Alcohol used	Mg. HCl	Yield of ester	Pseudo, % ester in mixture	Sapn. equiv. Calcd.	Sapn. equiv. Found	Calcd. for	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Isopropyl	6	90	92	158	156	$C_8H_{14}O_3$	60.7	60.7	8.9	8.8
Methylisobutylcarbinol	300	93	96	200	200	$C_{11}H_{20}O_3$	66.0	65.5	1.0	9.7
Cyclohexyl	38	95	90	198	197	$C_{11}H_{18}O_3$	66.7	66.7	9.1	9.3
Benzyl	25	92	93	206	206	$C_{12}H_{14}O_3$	70.0	69.8	6.8	6.7

indicating the presence of 45% of pseudo ester in the mixture.

Separation of the Pseudo Ester from the Normal Ester.—To 28 g. of the ester was added 80 ml. of methanol, 14.4 g. of semicarbazide hydrochloride, and 12.8 g. of potassium acetate. After shaking the mixture for twenty-four hours, 50 ml. of ether was added, and the mixture was filtered. The residue was washed with ether, and the ether added to the filtrate. The ether and methanol were evaporated at reduced pressure, and the pseudo methyl levulinate distilled b. p. 90–92° (15 mm.). Cold titer gave a neutral equivalent of 129 (calcd. 130). *Anal.* Calcd. for $C_6H_{10}O_3$: C, 55.4; H, 7.7. Found: C, 55.0; H, 8.0.

(b) From **Levulinyl Chloride and Methanol.**—To 50 g. of levulinic acid 60 g. of thionyl chloride was added dropwise with stirring; the reaction temperature was not allowed to exceed 50°. The mixture was then maintained at 50° under reduced pressure in order to remove hydrogen chloride, sulfur dioxide and excess thionyl chloride. The levulinyl chloride was then added under vigorous stirring to a mixture of 125 ml. of methanol and 50 g. of sodium carbonate. The addition rate was carefully controlled in order to keep the *p*H of the reaction mixture above 6 and avoid warming of the mixture above 30°. The mixture was stirred for thirty minutes after all levulinyl chloride had been added. Approximately 200 ml. of ether was then added, and the mixture was filtered. After evaporating the ether and excess methanol *in vacuo*, the ester b. p. 90–92° (15 mm.) was obtained in 62% yield; it titrated for 92% of the pseudo ester.

Pseudo Allyl Levulinate: To 25 ml. of α-angelica lactone 25 ml. of allyl alcohol containing 0.4 g. of hydrogen chloride was added. The temperature of the reaction mixture rose gradually to 60°. After allowing to stand for three hours the mixture was distilled yielding 36.5 g. of ester. Cold titer and saponification equivalent indicated the presence of 10% of normal ester in the distillate. Addition of 70 ml. of allyl alcohol, 5 g. of 2,4-dinitrophenylhydrazine and one drop of glacial acetic acid, shaking the mixture for twelve hours followed by filtration removed the normal ester. On distillation 25 g. of pseudo allyl levulinate was obtained b. p. 93° (3 mm.); sapn. equiv. calcd. 156, found 153 (cold titer 98% of sapn. equiv.). *Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.4; H, 7.5.

Pseudo Isopropyl, 4-Methyl-2-pentyl, Benzyl, and Cyclohexyl Levulinate: These esters were prepared from 25 ml. of α-angelica lactone and 35 ml. of the corresponding alcohol. The amount of hydrogen chloride used, yields obtained, and analytical data found are given in the table.

Rearrangement of Pseudo Esters to Normal Esters.—The pseudo ester was diluted with the corresponding alcohol containing a small amount of a mineral acid. As little as 0.3% hydrogen chloride was sufficient. The mixture was heated to boiling until the cold titer became constant and equal to the mineral acid present. The pure normal ester was obtained in a quantitative yield.

Summary

1. Alcohols add to α-angelica lactone to form pseudo esters of levulinic acid.

2. The pseudo esters of levulinic acid are quantitatively converted to the normal esters by heating in the presence of a mineral acid.

3. Pseudo esters do not form carbonyl derivatives and may thus be separated from the normal esters.

4. Pseudo esters of levulinic acid are readily hydrolyzed by cold water.

5. Several pseudo esters of levulinic acid have been prepared, and their properties are tabulated.

RECEIVED[7] MAY 13, 1948

(7) Original manuscript received January 15, 1947.

[CONTRIBUTION FROM STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

The Dipole Moments of Thiouracil and Some Derivatives

BY W. C. SCHNEIDER AND I. F. HALVERSTADT[1]

In certain molecules where oxygen or sulfur atoms are attached to carbon atoms adjacent to heterocyclic ring nitrogens, the amide-iminoalcohol, $-\overset{O}{\overset{\|}{C}}-NH- \rightleftarrows -\overset{OH}{\overset{|}{C}}=N-$, type of tautomerism may exist. The relative contributions of these tautomeric forms will be affected by changes in substituents, solvents, temperature, state, etc.

The thiouracil molecule contains two such groups, both of which are usually shown in the amide form. Classical structural formulas can be assigned to those derivatives in which the labile hydrogens of the amide groups have been replaced by alkyl, aralkyl, etc., substituents, but occasionally these formulas may not adequately represent the properties of the compound. In some of these cases the assumption of tautomeric forms having a separation of charge has proved helpful.

The structure of 2-thiouracil was of interest to us because of its marked antithyroid activity. Certain dipole moment and infrared absorption data on thiouracil and a large number of derivatives are reported in this paper. On this basis a tentative classification of the compounds according to classical structure is made.

(1) Associated with Cutter Laboratories, Berkeley, California.

Experimental

A heterodyne beat apparatus similar to that described by Hudson and Hobbs[1a] was used to make the electrical measurements. A cathode ray oscilloscope was used for a detector. The standard capacitor was a General Radio type 722-D variable condenser. By using the low capacity section of this condenser, it was possible to obtain a precision of about ± 0.002 $\mu\mu$f in the capacity measurements.

The dielectric constant cell was of the design used by Sayce and Briscoe as described in Le Fèvre.[2] The particular cell used had a replaceable capacity of approximately 30 $\mu\mu$f and a fixed capacity of about 4 $\mu\mu$f.

Densities were determined with a U-shaped pycnometer having calibrated capillaries in each arm. The 10-ml. pycnometer used allowed a precision of ± 0.00002 in the density.

All measurements were at 35°. This temperature was chosen to eliminate the need for cooling the bath during the summer months and to take advantage of any increased solubility at this temperature. An oil-bath was used to thermostat the dielectric constant cell and the pycnometer was thermostated in a water-bath. Both baths were regulated to ± 0.005°.

1,4-Dioxane, used as solvent, was purified by partial freezing, discarding the unfrozen liquid. After remelting, the partially purified material was dried by refluxing over sodium, and any remaining impurities were removed by

TABLE I

Compound	M. p. (cor.), °C.
2-Thiouracil	245
4-Thiouracil	294–295
2,4-Dithiouracil	280
3-Ethyl-2-thiouracil	165–165.5
5-Ethyl-2-thiouracil[a]	190–192
6-Ethyl-2-thiouracil	228–229
5-Cyano-2-thiouracil[b]	281–282
6-Trifluoromethyl-2-thiouracil[b]	247–249
2-Methylthio-pyrimidone-4	205.5–203
2-Methylthio-5-ethylpyrimidone-4[a]	187–189
2-Methylthio-4-thiouracil	192–193
2-Ethylthio-3-methylpyrimidone-4	76.5–77.5
2-Ethylthio-3-ethylpyrimidone-4	29–30
2-Ethylthio-4-ethoxypyrimidine	B. p. 123–124.5 at 10 mm.
2-Benzylthiopyrimidone-4	193.5–194.5
2-Benzylthio-3-methylpyrimidone-4	119.5–120.0
1-Ethyl-2-thiouracil	241–241.5
1-Methyl-2-ethylthiopyrimidone-4	133.5–134.0
1-Methyl-2-benzylthiopyrimidone-4	146–146.5
1-Ethyl-2-benzylthiopyrimidone-4	107–108
1,3-Diethyl-2-thiouracil	67–68

[a] Furnished by Dr. G. W. Anderson, Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company, Stamford, Conn. [b] Furnished by Dr. W. H. Miller, same laboratories.

TABLE II

w	ϵ	d	w	ϵ	d
2-Thiouracil			3-Ethyl-2-thiouracil		
0.0	(2.1870)[a]	1.01685	0.0	2.2126	1.01488
.0005409	2.1983	1.01713	0.0006835	2.2210	1.01508
.0007236	2.1990	1.01713	.001004	2.2249	1.01514
.0009306	2.2056	....	.001328	2.2287	1.01520
.001218	2.2081	1.01722	.001572	2.2311	1.01528
.001547	2.2131	1.01740			

(1a) B. E. Hudson and M. E. Hobbs, *Rev. Sci. Inst.*, **13**, 140 (1942).

(2) R. J. W. Le Fèvre, "Dipole Moments," Chemical Publishing Co., New York, 1938, p. 32.

4-Thiouracil

0.0	(2.2050)	(1.01658)
0.9002923	2.2106	1.01667
.0005090	2.2148	1.01675
.0006591	2.2179	1.01677
.0008120	2.2205	1.10685

2,4-Dithiouracil

0.0	(2.1922)	(1.01629)
0.0003293	2.1961	1.01646
.0004332	2.2004	1.01648
.0008025	2.2033	1.01655
.0008202	2.2076	1.10660

5-Cyano-2-thiouracil

0.0	2.1806	1.01692
0.0002360	2.1855	1.01703
.0004669	2.1907	1.01717
.0006617	2.1944	1.01719
.0008292	2.1979	1.01724

2-Methylthio-4-thiouracil

0.0	2.1940	1.01658
0.0004878	2.1987	1.01677
.0007971	2.2041	1.01696
.001006	2.2073	1.01697
.001695	2.2166	1.01716

2-Ethylthio-2-methylpyrimidone-4

0.0	2.1896	(1.01633)
0.0006813	2.1952	1.01644
.0008772	2.1962	1.01646
.001095	2.1982	1.01650
.001746	2.2057	1.01656

2-Ethylthio-4-ethoxypyrimidine

0.0	(2.1904)	1.06159
0.0006445	2.1934	1.01666
.001067	2.1953	1.01669
.001382	2.1964	1.01671
.001812	2.1992	1.01680

2-Benzylthio-pyrimidone-4

0.0	(2.2092)	1.01531
0.0006730	2.2125	1.01552
.0009503	2.2132	1.01554
.001408	2.2160	1.01566
.002030	2.2186	1.10582

1-Ethyl-2-benzylthiopyrimidone-4

0.0	2.2053	1.01531
0.0007093	2.2225	1.01552
.001518	2.2414	1.01573
.001859	2.2486	....
.002316	2.2586	....

2-Methylthiopyrimidone-4

0.0	2.1978	(1.01582)
0.0003144	2.2013	1.01588
.0006082	2.2032	1.01599
.0007098	2.2048	1.01601
.0008789	2.2056	1.01604

6-Trifluoromethyl-2-thiouracil

0.0	2.1987	(1.01582)
0.0002193	....	1.01591
.0003519	2.1995	1.01596
.0005568	2.2004	1.01604
.0008236	2.2013	1.01610

5-Ethyl-2-thiouracil

0.0	2.1834	1.01685
0.0004191	2.1910	1.01694
.0006755	....	1.01710
.0008580	2.1996	1.01704
.001139	2.2052	....
.001421	2.2112	....

6-Ethyl-2-thiouracil

0.0	2.1884	1.01685
0.0005190	2.1971	1.01694
.0006041	2.1983	....
.0008874	2.2033	1.01698
.001172	2.2079	1.01713
.001444	2.2141	1.01718

2-Ethylthio-3-ethylpyrimidone-4

0.0	(2.1882)	1.01650
0.0003961	2.1902	1.01655
.0007236	2.1930	....
.001270	2.1968	1.01666
.001524	2.1987	1.01669

2-Benzylthio-3-methylpyrimidone-4

0.0	2.2122	(1.01499)
0.0006900	2.2146	1.01504
.001359	....	1.01518
.001907	2.2194	1.01522
.002539	2.2239	1.10538

2-Methylthio-5-ethylpyrimidone-4

0.0	2.1876	(1.01670)
0.0004846	2.1905	1.01679
.001045	2.1948	1.01687
.001296	2.1966	1.01694
.001829	2.1992	1.01706

1-Ethyl-2-thiouracil

0.0	(2.1790)	(1.01685)
0.0009439	2.1959	1.01702
.001862	2.2112	1.01743
.003026	2.2313	1.01758
.004178	2.2487	1.01795

1-Methyl-2-ethylthiopyrimidone-4

0.0	(2.1950)	(1.01632)
0.0001992	2.2006	1.01637
.0002760	2.2032	1.01642
.0003762	2.2059	1.01644
.0005387	2.2106	1.01649

1-Methyl-2-benzylthiopyrimidone-4

0.0	(2.2065)	(1.01531)
0.0003383	2.2153	1.01542
.0006090	2.2229	1.01542
.001029	2.322	1.01557
.001341	2.399	1.01566

1,3-Diethyl-2-thiouracil

0.0	2.2033	(1.01603)
0.0005871	2.2101	1.01612
.0007859	2.2129	1.01618
.001098	2.2161	1.01615
.002194	2.2290	1.01640

[a] Values in parentheses obtained by extrapolation.

TABLE III

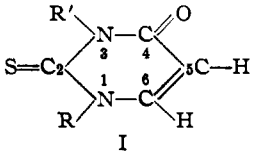
	α	β	$_\infty p_T$	Mol. wt.	$_\infty P_T$	P_D	P_O	$\mu \times 10^{11}$
2-Thiouracil	16.94	0.4240	3.013	128	385.7	30.7	355.0	4.21
4-Thiouracil	19.04	.3202	3.379	128	432.5	33.0	399.5	4.47
2,4-Dithiouracil	18.78	.4145	3.319	144	478.0	40.7	437.3	4.67
1-Ethyl-2-thiouracil	17.28	.2610	3.126	156	487.7	28.6	459.1	4.73
3-Ethyl-2-thiouracil	10.18	.2481	1.910	156	297.9	39.5	257.4	3.58
1,3-Diethyl-2-thiouracil	11.71	.1686	2.193	184	403.5	50.1	353.4	4.20
5-Ethyl-2-thiouracil	19.50	.2200	3.506	156	546.9	39.9	507.0	5.03
5-Cyano-2-thiouracil	20.98	.3929	3.712	153	568.0	36.0	532.0	5.15
6-Ethyl-2-thiouracil	16.64	.2264	3.016	156	470.6	39.9	430.7	4.64
6-Trifluoromethyl-2-thiouracil	3.157	.3764	0.7058	196	138.3	35.4	102.9	2.27
2-Methylthiopyrimidone-4	9.216	.2536	1.755	142	249.2	35.6	213.6	3.26
2-Methylthio-4-thiouracil	13.25	.3887	2.396	158	379.0	43.9	326.1	4.04
2-Methylthio-5-ethylpyrimidone-4	6.667	.1917	1.348	170	229.1	44.9	184.2	3.03
2-Ethylthio-3-methylpyrimidone-4	9.221	.1317	1.794	170	305.0	44.8	260.2	3.60
2-Ethylthio-3-ethylpyrimidone-4	6.908	.1378	1.404	184	259.1	46.8	213.3	3.26
2-Ethylthio-4-ethoxypyrimidine	4.636	.1048	1.030	184	189.5	50.4	139.1	2.64
2-Benzylthiopyrimidone-4	4.680	.2808	0.9852	218	214.8	54.8	160.0	2.83
2-Benzylthio-3-methylpyrimidone-4	4.218	.1858	0.9344	232	216.8	59.4	157.4	2.80
1-Methyl-2-ethylthiopyrimidone-4	29.33	.3156	5.114	170	869.4	44.8	824.6	6.42
1-Methyl-2-benzylthiopyrimidone-4	24.91	.2535	4.371	232	1014	59.4	954.7	6.90
1-Ethyl-2-benzylthiopyrimidone-4	23.29	.2833	4.095	246	1007	64.0	943.4	6.86

fractionation using an efficient distilling column. The best material obtained had the following physical properties: b. p. (uncor.) 100.5–100.7°, n^{35}_4 1.4150, d^{35} 1.01690 and ϵ_{35} 2.1776.

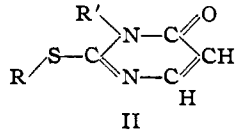
The compounds investigated and their melting points are listed in Table I. The experimental results are listed in Table II where w is weight fraction, ϵ is dielectric constant and d is density. Dipole moments were calculated by a modified Hedestrand method similar to that introduced by Halverstadt and Kumler,[3] differing in that densities were used rather than specific volumes. Atomic polarization was neglected, and the molecular refractions were calculated from the atomic refractions given in the Landolt-Börnstein "Tabellen." The values obtained from these calculations are listed in Table III where α and β refer, respectively, to the slopes of the dielectric constant and density curves as a function of concentration. $_\infty p_T$ is the specific polarization at infinite dilution and $_\infty P_T$ is the total molar polarization at infinite dilution. P_D and P_O represent the distortion and orientation polarizations, respectively, and μ is the dipole moment.

Discussion

Five possible classical structures may be postulated from a consideration of the various tautomeric positions of the two acidic hydrogen atoms in 2-thiouracil. These structures may be represented as



I



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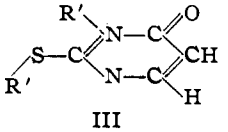
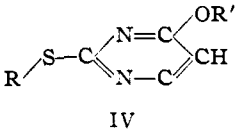
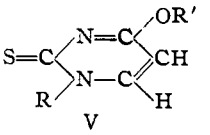


III

(3) I. F. Halverstadt and W. D. Kumler, THIS JOURNAL, **64**, 2988 (1942).



IV



V

where R and R′ may be hydrogen, methyl, ethyl or benzyl. Examples of all but Type V were found among the derivatives investigated.

Due to the complexity of the molecules, it was not feasible to assign structures by comparing the observed moments with theoretical, calculated moments. Instead the following procedure was used. Those thiouracils in which the two labile hydrogens were replaced by alkyl groups offered convenient starting points, inasmuch as at least their classical formulas were known. Structures were then assigned to the other compounds by a comparison of dipole moments, assuming that similar moments indicate similar structures. To illustrate the method, the dipole moment of 2-thiouracil is identical with that of 1,3-diethyl-2-thiouracil; accordingly, 2-thiouracil has a Type I structure. Following this procedure, the other derivatives were classified according to type and are listed in Table IV together with their moments. The classification of 3-ethyl-2-thiouracil is least certain since from dipole evidence alone it could have either a Type I or a Type II structure.

However, ultraviolet absorption measurements[4] indicate that the above assignment to a Type I structure is correct.

From a consideration of Austin's[5] work on the ultraviolet absorption spectra of uracils one would postulate a Type II structure for 2-thioura-

(4) Presented at the Atlantic City Meeting, A. C. S., April, 1947, by Dr. P. H. Bell, Stamford Research Laboratories, American Cyanamid Company, Stamford, Conn.

(5) J. E. Austin, THIS JOURNAL, **56**, 2143 (1934).

TABLE IV

Compound	$\mu \times 10^{18}$
Type I	
1,3-Diethyl-2-thiouracil	4.20
2-Thiouracil	4.20
4-Thiouracil	4.47
2,4-Dithiouracil	4.67
5-Ethyl-2-thiouracil	5.03
5-Cyano-2-thiouracil	5.15
6-Ethyl-2-thiouracil	4.64
6-Trifluoromethyl-2-thiouracil	2.27
3-Ethyl-2-thiouracil	3.58
1-Ethyl-2-thiouracil	4.73
Type II	
2-Ethylthio-3-ethylpyrimidone-4	3.26
2-Methylthio-pyrimidone-4	3.26
2-Ethylthio-3-methylpyrimidone-4	3.60
2-Methylthio-4-thiouracil	4.03
2-Methylthio-5-ethylpyrimidone-4	3.03
2-Benzylthiopyrimidone-4	2.83
2-Benzylthio-3-methylpyrimidone-4	2.80
Type III	
1-Methyl-2-ethylthiopyrimidone-4	6.42
1-Methyl-2-benzylthiopyrimidone-4	6.90
1-Ethyl-2-benzylthiopyrimidone-4	6.86
Type IV	
2-Ethylthio-4-ethoxypyrimidone	2.64

cil. Unfortunately, it was not possible to determine the dipole moment of uracil because the compound proved to be too insoluble in dioxane. However, there is no *a priori* reason why uracil and 2-thiouracil should have identical structures.

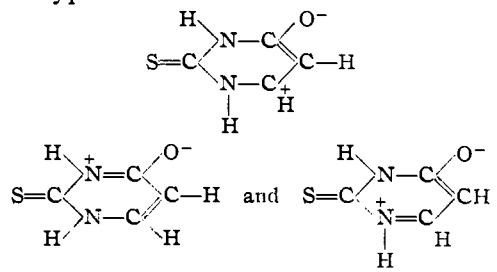
The above structure assignments are not consonant with some recent ultraviolet studies of Elion, Ide and Hitchings.[6] These workers concluded that uracil, thymine, 2-thiouracil, 4-thiouracil and 2,4-dithiouracil have a Type IV structure.

This conclusion was qualified by the statement that more work on substituted thiouracils was necessary to clarify the situation completely. However, it must be noted that although the present work was carried out in dioxane solution whereas the above workers employed aqueous solutions, the discrepancy between structure assignments cannot be simply attributed to a solvent effect, because ultraviolet studies in these laboratories,[4] using both dioxane solutions and aqueous solutions at various *p*H's, have indicated that in aqueous solution at the proper *p*H to assure the molecular form of the compound, the structures in dioxane and water are identical.

While most of the thiouracil derivatives are too complex for a detailed analysis of their electric moments, it is possible to attain fair agreement between observed and calculated moments for several of the Type I derivatives if certain assumptions are made concerning the carbon–oxygen and carbon–nitrogen link moments.

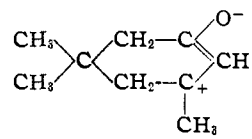
(6) G. Elion, W. Ide and G. Hitchings, THIS JOURNAL, **68**, 2137–2140 (1946).

The Carbon–Oxygen Moment.—The high moment of 2-thiouracil, 4.2*D*, would seem to indicate that the bond moment of the carbon-oxygen linkage is increased over its normal value of 2.5*D*. In all probability resonance structures of the types



with negatively charged oxygen are the direct cause of the observed high moment. Alkyl groups in the five and six positions seem to enhance the contributions from the ionic structures as can be seen from Table V. This behavior is reasonable when one considers that carbon is more negative than hydrogen and thus facilitates the transfer of negative charge to the oxygen. Although it is not possible to calculate the contributions of the various resonance structures to the total moment, one can estimate a value for the carbon–oxygen moment and then check the accuracy of this estimate by comparing the observed moments of a series of derivatives with calculated moments obtained using the assumed moment. In the present case a moment of 4.0*D* was assumed for the carbon–oxygen linkage.

This value is not unreasonable in view of the fact that Kumler and Fohlen[7] have observed a moment of 3.96*D* for isophorone where resonance structures of the type



which are similar to those proposed for 2-thiouracil, are assumed to account for the observed high moment. This high moment would indicate a carbon–oxygen moment of 3.6*D* in isophorone.

TABLE V

Compound	$\mu \times 10^{18}$	$\Delta\mu \times 10^{18}$
2-Thiouracil	4.21	....
6-Ethyl-2-thiouracil	4.64	+0.43
5-Ethyl-2-thiouracil	5.03	+0.82

The Carbon–Nitrogen Moment.—Although the classical structures for heterocyclic ring systems involving nitrogen are written with both single and double bonds between the nitrogen atom and adjacent carbon atoms, the situation is perhaps better represented by assuming some type of hybrid bond between the ring nitrogen and

(7) W. D. Kumler and G. M. Fohlen, *ibid.*, **67**, 437-441 (1945).

all attached atoms. The ring nitrogen will have a definite electronegativity, and the link moment between this nitrogen and attached atoms will depend upon the electronegativity difference. Measurements on simple heterocyclic compounds[8] indicate a moment of 1.9*D* for the carbon–nitrogen linkage. Further evidence supporting this value can be obtained by considering 2-thiouracil and its 1,3-diethyl derivative. These compounds have identical moments; accordingly, the carbon–nitrogen moment would seem to approximate the hydrogen–nitrogen moment which is about 1.3*D*.

If, as indicated above, a value of 4.0*D* is assigned to the carbon–oxygen linkage, a value of 1.9*D* to the carbon–nitrogen linkage and a plane hexagonal ring assumed, one obtains the calculated values listed in Table VI, together with observed values. The various bond moments used in these calculations are listed in Table VII. The agreement obtained is excellent and in view of the number of derivatives considered would seem to be more than simply fortuitous. Although the nature of the assumptions used in the above calculation precludes using the results in Table VI to confirm the structural assignments made earlier (Table IV), the agreement obtained is certainly good enough to indicate that the assumptions themselves are reasonably correct.

TABLE VI

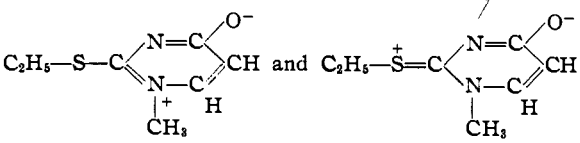
Compound	$\mu_{calcd.} \times 10^{18}$	$\mu_{obs.} \times 10^{18}$
2-Thiouracil	4.1	4.21
1,3-Diethyl-2-thiouracil	4.0	4.20
1-Ethyl-2-thiouracil	4.6	4.73
3-Ethyl-2-thiouracil	3.6	3.58
5-Cyano-2-thiouracil	5.2	5.15
6-Trifluoromethyl-2-thiouracil	2.3	2.27

TABLE VII

$\mu_{C=S}$	2.5*D*	$\mu_{C-C\equiv N}$	4.0
μ_{H-N}	1.3*D*	μ_{C-F}	1.4
μ_{H-C}	0.4*D*		

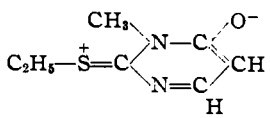
When the positions of the oxygen and sulfur atoms in 2-thiouracil are interchanged to give 4-thiouracil, the moment changes from 4.21*D* to 4.47*D*. This increase is probably a consequence of the larger size of the sulfur atom, since an additional increase in the electric moment results when the other oxygen is replaced by sulfur to give 2,4-dithiouracil with a moment of 4.67*D*, the average increase per sulfur atom being about 0.25*D*. However, these differences are relatively small and may result from solvent effects, atomic polarization, which was neglected in the moment calculations, or errors in the molecular refractions which were calculated from atomic refractions and not measured directly.

Measurements on several Type III compounds yielded rather unexpected results; an exceedingly large moment of 6.4–6.9*D* was obtained. Varying the substituent groups by measuring 1-methyl-2-benzylthiopyrimidone-4, 1-ethyl-2-benzylthiopyrimidone-4 and 1-methyl-2-ethylthiopyrimidone-4 resulted in no significant change in the order of the moment. Accordingly, this increased moment is attributed to the presence of forms having a separation of charge, which in the case of 2-ethylthio-1-methylpyrimidone-4 may be represented by



A structure analogous to the first form probably exists in 4-oxopyridine according to Leis and Curran,[9] who report a moment of 6.0 in dioxane solution.

The latter form provides a convenient correlation with the enhanced lability of the 2-alkyl group, which can be much more readily split from the sulfur atom by dry hydrogen chloride than it can in those isomers in which the N-alkyl group is in the 3-position. For the 3-isomer the analogous form having the positive charged sulfur



would involve a shift of the relatively fixed[10] 5,6 double bond and therefore might be expected to be less likely.

As a matter of general interest the vibration frequency of the carbonyl group in the compounds investigated was determined from infrared absorption spectra.[11] Since a carbonyl frequency was obtained for every compound where it might

TABLE VIII

Compound	ω cm.$^{-1}$
2-Thiouracil (6)[a]	1700
1,3-Diethyl-2-thiouracil (14)	1690
1-Ethyl-2-thiouracil (8)	1670
3-Ethyl-2-thiouracil (4)	1670
5-Ethyl-2-thiouracil (10)	1650
5-Cyano-2-thiouracil (9)	1675
6-Ethyl-2-thiouracil (7)	1671
6-Trifluoromethyl-2-thiouracil (15)	1692
2-Methylthiopyrimidone-4 (3)	1649
2-Benzylthiopyrimidone-4 (2)	1664
2-Ethylthio-3-methylpyrimidone-4 (5)	1700
2-Benzylthio-3-methylpyrimidone-4 (1)	1668
1-Methyl-2-ethylthiopyrimidone-4 (11)	1637
1-Methyl-2-benzylthiopyrimidone-4 (13)	1638
1-Ethyl-2-benzylthiopyrimidone-4 (12)	1640

[a] Numbers refer to points on plots given in Figs. 1 and 2.

(8) William C. Schneider, THIS JOURNAL, **70**, 627–630 (1948).

(9) D. G. Leis and B. C. Curran, *ibid.*, **67**, 79 (1945).

(10) In the catalytic hydrogenation of uracil, the first product is 5,6-dihydrouracil, indicating that the double bond acts like an isolated double bond rather than a benzenoid bond.

(11) Measurements carried out by R. C. Gore, Stamford Research Labs., American Cyanamid Company, Stamford, Conn.

be expected, it is reasonably certain that no compound has a Type V structure. The experimental values of the vibration frequencies are listed in Table VIII. A relatively large number of these are considerably lower than the normal vibration frequency, 1710–1720 cm.$^{-1}$, of an isolated carbonyl group. Since the lowering of the carbonyl frequency can result from conjugation or electrical charging effects, the observed lowering can be considered as a measure of the relative contribution of ionic resonance structures. In the compounds studied these ionic forms tend to increase the dipole moment; accordingly, there should be an increase in dipole moment with decreasing carbonyl frequency.

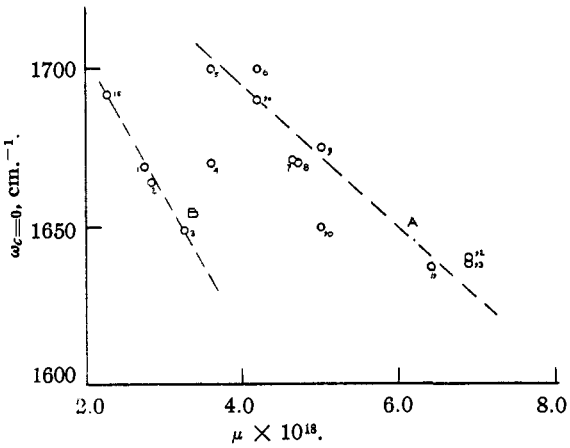


Fig. 1.—Relation between carbonyl vibration frequency and dipole moment for several thiouracil derivatives.

In Fig. 1 the vibration frequencies listed in Table VIII are plotted as a function of the dipole moment. As predicted, there is an increase in dipole moment with decreasing carbonyl frequency, and with the Type III compounds the lowest observed carbonyl frequency 1640 cm.$^{-1}$ is associated with the highest dipole moment, 6.9*D*. In the above plot the points are rather widely scattered and appear to be divided into two distinct groups, A and B. This results from neglecting the effects of different types of structures and substituent groups upon the dipole moment. These effects can be greatly reduced by considering a series of compounds having identical structures and similar substituent groups. 2-Thiouracil (6) and its 1,3-diethyl (14), 1-ethyl (8), 5-ethyl (10) and 6-ethyl (7) derivatives form such a series, which is plotted in Fig. 2. This plot clearly shows the nature of the relation between carbonyl frequency and dipole moment.

Acknowledgment.—The authors wish to express their indebtedness to Dr. P. H. Bell of the Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut, for much helpful discussion and criticism and to the American Cyanamid Company for permission to publish these results.

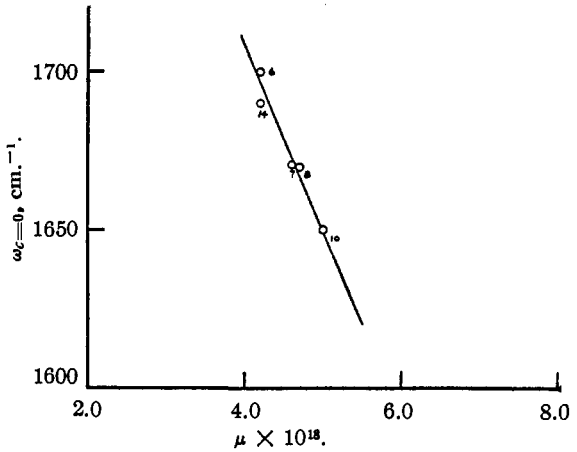


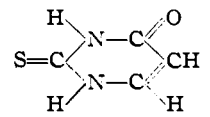
Fig. 2.—Relation between carbonyl vibration frequency and dipole moment for a series of thiouracil derivatives having similar structures.

Summary

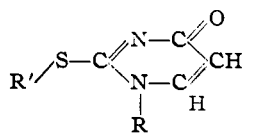
It must be emphasized that the following conclusions apply only to the form of the compound existing in dioxane solution. In aqueous solution the particular form present is a function of the *p*H, therefore, it is not permissible to make conclusive statements about the behavior of the compounds in water.

(1) The dipole moments in dioxane solution at 35° have been determined for 4-thiouracil, 2,4-dithiouracil, 2-methylthio-4-thiouracil and 2-thiouracil and seventeen derivatives.

(2) Thiouracil in dioxane solution is best represented by the formula



(3) Compounds of the type



have the abnormally high dipole moments of 6.4–6.9 *D*.

(4) The carbonyl group in 2-thiouracil seems to be activated in the same manner as in isophorone due to conjugation with a double bond.

(5) Alkyl groups substituted in the five or six position slightly increase this activation.

RECEIVED APRIL 5, 1948