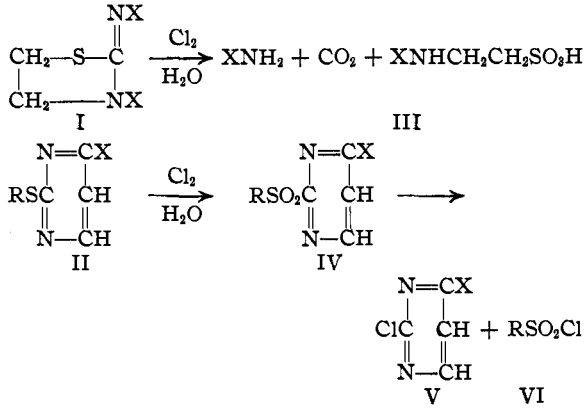
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

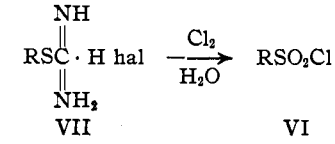
A New Method for the Preparation of Alkyl Sulfonyl Chlorides

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

2-Imido-4,5-dihydrothiazoles I (X = H, CH_3, etc.) and 2-mercaptopyrimidines II (R = CH_3, C_2H_5, etc., X = H, CH_3, C_2H_5) are characterized by their chemical behavior when subjected to the action of chlorine and bromine in aqueous solution. The thiazoles[2] I undergo complete degradation by the action of either of these halogens with formation of an amine, carbon dioxide, and a taurine derivative III. A mercaptopyrimidine II interacts with chlorine under the same experimental conditions to give the corresponding sulfone derivative IV without degradation of the pyrimidine ring. This reaction with chlorine proceeds still further in the case of certain mercaptopyrimidines leading to replacement of the sulfone grouping by halogen V and formation of an alkyl sulfonyl chloride VI. Furthermore, it has been shown that this oxidation reaction is applicable to both 2- and 6-mercaptopyrimidines[3] yielding the corresponding sulfones, respectively.



Because of the similarity in constitution of the imido-4,5-dihydrothiazoles I and the 2-mercaptopyrimidines II, respectively, and the accepted ammonium structure of the S-alkyl-isothiourea salts[4] VII, the behavior of these latter acyclic substances toward chlorine has now been investigated. We find, when chlorine gas is passed into a cold aqueous solution of these S-alkyl-isothiourea salts VII, that the corresponding alkyl sulfonyl chlorides VI are formed in good yields. In fact, this method of synthesis opens up a new and practical procedure for the replacement of a halogen atom in an aliphatic halide by the sulfonyl chloride grouping (–SO_2Cl). If bromine is used instead of chlorine the corresponding sulfonyl bromide (–SO_2Br) is formed. This process introduces thiourea in place of phosphorus halide as the key reagent for the preparation of aliphatic sulfonyl chlorides, and also furnishes an interesting and instructive field for further study, which hitherto has received little notice. This program will receive further attention in this Laboratory.[5]



Rathke[6] observed the formation of ethylsulfonic acid from S-ethyl-N,N-diphenyl-isothiourea salts by the action of chlorine or bromine. The formation of sulfonic acids from S-alkyl-isothioureas by oxidation with potassium chlorate is also reported in the literature.[7] The direct formation of alkyl sulfonyl halides by the action of halogen on S-alkyl-isothiourea salts has not, however, been previously reported. The cleavage of a carbon–sulfur linkage by chlorine with the formation of an alkyl sulfonyl chloride or sulfonic acid has been observed with other types of sulfur compounds.[8]

The yields of alkyl sulfonyl chlorides obtained from the various alkyl-isothiourea salts are given in Table I. Since bromine also reacts with these salts to form alkyl sulfonyl bromides, it was necessary first to remove the hydrobromic acid when using the hydrobromide salts for preparation of sulfonyl chlorides by treatment with chlorine gas.

(1) Sterling Professorship of Chemistry Research Assistant, 1935–1936.

(2) (a) Gabriel, *Ber.*, **22**, 1142 (1889); (b) Avenarius, *ibid.*, **24**, 266 (1891); (c) Andreasch, *Monatsh.*, **8**, 411 (1888); see also *Ber.*, **23**, 158 (1890).

(3) Sprague and Johnson, THIS JOURNAL, **57**, 2252 (1935); **58**, 423 (1936).

(4) (a) Taylor, *J. Chem. Soc.*, **111**, 650 (1917); (b) Werner, *ibid.*, **57**, 283 (1890); (c) Wheeler and Merriam, *Am. Chem. J.*, **29**, 482 (1903); (d) Wheeler and Bristol, *ibid.*, **33**, 440 (1905); (e) Lecher *et al.*, *Ann.*, **438**, 169 (1924); **445**, 35, 77 (1925).

(5) United States patent application, Serial No. 72983, filed April 6, 1936.

(6) Rathke, *Ber.*, **14**, 1774 (1881).

(7) (a) Andreasch, *Monatsh.*, **1**, 446 (1880); **4**, 131, 142 (1883); (b) Kucera, *ibid.*, **35**, 145 (1914).

(8) (a) Spring and Winssinger, *Bull. soc. chim.*, [2] **49**, 72 (1888); *Ber.*, **15**, 447 (1882); (b) Gabriel and Heymann, *ibid.*, **23**, 158 (1890); (c) Gabriel, *ibid.*, **22**, 1154 (1889).

TABLE I

$$R\ Hal \rightarrow RSC\begin{matrix}NH_2\\ \diagdown\!\!\diagup\\ NH\end{matrix}\cdot H\ hal,\ SO_4,\ etc. \longrightarrow RSO_2Cl$$

R =	Salt Acid =	Yield, %	B. p. or m. p., °C.	Mm.	$n^{25}D$
CH_3—	SO_4	76	B. 60.5–61.5	21	1.4490
C_2H_5—	Cl	66			
	Br[a]	82	B. 77–77.5	26	1.4506
	SO_4	78			
i-C_3H_7—	Cl	40	B. 74–75	19	1.4525
	Br[a]	54			
i-C_4H_9—	Br[a]	53	B. 73–75	11	1.4520
n-C_7H_{15}—	Br[a]	50	B. 124–126	9	1.4564
	Acetate	80			
1,2-C_2H_4—	Br[a]	63	M. 91–92		
	Cl	74			
	Acetate	72			
$C_6H_5CH_2$—	Cl	92	M. 91–92		
	SO_4	96			
	NO_3	91			
$C_6H_5CH_2CH_2$—	Cl	89–95	B. 121–123 M. 32–33	3	1.5390^{35}

[a] The bromine was removed with an equivalent of silver nitrate before treatment with chlorine.

Otherwise a mixture of sulfonyl chloride and bromine was obtained.[9]

With branched alkyl groups, as isopropyl and isobutyl, lower yields of sulfonyl halides were obtained. Both the low (148°) and the high melting (174°) forms of S-benzyl-isothiourea hydrochloride[4a,e] behaved identically on chlorination.

Although the S-alkyl-isothiourea[4] hydrobromides are easily prepared from the alkyl bromides and thiourea, the simple alkyl chlorides react very slowly with thiourea under similar conditions.[10] Since the practicability of the method here described for the preparation of alkyl sulfonyl chlorides depends on the ease of preparation of the S-alkyl-isothiourea salts, an attempt was made to improve the preparation of the hydrochlorides. This may be accomplished by heating the respective alkyl chloride with thiourea in an autoclave (see ethyl and isopropyl, Table II). However, a more convenient process is that used by Stevens[10] for the preparation of S-ethyl-isothiourea hydrochloride. This investigator found that this salt could be obtained by heating thiourea hydrochloride with ethyl alcohol. We have now found that this procedure may be applied with success to the higher aliphatic alcohols.

$$ROH + HCl + NH_2CSNH_2 = RSC(=NH)NH_2 \cdot HCl$$
VII

The S-alkyl-isothiourea hydrochlorides VII were not isolated from this reaction but were treated directly with chlorine in aqueous solution. The maximum yields of sulfonyl chlorides were obtained after heating the above reaction mixture for three or four days on a steam-bath. The lower yields of ethyl, isopropyl and isobutyl compounds may be attributed to several factors, such as temperature of the reaction, boiling point of the alcohol, volatility of the alkyl chloride and the effect of a branched chain (compare Table I). The results of this method are summarized in Table II. The yields are based on the amount of thiourea used.

Methyl, ethyl and *n*-heptyl sulfonyl bromides were prepared by the action of bromine on the corresponding S-alkyl-isothiourea salts in yields of 43.5, 64.8 and 36%, respectively.

The identity of the nitrogenous product resulting from the preparation of the alkyl sulfonyl halides from S-alkyl-isothioureas, and the mechanism of these transformations, are being studied further and will be discussed in a future paper from this Laboratory.

(9) In our first experiments silver nitrate was employed to replace the bromine ion, thereby forming the corresponding isothiourea nitrate which reacted smoothly with chlorine. This method of precipitation, however, cannot be recommended for practical synthesis and we have found that organic acid salts of isothiourea serve our purpose well when bromine is a conflicting reagent. Very little attention has been paid to the study of this class of salts but we have found in this Laboratory that they can perform a practical service in many operations. Treatment of an alkyl-isothiourea hydrobromide, for example, with potassium acetate leads to the quantitative formation of the acetate of the alkylisothiourea which interacts smoothly with chlorine to give the desired alkyl sulfonyl chloride. Other organic acid salts react in a similar manner and with production of the sulfonyl chlorides in excellent yields. The description of a series of these characteristic organic acid salts is given in a paper from This Laboratory by Dr. John J. Donleavy (THIS JOURNAL, **58**, 1004 (1936)).

(10) Stevens, *J. Chem. Soc.*, **81**, 79 (1902).

TABLE II

$$ROH \longrightarrow RSC(=NH)(NH_2)\cdot HCl \longrightarrow RSO_2Cl$$

R =	Hours	Yield, %	B. p., °C.	Mm.	$n^{25}D$
C_2H_5—	72	30	70–71	20	1.4508
	120	61			
n-C_3H_7—	24	50	66–68	9	1.4518
	48	72			
	120	82			
i-C_3H_7—	120	15.5	61–62	9	1.4522
n-C_4H_9—	120	47	73–75	10	1.4517
i-C_5H_{11}—	24	54	87–88.5	9	1.4530
	48	76			
	72	81			
	120	83			

Experimental Part

S - Alkyl - isothiourea Salts, $RSC(NH_2)=NH\cdot HCl$.—The following salts which were used in this investigation have been prepared previously: S-methyl-isothiourea sulfate,[4a] S-ethyl-isothiourea sulfate,[4a] S-ethyl-isothiourea hydrobromide,[4c] S-isobutyl-isothiourea hydrobromide,[4d] S,S-ethylenedi-isothiourea hydrobromide,[7] S-benzyl-isothiourea hydrochloride,[4a] nitrate[4a] and sulfate.[4a]

The general procedure for the preparation of the S-alkyl-isothiourea hydrohalide salts is that described by Wheeler and Bristol.[4d] A volume of alcohol equal to the volume of alkyl halide was used, except in the cases of ethylene dibromide and ethylene dichloride. In these cases 3 or 4 volumes of alcohol was used and the insoluble S,S-ethylenedi-isothiourea salts were filtered off. After the thiourea had dissolved completely, the alcohol solutions were heated at water-bath temperature until a sample gave no silver sulfide precipitate with ammoniacal silver nitrate. S,S-Ethylenediisothiourea hydrochloride has been prepared previously from the hydrobromide.[7a]

S-n-Heptyl-isothiourea hydrobromide was obtained in a crystalline form by shaking a concentrated alcohol solution of the salt with ether. S-n-Heptyl-isothiourea acetate was prepared by treating a concentrated aqueous solution of the hydrobromide with a saturated solution of potassium acetate. The precipitated acetate was recrystallized from water. S,S-Ethylenedi-isothiourea acetate was prepared and purified in an analogous manner. S-β-Phenylethyl-isothiourea hydrochloride was recrystallized from concentrated hydrochloric acid.

Ethyl chloride and isopropyl chloride in several volumes of alcohol were refluxed for weeks with thiourea without complete transformation to the corresponding S-alkyl-isothioureas. On heating at 110–120° for six to ten hours in an autoclave there was still unchanged thiourea. However, these crude reaction products were chlorinated and with successful formation of the corresponding alkyl sulfonyl chlorides (Table I). The analytical data on new compounds prepared in this research are recorded in Table III.

Alkyl Sulfonyl Chlorides.—(A) The S-alkyl-isothiourea salts (0.05–1.0 mole) were dissolved in water (50–135 cc.) and the solution cooled to 10°, or below, in an ice-bath. Chlorine gas was conducted into this aqueous solution at such a rate that the temperature did not rise above 15° in order to avoid hydrolysis of the sulfonyl chloride with formation of a sulfonic acid. An occasional rise of temperature to 20° did not seriously lower the yields. The treatment with chlorine was continued until the oil (sulfonyl chloride) had completely settled out and the aqueous layer was distinctly green due to the excess of chlorine. This operation usually required about twenty to thirty minutes. The oil (sulfonyl chloride) was then extracted with ether and the excess of chlorine removed by washing several times with small portions of dilute sodium bisulfite solution (5%). After washing with water the ether extract was dried over calcium chloride and distilled.

Benzyl sulfonyl chloride, $C_6H_5CH_2SO_2Cl$, and ethane-1,2-disulfonyl chloride precipitated as solids directly during the chlorine treatment. They were dried over sulfuric acid and purified by crystallization from chloroform or benzene. However, the melting points of the crude material were only a degree or two lower than those of the purified substances.

The low melting β-phenylethyl sulfonyl chloride ($C_6H_5CH_2CH_2SO_2Cl$, m. p. 32–33°) was occasionally obtained as a solid directly, but usually it was necessary to extract with ether as directed above. On removing the ether a solid was always obtained. This sulfonyl chloride also may be purified by distillation.

The bromine of the S-alkyl-isothiourea hydrobromides was removed by adding an equivalent of silver nitrate and the resulting solution concentrated to the desired volume. Chlorination and ether extraction were carried out as previously described. However, with S-n-heptyl-isothiourea hydrobromide and S,S'-ethylenedi-isothiourea hydrobromide this procedure was unsatisfactory because of the

TABLE III

ANALYSES OF NEW COMPOUNDS

Compound	B. p. or m. p., °C.	Mm.	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Halogen, % Calcd.	Halogen, % Found
S-Isopropyl-isothiourea hydrobromide	M. 76–78		14.07	14.10	...	...	40.16	40.42
S-n-Heptyl-isothiourea hydrobromide	M. 92–94		10.97	10.90	...	...	31.33	31.62
S-n-Heptyl-isothiourea acetate	M. 136–137		11.95	11.80	...	...	...	...
β-Phenylethyl-isothiourea hydrochloride	M. 113–114		12.92	13.03	...	...	16.36	16.57
S,S-Ethylenedi-isothiourea hydrochloride	M. 247–248		22.30	22.18	...	...	28.23	28.33
S,S-Ethylenedi-isothiourea acetate	M. 157–158		18.78	18.81	...	...	...	...
n-Heptylsulfonyl chloride	B. 124–126	9	...	...	...	...	17.85	17.62
n-Heptylsulfonamide	M. 74–75·		7.81	7.66	17.90	18.21	...	...
β-Phenethylsulfonyl chloride	B. 121–123	3						
	M. 32–33		...	...	...	...	17.32	17.38
β-Phenethyl sulfonamide	M. 121.5–122.5		7.56	7.44	17.31	17.55	...	...

sparing solubility of the resulting nitrates. The use of a large volume of solution to dissolve the nitrate at the low temperature (10–15°) resulted in a low yield of the sulfonyl chloride. Consequently, in these two cases the acetates were used. These organic salts are more soluble in water than the nitrates. The addition of a small volume of strong hydrochloric acid aids the solution of these salts, (see Table I).

Alkyl Sulfonyl Chlorides.—(B) Seventy-five cubic centimeters of the alcohol containing 4.5–5.0 g. of hydrogen chloride and 7.6 g. (0.1 mole) of finely powdered thiourea were heated on a steam-bath under a reflux condenser for various lengths of time as recorded in the second column of Table II. With frequent vigorous shaking the thiourea dissolved within a few minutes after heat was applied. Some hydrogen sulfide is evolved during the reaction. At the end of the heating period the excess of alcohol was removed under diminished pressure and the viscous residue dissolved in warm water (75–100 cc.). Tests applied to these aqueous solutions with alkaline lead acetate or ammoniacal silver nitrate showed that the thiourea had disappeared completely after seventy-two to ninety-six hours in the case of *n*-propyl-, *n*-butyl and isoamyl alcohol. With ethyl, isopropyl and isobutyl alcohols unchanged thiourea was present after five days of digestion. No attempt was made to isolate the respective S-alkyl-isothiourea hydrochlorides from these reactions. The solution was cooled to the desired temperature and the chlorination operation applied as directed under (A).

That concentrated aqueous hydrochloric acid solution may be used instead of dry hydrochloric acid gas was shown in one experiment: 75 cc. of *n*-butyl alcohol, 10 cc. of concentrated hydrochloric acid and 7.6 g. of thiourea were heated together for forty-eight hours. A yield of 72% of *n*-butyl sulfonyl chloride was obtained as compared to 76% with hydrochloric acid gas. These results are recorded in Table II. The yields given are based on the quantity of thiourea used.

The alkyl sulfonyl chlorides described in (A) and (B) were characterized by chlorine analyses and by melting points of their corresponding acid amides or anilides.[11]

n-Heptyl sulfonamide was prepared by shaking the corresponding sulfonyl chloride with concentrated ammonia. The amide separated in crystalline form and was purified by crystallization from an ether–petroleum ether mixture. β-Phenylethyl sulfonamide was prepared in a similar manner and recrystallized either from dilute alcohol or an ether–petroleum ether mixture.

Ethyl Sulfonyl Bromide, $C_2H_5SO_2Br$.[12]—S-Ethyl-isothiourea hydrobromide (18.5 g.) or sulfate (15.3 g.) was dissolved in 200 cc. of water and the solution cooled to 0–5°. During vigorous stirring 125 g. (0.78 mole) of bromine was added from a dropping funnel during one hour. The temperature was not allowed to rise above 5°, and the solution was stirred for two to three hours at this temperature after the final addition of the bromine. The oil (sulfonyl bromide) was extracted with ether and the excess of bromine removed by washing with 5% sodium bisulfite solution. After washing with water the ether extract was dried over calcium chloride and distilled. The yield was 11.21 g. (64.8%); b. p. 85–86° (18 mm.); $n^{25}D$ 1.5010. *Anal.* Calcd. for $C_2H_5O_2SBr$: Br, 46.19. Found: Br, 45.93.

The use of a larger amount of bromine did not greatly increase the yield. For example, 150 g. (0.94 mole) gave a yield of 67.6%. However, the use of less than 125 g. of bromine gave lower yields: 108 g. gave a yield of 60% of the sulfonyl bromide. Higher reaction temperatures also reduced the yield. Ethyl sulfonyl bromide decomposes with evolution of sulfur dioxide when distillation is applied at ordinary pressure.

Methyl Sulfonyl Bromide, CH_3SO_2Br.[12]—S-Methyl-isothiourea sulfate (13.9 g.) was treated with 125 g. of bromine as described above except that the stirring period after final addition of bromine was increased to five hours. A shorter period of stirring gave a lower yield. The yield was 6.92 g. (43.5%); b. p. 80–80.5° (22 mm.); $n^{25}D$ 1.5080. *Anal.* Calcd. for CH_3O_2SBr: Br, 50.27. Found: Br, 50.25.

***n*-Heptyl Sulfonyl Bromide.**—S-*n*-Heptyl-isothiourea hydrobromide (25.5 g.) under the above conditions gave a 36% yield of this sulfonyl bromide of b. p. 135–137° at 9 mm. There was some decomposition on distillation. The sulfonamide melted at 74–75°.

Action of Chlorine on Hydrobromides of S-Alkyl-isothioureas

An aqueous solution of S-ethyl-isothiourea hydrobromide (18.5 g.) was treated with chlorine as described for the preparation of alkyl sulfonyl chlorides. The chlorination was continued until the bromine color had completely disappeared. The resulting oil was then extracted with ether, washed and dried as previously described. There was obtained 14–16 g. of material of b. p. 90–92° at 23 mm., $n^{25}D$ 1.4960–1.4970. This product contained bromine and a comparison of the refractive index and results of sulfur and halogen analyses indicated a mixture of ethyl sulfonyl chloride (8–12%) and ethyl sulfonyl bromide (88–92%). Ethyl sulfonamide was prepared from the mixture melting at 59°. An aqueous solution of S,S-ethylene-diisothiourea hydrobromide on chlorination gave a solid product containing bromine melting at 95–96° after crystallization from chloroform.

Summary

1. S-Alkyl-isothiourea salts interact in aqueous solution at low temperature with chlorine and bromine to form the corresponding alkyl sulfonyl chlorides and sulfonyl bromides, respectively, in good yields.

2. An alkyl halide and thiourea serve as key reagents in this reaction.

3. A method has been developed for preparing alkyl sulfonyl chlorides directly from an aliphatic alcohol and thiourea as key reagents. Advantage is taken here of an old observation made by Stevens for the preparation of pseudothioureas.

4. The new method of synthesis is superior to

(11) Dugeut, *Rec. trav. chim.*, **21**, 76 (1902); **25**, 215 (1906).

(12) Cherbuliez and Schnauder, *Helv. Chim. Acta*, **6**, 249 (1923).

any technique involving the use of phosphorus halides for conversion of sulfonic acids to their sulfonyl halides.

5. This investigation is to be continued in this Laboratory.

NEW HAVEN, CONN. RECEIVED APRIL 13, 1936

[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

Some Alkyl and Aryl Amides and Ureides as Hypnotics[1]

BY E. H. VOLWILER AND D. L. TABERN

A considerable number of simple and substituted acetamides and acetyl ureas have been prepared from time to time and subjected to pharmacologic study. Many have been found to possess distinct hypnotic activity, and at least five, Adalin (bromodiethylacetyl urea), Neodorm (isopropylethylacetamide), Bromural (bromo-isovaleryl urea), Sedormid (allylisopropylacetyl urea), and Novonal (diethylallyl acetamide), are employed in medical practice. In their properties, these compounds appear to stand intermediate between the comparatively powerful barbiturates and the milder bromides, being chiefly used as sedatives in neuropsychic disorders.

Recent studies in the field of barbiturate hypnotics have demonstrated that certain members, particularly those containing secondary amyl groups in addition to ethyl or allyl, possess unique properties. The member most extensively investigated clinically, ethyl-1-methylbutylbarbituric acid, has been found to be characterized by its unusual rapidity of action, and by the fact that while its hypnotic action is intense, it disappears quite rapidly. As has been repeatedly pointed out,[2] this rapidity of recovery from depressant effects, is a valuable property when the drug is to be used as a preanesthetic sedative. Again, clinical reports indicate that in certain of these higher members, the sedative as contrasted to the true hypnotic properties seem to be accentuated.

It seems desirable, therefore, to prepare a series of acetyl ureas and acetamides, and the bromo analogs, containing the 1-methylbutyl and other similar secondary alkyl groups, in order to see whether the typical properties just enumerated are retained.

(1) The material covered in this paper was presented in part at the Cleveland meeting of the American Chemical Society, September, 1934, and in part at the New York meeting, April, 1935.

(2) (a) Barlow, *Arch. Surg.*, **29**, 527 (1934); (b) Waddy, "The Fear of Anaesthesia," Thesis, University of Manchester, 1934.

Experimental

The requisite malonic esters were prepared in the usual way, in absolute alcohol, employing the respective alkyl bromides (in the case of the diethylcarbinyl derivatives the *p*-toluene sulfonyl ester was utilized), and purified by fractionation.

Certain of the higher esters were very difficult to hydrolyze, prolonged refluxing with 40% potassium hydroxide in dilute alcohol being necessary. After removing the alcohol *in vacuo*, the solid mass was dissolved in cold water and carefully neutralized with hydrochloric acid until permanently acid to congo, the organic acids extracted with ether, heated to eliminate carbon dioxide, and distilled *in vacuo*. Bromo acids were synthesized essentially according to the method of "Organic Syntheses."[3]

The acetic acids were then converted to the acid chlorides by a 10% excess of thionyl chloride at room temperature and purified by fractionation *in vacuo*. No attempt was made to secure highest purity.

For the preparation of the amides, a solution of ammonium hydroxide saturated at 10° was prepared and the acid chlorides gradually dropped in at this temperature, or below, ammonia concentration being maintained by passage of a slow stream of ammonia gas. After several hours of stirring, the solid was filtered off, dried and recrystallized either from dilute alcohol, or a mixture of ether and petroleum ether, or in most cases both.

A generally more satisfactory method of preparing the amides lies in the use of the cyanoacetic esters.[4] For example: ethyl cyanoacetate was condensed by sodium ethylate in absolute alcohol by adding somewhat more than one mole of 1-ethylpropyl bromide ($\alpha^{20}D$ 1.4440) at below 60°. The separation of sodium bromide was rapid. Next morning the mass was heated to boiling and allowed to stand overnight. The ester boiled at 150–160° at 35 mm. This was ethylated by ethyl bromide and sodium ethylate, the reaction again proceeding readily. The ethyl-1-ethylpropylcyanoacetic ethyl ester boiled at 150–155° at 32 mm.

One hundred grams of this ester was refluxed with 100 g. of potassium hydroxide and 200 cc. water for twelve hours or longer. The solvent was distilled *in vacuo*, the cyanoacetic acid liberated by an excess of hydrochloric acid and extracted with benzene. On distillation through a tall column, carbon dioxide was evolved and the redistilled nitrile boiled at 190–200°.

(3) "Organic Syntheses," Coll. Vol. I, 1932, p. 108.

(4) See U. S. Patent 1,482,343 (1934).