups attached to the sulfur of isothioureas favor the elimination of the sulfur as sulfate and, thereby, limit the yield of sulfonyl chloride. These two competing reactions are expressed below.

(1) Sterling Professorship of Chemistry Research Assistant, 1936–1937.

(2) (a) Johnson and Sprague, THIS JOURNAL, **58**, 1348 (1936); (b) Sprague and Johnson, *ibid.*, **59**, 1837 (1937).