The following points about the chemical work are worthy of comment. 1. The addition of a small amount of acetic acid facilitated the reaction of thiosemicarbazide with the carbonyl compounds, so that it was essentially complete in one-half to one hour. Anderson, *et al.*,[4] reported the reaction time to vary from 8 to 80 hours when no acetic acid was added. 2. The synthesis of 5-chloro-2-thenaldehyde in 50–55% yield by formylation of thiophene with N-methylformanilide was recently reported.[10] It was therefore interesting to carry out the synthesis of this compound by the Sommelet procedure, in order to compare the yields by the two methods. When 5-chloro-2-methylthiophene was converted to the thenyl bromide with N-bromosuccinimide, and thence to the aldehyde, a 33% yield was obtained. When 2-chlorothiophene was chloromethylated by the procedure of Cairns and McKusick[11] and the thenyl chloride converted to the aldehyde, a 25% yield was obtained. Thus neither process is as efficient as the formylation procedure.[10]

Experimental

Thiosemicarbazones.—The general procedure for the preparation of all the thiosemicarbazones was as follows: 0.1 mole of the carbonyl compound was dissolved in 100 ml. of 50% ethanol (95% ethanol was used for the less soluble compounds) and approximately 2 ml. of glacial acetic acid and 9.1 g. (0.10 mole) of thiosemicarbazide added. The solution was warmed with occasional swirling until the thiosemicarbazide dissolved and then refluxed for approximately one hour. After cooling, the crystalline thiosemicarbazone was collected and recrystallized from 50% ethanol or methanol. The crude yields ranged from 90–96%. The thiosemicarbazones are all yellow crystalline compounds, but occasionally on fresh crystallization, some of them appear almost white. After drying and exposure to air, however, they assume a yellow tinge.

Intermediate Carbonyl Compounds.—Although all of the thenaldehydes and acetothienones have been previously reported, some of them were prepared by methods not previously applied to these compounds and these are briefly described. 3-Thenaldehyde was prepared by the Sommelet procedure, as previously described,[12] as were 2-chloro-, 2-bromo-, and 2,5-dichloro-3-thenaldehyde.[13] In the latter case, 54 g. (59%) of crude 2,5-dichloro-3-thenaldehyde was obtained from 108 g. (0.65 mole) of 2,5-dichloro-3-methylthiophene and 0.6 mole of N-bromosuccinimide, which is a considerable improvement over the yield previously reported, although no changes were made in the procedure.

5-Nitro-2-thenaldehyde was prepared by the method of Patrick and Emerson.[14] The observation of Dullaghan, *et al.*,[15] that this compound could not be obtained by application of the Sommelet procedure to the product obtained on treatment of 5-nitro-2-methylthiophene with N-bromosuccinimide was confirmed.

5-Methyl-, 3-methyl-, 5-*t*-butyl- and 5-acetamido-2-thenaldehyde were obtained by the dimethylformamide formylation procedure described by Campaigne and Archer.[16] The various 2-acetothienones were samples previously prepared in this Laboratory.[17]

5-Chloro-2-thenaldehyde.—A mixture of 125 g. (0.94 mole) of 5-chloro-2-methylthiophene[18] and 1 g. of benzoyl peroxide was refluxed in 250 ml. of dry benzene, and 160 g. (0.9 mole) of N-bromosuccinimide mixed with 1 g. of benzoyl peroxide was added portionwise at such a rate as to maintain vigorous refluxing of the benzene. When addition was complete, the mixture was refluxed vigorously for about 5 minutes, then cooled and filtered with suction. Most of the benzene was removed by distillation at water-pump vacuum, and the crude 5-chloro-2-thenyl bromide was added dropwise to a refluxing stirred solution of 132 g. (0.94 mole) of hexamethylenetetramine in 200 ml. of chloroform. The heavy crystalline precipitate was collected, washed repeatedly with chloroform and dried *in vacuo*, yielding 220 g. (0.62 mole) of hexamine salt of 5-chloro-2-thenyl bromide. Without further purification, this salt was dissolved in 1 l. of 50% acetic acid and the solution rapidly steam distilled. Extraction of the distillate with ether yielded 43.9 g. (33.4% over-all yield) of 5-chloro-2-thenaldehyde, b.p. 85–88° (5–6 mm.). Oxidation of a small sample with silver oxide gave an acid melting at 147–148°.[19]

5-Bromo-2-thenaldehyde.—5-Bromo-2-thenyl chloride[20] was converted to the hexamine salt by refluxing with hexamine in chloroform and the crude salt steam-distilled in 1 l. of 50% acetic acid. After working up by the usual procedure, a 32% yield of 5-bromo-2-thenaldehyde, b.p. 81–84° (4 mm.), was obtained. Oxidation gave an acid which melted at 141–142°.[21] This process does not afford as good yields of this aldehyde as the phosphorus oxybromide formylation reported by King and Nord.[22]

(10) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 635 (1948).
(11) T. L. Cairns and B. C. McKusick, *ibid.*, **15**, 790 (1950).
(12) E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).
(13) E. Campaigne and W. M. LeSuer, *ibid.*, **71**, 333 (1949).
(14) T. M. Patrick and W. S. Emerson, *ibid.*, **74**, 1356 (1952).
(15) M. E. Dullaghan, L. J. Owen and F. F. Nord, *ibid.*, **74**, 2676 (1952).
(16) E. Campaigne and W. L. Archer, *ibid.*, **75**, 989 (1953).
(17) E. Campaigne and J. L. Diedrich, *ibid.*, **73**, 5240 (1951).
(18) E. Campaigne and W. M. LeSuer, *ibid.*, **70**, 415 (1948).
(19) J. F. Bunnett, D. M. Bachman, L. P. Snipper and J. H. Maloney, *ibid.*, **71**, 1493 (1949).
(20) R. C. Clapp, *et al.*, *ibid.*, **69**, 1549 (1947).
(21) H. D. Hartough and L. G. Conley, *ibid.*, **69**, 3096 (1947).
(22) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949).

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The Use of Dimethylformamide as a Formylation Reagent[1]

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The direct formylation of the thiophene nucleus by N-methylformanilide and phosphorus oxychloride has been recently reported.[3,4] Dimethylformamide has been reported in the patent literature as an effective substitute for N-methylformanilide in formylation of aromatic tertiary amines.[5] Tyson and Shaw[6] obtained a 72% yield of 3-indolecarboxaldehyde upon formylation of indole with dimethylformamide, and the application of this formylating agent to thiophenes has been patented.[7]

This formylation agent has two strong advantages despite the somewhat lower yields of aldehydes as compared to the N-methylformanilide procedure. Firstly, dimethylformamide is commercially an inexpensive reagent as compared to N-methylformanilide and therefore can be used in liberal excess as solvent, and secondly the weight of formyl group per mole of dimethylformamide is approximately twice the available formyl weight afforded by N-methylformanilide.

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(2) Abstracted from the thesis of Wesley L. Archer, to be submitted to Indiana University in partial fulfillment for the Degree of Doctor of Philosophy.
(3) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 635 (1948).
(4) A. W. Weston and R. J. Michaels, Jr., THIS JOURNAL, **72**, 1422 (1950).
(5) C. D. Wilson, U. S. Patents 2,437,370 (1948), 2,558,285 (1951).
(6) F. T. Tyson and J. T. Shaw, THIS JOURNAL, **74**, 2273 (1952).
(7) W. S. Emerson and T. M. Patrick, U. S. Patent 2,581,009 (1952).

In order to compare the two methods, several thiophenes and two other aromatic compounds were formylated with dimethylformamide. Table I records the constants of the aldehydes prepared and compares the yields with those previously reported by the N-methylformanilide procedure.[4] In three instances, thiophene, 3-methylthiophene and 2-*t*-butylthiophene, the aldehydes were obtained in yields approximately equal to those obtained by the N-methylformanilide method, while dimethylaniline gave *p*-dimethylaminobenzaldehyde in yields that exceeded the previously reported yield with N-methylformanilide.[8]

TABLE I

ALDEHYDES PREPARED BY DMF PROCEDURE

Aldehyde	B.p.,[a] °C.	Mm.	Yield, % using D-MF[b]	Yield, % using M-FA[b]	Acid, m.p., °C.
2-Thenaldehyde	44–45	1.1	72	77[d]	129–130[e,f]
5-Chloro-[g]	52–53	0.5	43	59[d]	152–152.5[e,f]
5-Methyl-[g]	84–85	3.5	66	81[d]	136–137[e,f]
3-Methyl-[g]	84–85	3.5	80	83[d]	147–148[e,f]
5-*t*-Butyl-[g]	107–108	3.6	76	76[d]	126.5–127[e,f]
5-Acetamido-[g]	183.5–184[c]		47	...	271–272[e,h]
4-Dimethylamino-benzaldehyde	71–71.5[c,i]		71	50[j]	...[k]
9-Anthraldehyde[l]	103.5–104[c,i]		63	84	...[m]

[a] See ref. 1 and 2 for other b.p. values. [b] DMF is dimethylformamide, MFA is N-methylformanilide. [c] Melting point (all melting points are uncorrected). [d] See ref. 3. [e] Thiosemicarbazone derivatives of the 2-thenaldehyde compounds correspond to the derivatives described by E. Campaigne, *et al.*, THIS JOURNAL, **75**, 988 (1953). [f] These values agree with those given by Weston and Michaels, ref. 4. [g] Substituted 2-thenaldehyde derivatives. [h] M.p. 272–273°, ref. 13. [i] R. Adams, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 214, reports m.p. 73°. [j] Ref. 6. [k] Thiosemicarbazone of this aldehyde melted at 208–209° (dec.) which agrees with the reported m.p. given by Bernstein, *et al.*, THIS JOURNAL **73**, 906 (1951). [l] L. F. Fieser, *Org. Syntheses.* **20**, 11 (1940), reports m.p. 104.5–105°. [m] Thiosemicarbazone melts at 194–195°. Calcd. for $C_{16}H_{13}N_3S$: N, 15.05. Found: N, 15.09.

A previously unreported compound, 5-acetamido-2-thenaldehyde, has been synthesized by means of dimethylformamide. Repeated attempts to formylate 2-acetamidothiophene using the more active N-methylformanilide in benzene gave only tars, but when no solvent was used a very low yield of the desired aldehyde was obtained. Possibly the active hydrogen on the nitrogen atom of the acetamido group is competing with the α-hydrogen of the thiophene nucleus in the formylation reaction and as a result of this competition tars are the principal products. In the case of dimethylformamide a 47% yield of the 5-acetamido-2-thenaldehyde, which melted at 183.5–184°, was obtained.

It is interesting to note that Weston[4] reported that unsubstituted formamide gave only traces of aldehyde. In the case of dimethylformamide it was found that the best yields were obtained when the reaction mixture was heated on a steam-bath for a period of one to two hours. The strong exothermic reaction at the first heating sometimes became violent unless properly suppressed by cooling in an ice-bath. In all cases phosphorus oxychloride was used as the condensing agent and often an excess of the dimethylformamide was necessary in order to give a homogeneous mixture. In most cases a slight excess of dimethylformamide and phosphorus oxychloride gave maximum yields.

In an attempt to use the modification of Weston,[4] in which the reactants were allowed to stand at room temperature for 16 hours, only 28% of 2-thenaldehyde was obtained when thiophene, dimethylformamide and phosphorus oxychloride were mixed and allowed to stand at room temperature for 72 hours. This indicates that the dimethylformamide is somewhat less reactive than the N-methylformanilide.

For purposes of identification the thiophene aldehydes were converted to the corresponding acids by oxidation with silver oxide, except in the case of the 5-acetamido-2-thenaldehyde, which was oxidized quantitatively with aqueous Fehling solution.

Acknowledgment.—We are indebted to the Socony–Vacuum Laboratories for samples of 2-methylthiophene and 2-*t*-butylthiophene, and to the Sterling–Winthrop Research Institute for a sample of 3-methylthiophene. We are also indebted to the E. I. du Pont de Nemours Company for the DMF used in these experiments.

Experimental

Substituted 2-Thenaldehydes.—The various 2-thenaldehydes were all prepared by the same method, and the boiling points and yields are reported in the table. Examples of the method are given in the following specific preparations.

2-Thenaldehyde.—To a solution of 42.0 g. (0.5 mole) of thiophene and 46.0 g. (0.64 mole) of dimethylformamide[9] which was cooled and shaken in a 500-ml. flask equipped with a reflux condenser and calcium chloride drying tube was added slowly 96.0 g. (0.62 mole) of phosphorus oxychloride. The flask was carefully heated on a steam-bath until a strong exothermic reaction commenced, after which the reaction was modified by cooling in an ice-bath until the rapid evolution of hydrogen chloride ceased. The mixture was finally heated on a steam-bath for one hour with occasional shaking, and then cooled and poured with stirring into a beaker containing 500 g. of cracked ice, after which the acidic solution was neutralized with a saturated solution of sodium acetate. The oily layer was separated and combined with the ether extracts of the aqueous solution. The ether solution was washed free of all traces of acid with dilute sodium bicarbonate solution, dried over anhydrous sodium sulfate and finally concentrated. Vacuum distillation of the resulting red oil gave 40.7 g. (72.7%) of 2-thenaldehyde, b.p. 44–45° (1.1 mm.). A forerun of unreacted thiophene was also obtained.

5-Acetamido-2-thenaldehyde.—Fourteen grams (0.1 mole) of 2-acetamidothiophene, prepared in 33% yield from 2-nitrothiophene[10] by the method of Steinkopf,[11] was dissolved in 54.0 g. (0.75 mole) of dimethylformamide contained in a 500-ml. flask equipped with a reflux condenser and calcium chloride drying tube. This solution was shaken and cooled while 18.5 g. (0.12 mole) of phosphorus oxychloride was added slowly. The flask was then heated on a steam-bath with occasional shaking for a period of one hour. A green suspension developed after 15 minutes of heating. The contents of the flask were added to 500 g. of cracked ice and neutralized by the slow addition of a saturated solution of sodium acetate. Solid sodium acetate was then added until the solution was saturated and the ruby-red solution was stirred with a mechanical stirrer for one or two hours until the aldehyde began to crystallize. At this point the mixture was allowed to stand in a refrigerator overnight and then filtered to give 14.0 g. of dark tan

(8) A. Vilsmeier and A. Haack, *Ber.*, **60**, 119 (1927).

(9) The dimethylformamide was technical DMF obtained from Grasselli Chemicals Dept., E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(10) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 466.

(11) W. Steinkopf, *Ann.*, **403**, 17 (1914).

crystals. Recrystallization from the minimum amount of water gave 8.0 g. of white crystals (47.5%), which melted at 183.5–184°. The loss encountered in the recrystallization was due to the inclusion of excess sodium acetate in the crude precipitate.

Anal. Calcd. for $C_7H_7ON_2S$: N, 8.28. Found: N, 8.23.

5-Acetamido-2-thenaldoxime.—This aldehyde gives an immediate deep violet precipitate with 2,4-dinitrophenylhydrazine in alcohol, but the melting point of this derivative was above 300° and it was too insoluble to be readily crystallized. The oxime was readily formed by the usual procedure and crystallized in glistening white needles which, even after repeated crystallization from water, had a broad melting range, 198–202°. This may be due to the presence of *syn* and *anti* isomers, since the analysis was satisfactory.

Anal. Calcd. for $C_7H_8O_2N_2S$: N, 15.21. Found: N, 15.35.

5-Acetamido-2-thenoic Acid.—Three-tenths of a gram of 5-acetamido-2-thenaldehyde (0.00177 mole) was dissolved in 60 ml. of stock Fehling solution[12] (30 ml. of solution I and 30 ml. of solution II) and 100 ml. of water and the blue solution allowed to stand at room temperature for three days. The red precipitate of cuprous oxide was then filtered off, the aqueous solution concentrated to approximately 50 ml. and cooled to give 0.32 g. (quantitative yield) of white crystalline 5-acetamido-2-thenoic acid, which when recrystallized from hot water melted at 271–272°, as previously reported.[13]

Anal. Calcd. for $C_7H_7NO_3S$: neut. equiv., 185. Found: neut. equiv., 182.

***p*-Dimethylaminobenzaldehyde.**[14]—Fifty-one grams (0.34 mole) of phosphorus oxychloride was added dropwise with stirring and cooling to 88.0 g. (1.2 moles) of dimethylformamide contained in a 500-ml. three-necked flask equipped with a reflux condenser, drying tube, stirrer, and dropping funnel. To this mixture was added dropwise with stirring 40.0 g. (0.34 mole) of technical dimethylaniline, after which the solution was heated with stirring on a steam-bath for two hours. The mixture was poured over ice and neutralized by dropwise addition of aqueous sodium acetate with vigorous stirring. Any excessive increase in temperature of the aqueous solution during neutralization led to the formation of greenish-blue dyestuffs which could not be removed from the product by recrystallization or acidification and reprecipitation by alkali. White crystalline *p*-dimethylaminobenzaldehyde which weighed 34.8 g. (70.5%), was obtained from the neutral solution after standing overnight in a refrigerator. The product was essentially pure as it precipitated from the reaction mixture.

9-Anthraldehyde.—In a 1-l. three-necked flask equipped with a reflux condenser, drying tube and stirrer was placed 18.0 g. (0.104 mole) of anthracene (m.p. > 215°), 16.0 g. (0.22 mole) of technical dimethylformamide, 28.0 g. (0.118 mole) of phosphorus oxychloride and 20 cc. of *o*-dichlorobenzene. The suspension was stirred and heated on a steam-bath for 30 minutes to complete solution, after which the heating was continued for an additional 90 minutes. The cool reaction solution was then neutralized with aqueous sodium acetate and diluted with water to a volume of 2 liters. After standing overnight in a refrigerator the yellow precipitate was filtered from the mother liquor and recrystallized from 50 ml. of glacial acetic acid. Washing the acetic acid from the resulting crystals with a small amount of cold methanol gave 13.0 g. (62.5%) of beautiful yellow needles of 9-anthraldehyde. An attempt to use excess dimethylformamide to replace the *o*-dichlorobenzene solvent resulted in a lower yield of aldehyde which was more difficult to purify. The *o*-dichlorobenzene held the unreacted anthracene in solution at the point of neutralization and prevented contamination of the product.

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(12) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 86.

(13) H. D. Hartough, "Thiophene and its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 380.

(14) The preparation of this compound by the DMF procedure is not original (British Patent 607,920 (1948); *C. A.*, **43**, 2232 (1949)) but is repeated for convenience.

Acidity and Infrared Absorption of Fluorinated Alcohols

BY ALBERT L. HENNE AND WILLIAM C. FRANCIS

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It is now firmly established that the ionization constant of alcohols perfluorinated in the α-position is of the order of magnitude of $K_1 = 10^{-12}$. Specifically, we have reported 4.0×10^{-12} for CF_3CH_2OH,[1] and 1.2×10^{-11} and 4.1×10^{-12} for the first and second constants of $HOCH_2CF_2CF_2CH_2OH$,[2] in good agreement with similar results reported from other laboratories.[3] Perfluorinated primary alcohols are thus about 10^6 times more acid than their unfluorinated analogs, and we have wondered whether this increase might be about doubled in secondary alcohols, and perhaps almost tripled in tertiary alcohols. This was found not to be the case. Specifically, ionization constants were measured as 4.3×10^{-12} for $C_3F_7CH_2OH$, 4.3×10^{-12} for $C_3F_7CH(OH)C_3H_7$ and 2.2×10^{-11} for $C_3F_7CH(OH)C_3F_7$. The bulk of the inductive effect is thus exercised by the first fluorinated group, and we can now predict that perfluorinated tertiary alcohols will prove comparable to phenol in acidity, at best.[4]

The three alcohols were prepared as follows: $C_3F_7CH_2OH$ by reduction of the acid with lithium aluminum hydride, $C_3F_7CH(OH)C_3F_7$ by reduction of the ketone with the same reagent, and $C_3F_7CH(OH)C_3H_7$ by condensation of C_3F_7MgI with butyraldehyde; the preparations of C_3F_7MgI, $C_3F_7COC_3F_7$ and $C_3F_7CH(OH)C_3H_7$ are given in an accompanying paper.[5]

The ionization constants were determined by glass electrode measurements of the *p*H at the half-equivalence point in 50% aqueous methanol, using tenth normal sodium hydroxide in the same solvent.

Perfluorinated secondary heptanol, $C_3F_7CH(OH)C_3F_7$, boils at 58° under 78 mm., and has d^{20}_4 1.6735; its refractive index at 20° is well below the scale of an Abbe refractometer (1.30); a sample sent to Minnesota Mining Co. was reported back as $n^{25}D$ 1.2911; its 3,5-dinitrobenzoate, melting at 84.0–84.2°, was analyzed. Calcd.: C, 29.9; H, 0.7; N, 5.0. Found: C, 30.2; H, 0.9; N, 5.6.

$C_3F_7CH(OH)C_3H_7$ boils at 63.5° under 45 mm., $n^{20}D$ 1.3391, was analyzed. Calcd.: C, 34.71; H, 3.72. Found: C, 34.18; H, 3.05. Its 3,5-dinitrobenzoate melts at 63.5–63.8°, and calcd.: N, 6.42. Found: N, 6.91.

The infrared spectra of the three alcohols were taken on the pure liquids at a cell thickness of 0.025 mm. with a Baird spectrophotometer. Each shows carbon–fluorine stretching in the range 7.1 to 10.0 μ. The carbon–hydrogen absorption at about 3.4 to 3.5 μ is in agreement with the assigned structures. For instance, in the case of C_3F_7CH-

(1) A. L. Henne and R. L. Pelley, THIS JOURNAL, **74**, 1426 (1952).

(2) A. L. Henne and S. Richter, *ibid.*, **74**, 5420 (1952).

(3) E. T. McBee, W. F. Marzluff and O. R. Pierce, *ibid.*, **74**, 444 (1952).

(4) In agreement, Dr. R. N. Haszeldine reported at the September, 1952, Meeting of the A.C.S., the following values for perfluorinated alcohols: primary alcohols, 4×10^{-12}; secondary alcohols, 3×10^{-11}; tertiary alcohols, 3×10^{-10} for $(CF_3)_3COH$, 1×10^{-10} for $(C_3F_7)_3COH$.

(5) A. L. Henne and W. C. Francis, THIS JOURNAL, **75**, 992 (1953).