tion, extraction with methylene chloride, and removal of the solvent a small amount of white solid. This solid was recrystallized twice from hexane to yield white needles of **α-*t*-butoxy-α-mesitylacetophenone-*o*-carboxylic acid**, m.p. 115–116°.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39; mol. wt., 354.43. Found: C, 74.50; H, 7.36; mol. wt., 392 and 311.

Removal of the *t*-Butyl Group in Compound VI.—A solution of 250 mg. of VI in 15 ml. of dioxane and 5 ml. of 6 *N* hydrochloric acid was heated on a steam bath for 2 hr. During this time the solution was reduced to half the volume, with formation of light ivory colored needles. The mixture was diluted with 25 ml. of water, the solid was collected and chromatographed on silica gel. The ether eluate on removal of the solvent gave white crystals of **2-hydroxy-2-mesityl-1,3-indandione (VIII)**, which was purified by two sublimations at 150–175° (0.05 mm.) to yield white needles, m.p. 198–199°.

The infrared spectrum showed a hydroxyl band at 3500 cm.$^{-1}$, carbonyl bands at 1710 and 1640 cm.$^{-1}$, the latter arising from hydrogen bonding of one of the carbonyl groups with the hydroxyl group. Other bands in the spectrum included a C–O stretching at 1100 cm.$^{-1}$, characteristic of tertiary alcohols, along with CH_3 and mesityl absorption.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.76. Found: C, 76.99; H, 5.86.

Hydrolysis of 2-Mesityl-3-mesityloxy-1-indenone.—A solution of 885 mg. (2.32 mmoles) of VII in 25 ml. of dioxane and 25 ml. of 6 *N* hydrochloric acid was refluxed for 3 days with stirring. The mixture was then concentrated to about 20 ml., diluted with 50 ml. of methylene chloride, and extracted five times with 1 *N* sodium hydroxide. The organic layer contained unchanged starting material. The red aqueous phase on acidification, extraction with methylene chloride, and removal of solvent yielded after trituration of the residue with ether 245 mg. (0.93 mmole, 40%) of pale yellow needles of **2-mesityl-1,3-indandione (V)**, m.p. 223–224°. The reaction mixture had a strong odor of mesitol, but no attempt was made to isolate it.

2-Mesityl-1,3-indandione with Diphenyliodonium Chloride.—To a solution of 84.8 mg. (0.76 mmole) of potassium *t*-butoxide in 20 ml. of *t*-butyl alcohol there was added with stirring 200 mg. (0.76 mmole) of V and 243 mg. (0.76 mmole) of diphenyliodonium chloride. The orange solution was refluxed overnight, during which time it turned a light yellow, and all the iodonium cation was consumed. The solvent was removed, and the residue was chromatographed on a 100-g. Florisil column. The ether eluate yielded a yellow oil which after two distillations at 180–200° (0.05 mm.) gave 188 mg. (0.55 mmole, 73%) of a yellow glass of **2-mesityl-3-phenoxy-1-indenone (IX)**. A small sample of this glass was crystallized from isopropyl alcohol to give a pale yellow solid, m.p. 70.2–71°; ultraviolet absorption maximum, λ_{max}^{EtOH} 246 mμ (ϵ_{max} 42,200).

Anal. Calcd. for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.94; H, 6.06.

The infrared spectrum of this compound was similar to that of compound VII.

The acetone eluate from the chromatography column yielded 30 mg. of unchanged starting material.

When the reaction was run with sodium *t*-butoxide as the base, the reaction time was shortened to 0.5 hr., with otherwise identical results.

Hydrolysis of 2-Mesityl-3-phenoxy-1-indenone.—A solution of 50 mg. of IX in 3 ml. of isopropyl alcohol and 3 ml. of 3 *N* hydrochloric acid was heated on a steam bath for 3 hr. The mixture was concentrated to *ca.* 3 ml. by solvent removal; an odor of phenol was detected. The mixture was diluted with 5 ml. of water, and the gummy solid formed was collected. Trituration with ether gave an ivory solid, m.p. 219–222°, whose infrared spectrum was identical with that of **2-mesityl-1,3-indandione (V)**.

An Improved Synthesis of Carbamates

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A simple synthesis of the hitherto difficultly prepared carbamates of tertiary alcohols has been developed. The method also has been found applicable to the synthesis of the carbamates of other alcohols (including steroids, as well as primary and secondary alcohols), polyols, phenols, mono- and polythiols, and oximes. Stereoisomeric (*syn* and *anti*) ketoximes were converted to the corresponding stereoisomeric oxime carbamates. The preparation of any of these involves simply stirring the substrate, sodium cyanate, and trifluoroacetic acid in an inert solvent for several hours at room temperature.

Although the carbamates of primary and secondary alcohols, and the N-substituted carbamates of tertiary alcohols are relatively easily prepared,[1] the synthesis of unsubstituted carbamates of tertiary alcohols is generally quite difficult, owing to the ease of dehydration and rearrangement of the alcohols.[2,3] The method usually employed involves conversion of the alcohol to a mixed carbonate using phenyl chloroformate, then treatment with liquid ammonia.[2,3]

During the course of a study which necessitated the preparation of a number of carbamates of tertiary alcohols, we developed a simple method for their synthesis which has been found to be broadly applicable not only to the synthesis of the carbamates of alcohols (primary, secondary, and tertiary alcohols, steroids, polyols, and phenols), but also to the synthesis of the carbamates of mono- and polythiols and oximes.

This method involves stirring the alcohol (mercaptan, oxime, etc.) with sodium cyanate and trifluoroacetic acid in certain solvents at room temperature.

Although the reaction of alcohols with cyanic acid had been presumed always to give allophonates,[2,4,5] Werner[6] reported a 56% yield of urethan from the reaction of ethanol in an aqueous solution of sodium cyanate and hydrochloric acid. McLamore[2] reported, however, that reaction of a tertiary alcohol with potassium cyanate in acetic acid led to dehydration or rearrangement and gave *no* carbamate. Moderate (approximately 50%) yields of the carbamates of tertiary alcohols were described by Marshall,[7] employing *in situ* generation of cyanic acid from an anhydrous mixture of sodium cyanate in trichloroacetic acid.

(1) Houben-Weyl, "Methoden der Organischen Chemie," Vol. VIII, 4th Ed., Georg Thieme Verlag, Stuttgart, 1952, pp. 103, 115, 137.

(2) W. M. McLamore, S. Y. P'An, and A. Bavley, *J. Org. Chem.*, **20**, 1379 (1955).

(3) B. Melander, *J. Med. Pharm. Chem.*, **1**, 443 (1959).

(4) W. J. Close and M. A. Spielman, *J. Am. Chem. Soc.*, **75**, 4055 (1953).

(5) H. W. Blohm and E. I. Becker, *Chem. Rev.*, **51**, 471 (1952), give a comprehensive review of the synthesis of allophonates and point out the erratic results obtained by various investigators.

(6) A. Werner, *Sci. Proc. Roy. Dublin Soc.*, **24**, 209 (1947); *Chem. Abstr.*, **41**, 6533*e* (1947).

(7) P. G. Marshall, J. H. Barnes, and P. A. McCrea, U. S. Patent 2,814,637 (1957). The same procedure was later used by W. Stuehmer and S. Funke, U. S. Patent 2,878,158 (1959), and J. H. Barnes, *et al.*, *J. Pharm. Pharmacol.*, **13**, 39 (1961).

On modifying this procedure we found that significantly improved yields of carbamates were readily and consistently obtained; thus, the yield of *t*-butyl carbamate was raised to over 90%.

The compounds prepared by this procedure are listed in Table I (pp. 3424 and 3425).

The most significant factor leading to improved yields was substitution of trifluoroacetic for trichloroacetic acid. This beneficial effect does not appear to be solely related to increased acid strength, for hydrochloric and methanesulfonic acids gave only *traces* of product when used in place of trifluoroacetic acid under the same conditions.[8]

Another factor markedly influencing the yield was the choice of solvent; benzene and methylene chloride gave markedly better yields than other inert solvents such as ether, carbon tetrachloride, or tetrahydrofuran.

Substitution of potassium cyanate for sodium cyanate reduced the yield to less than 5%.

The reaction is generally over in less than two hours, and the crude yields of product are high (60 to 90%). In some instances, the final yield of analytically pure product was low; this was generally due to losses occurring during purification, as the result of the inherent thermal or hydrolytic instability or volatility of the products. In most cases, the "crude" product was actually quite pure.

Primary, secondary, and tertiary alcohols are all smoothly converted to the corresponding carbamates (compounds **1** to **7**). Even the relatively unstable propargyl alcohol was easily converted to its carbamate (compound **5**).[9] The melting point of menthol carbamate (**6**) which we prepared differed from that reported by Bedos,[10] but agrees with that reported by other investigators.[11]

Both cyclic and acyclic 1,3-diols gave the simple dicarbamates (**10** to **12**) as the major products. However, 1,2-diols gave cyclic *carbonates* (**25** and **26**), along with mixtures of other products, probably mono- and dicarbamates.

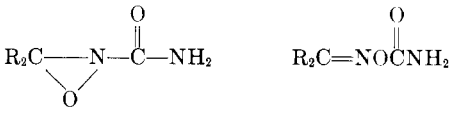
Attempts were made to extend these reactions to the preparation of carbamates from 1,1-(*gem*) diols and dithiols. Dihydroxymalonic acid (mesoxalic acid hydrate) was recovered unchanged from the reaction mixture, and biphenylglyoxal hydrate gave a high melting, insoluble mixture of products.[12]

The only simple alcohols from which carbamates could not be isolated were diphenylethylcarbinol (which gave 1,1-diphenylethylene) and trichloro- and trifluoromethylcarbinols (these gave complex mixtures of products).

Phenols easily gave the corresponding carbamates (**8** and **9**).

The carbamates of surprisingly few primary and secondary mercaptans, and of no tertiary mercaptans, are known. These (**15**–**17**) and the carbamate of a 1,3-dithiol (**18**)[13] were readily prepared. The odors of the freshly prepared thiolcarbamates were not particularly unpleasant; however, on prolonged standing a typical mercaptan odor developed. A *gem*-dithiol, 2,2-dimercapto-1,3-diphenylpropane,[14] did not react and was recovered unchanged from the reaction mixture.

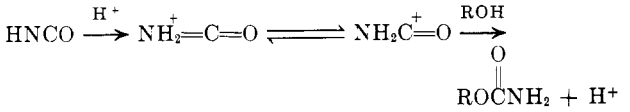
Oxime carbamates were first prepared by Conduche[15] in 1909 by the reaction of a carbonyl compound with isohydroxyurea, but were assigned the incorrect azoxirane structures I. Exner[16] recently showed that the structure was II.



I II

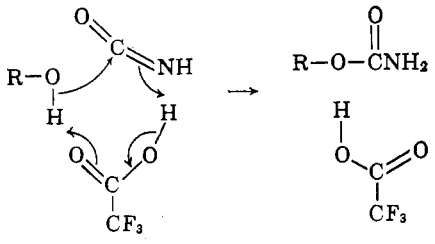
We have found that aldoximes and ketoximes react smoothly by our procedure to give the oxime carbamates corresponding to II (**19**–**24**).[17] *syn*- and *anti*-isobutyrophenone oximes[18] give stereoisomeric oxime

(8) Although the reaction may under some conditions proceed by direct reaction of the alcohol with the organic acid, *viz.*



the significant increase in yield resulting from the use of trifluoroacetic acid suggests that trifluoroacetic acid may be more directly involved, possibly through intermediate ester formation with the alcohol, through formation

of a mixed carbamic acid anhydride (CF_3COCNH_2), or through involvement in a cyclic reaction such as



(9) M. D. Cameron, U. S. Patent 2,844,590 (1958), prepared this compound in 30% yield by heating propargyl alcohol and urea for 12 hr.

(10) P. Bedos, *Bull. soc. chim. France*, **39**, 674 (1926). The compound which this author described was prepared by boiling the allophonate of a synthetic "menthol" of unproven structure with potassium hydroxide. In view of the method of preparation and the alkali stability of his product, the structure of his material is questionable.

(11) B. Holmberg and W. Rosen, *Ber.*, **58**, 1834 (1925); M. O. Forster and H. Stötter, *J. Chem. Soc.*, **99**, 1337 (1911).

(12) The product from chloral hydrate will be described in another communication.

(13) The thiol analog of meprobamate.

(14) G. A. Berchtold, *et al.*, *J. Am. Chem. Soc.*, **81**, 3148 (1959).

(15) A. Conduche, *Ann. chim. phys.*, **12**, 533 (1907); **18**, 1 (1908); *Chem. Abstr.*, **2**, 658 (1908); **2**, 999 (1908).

(16) O. Exner and M. Horak, *Collection Czech. Chem. Commun.*, **24**, 2992 (1959).

(17) After our work was completed, an article by G. Zinner, *Arch. Pharm.*, **292**, 1 (1959), appeared, describing the synthesis of the carbamates of some aliphatic oximes by reaction of the oximes at −10° with aqueous potassium cyanate and hydrochloric acid. Zinner points out, however, that he could only prepare the carbamates of oximes having some water solubility, and furthermore, that aromatic oximes did not react. The procedure described in the present paper worked for all oximes tried and, also, as indicated, permits synthesis of the stereoisomeric *syn*- and *anti*-ketoxime carbonates.

(18) The oxime prepared from isobutyrophenone was first reported having m.p. 58° [V. Meyer, *et al.*, *Ber.*, **20**, 506 (1887)]. Later, A. Lapworth and V. Steele, *J. Chem. Soc.*, 1882 (1911), reported a m.p. of 96° and claimed that the earlier figure was incorrect. However, papers continued to appear reporting only 56 to 58° melting products [A. Magnam and S. M. McElvain, *J. Am. Chem. Soc.*, **60**, 819 (1938); P. L. deBenneville, *J. Org. Chem.*, **6** 462 (1941); and G. P. Men'shikov, *J. Gen. Chem. USSR*, **9**, 1851 (1939)]. In 1950, Kissman and Williams[19] reported that the 58 to 60° material, on slow crystallization from pentane, deposited a mixture of two different types of crystals which they separated manually and showed to be the *syn* (m.p. 89–90°) and *anti* (m.p. 95–96°) isobutyrophenone oximes (m.m.p. 57–60°). The oximes could not be separated satisfactorily by chromatography. In subsequent papers, only the laborious manual method of isolating the two forms has been employed [H. M. Kissman, D. S. Tarbell, and J. Williams, *J. Am. Chem. Soc.*, **75**, 2959 (1955), and R. F. Brown, N. M. vanGulick, and G. H. Schmid, *ibid.*, **77**, 1094 (1955)]. In the Experimental, we describe a convenient synthesis of the pure isomers.

(19) H. M. Kissman and J. Williams, *J. Am. Chem. Soc.*, **72**, 5323 (1950).

(20) F. D. Chattaway and E. Saerens, *J. Chem. Soc.*, 708 (1920).

(21) W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

carbamates; however, *syn-* and *anti-p*-chlorobenzaldoximes gave the same product.

The extension of this reaction to more complex alcohols, *i.e.*, those in which still other functional groups are present, is underway. Preliminary work indicates that when a basic tertiary nitrogen is present in the molecule, the yield of carbamate is very low.

Although, as pointed out earlier, the usual products from the reaction of cyanic acid with alcohols have been reported to be allophonates, we have never observed allophonate formation in our procedure. The only by-product occasionally observed is trifluoroacetamide; however, it is not usually isolated and does not present any problem because of its very high solubility in water and in organic solvents.

When sodium thiocyanate and trifluoroacetic acid reacted with alcohols and mercaptans in attempts to extend this synthetic method to the synthesis of thionecarbamates and dithiocarbamates, only complex mixtures of odorous products resulted.

Experimental[26]

General Procedure.—Most of the study of the effect of changing the experimental variables on yield was done using *t*-butyl alcohol.

As already pointed out in the discussion, trifluoroacetic acid gives far better yields than trichloroacetic acid, and other acids under the same conditions give negligible yields. For each hydroxyl group 2 equiv. of trifluoroacetic acid and 2 equiv. of sodium cyanate are used. Excess trifluoroacetic acid has no effect, but smaller amounts of the acid or cyanate cause a big drop in yield.

Another important factor influencing the yield is solvent. In most instances, the use of benzene or methylene chloride gives yields superior to those obtained even using similar solvents such as carbon tetrachloride or ether. A few instances were found where benzene or methylene chloride did not give any product, but tetrahydrofuran did; but, in general, tetrahydrofuran as solvent led to negligible yields of product. With a new alcohol, therefore, the procedure was first to try benzene or methylene chloride (the choice of these depending on the solubility of the alcohol) and, if this did not give any product, then to try tetrahydrofuran as solvent. In every case, the yield is much higher when the alcohol is soluble in the diluent used.

The order of addition of reagents is not important; however, the procedure we generally use involves adding the acid to a *slowly* stirring mixture of the cyanate and alcohol in the solvent. Vigorous agitation markedly decreases the yield.

The temperature, within the limits of 20 to 50°, has no effect on yield. A contact time of 2 hr. is usually sufficient. Increasing the reaction time to 24 hr. has no effect on the yield; for convenience the reaction mixture is usually allowed to stir overnight at room temperature.

After the reaction is completed, a small amount of water is added to the mixture to dissolve the salts; then the organic solution is separated, dried, and concentrated *in vacuo* (usually at 50°, since most of the carbamates proved to be thermally unstable or volatile). Rinsing of the organic solution with dilute bicarbonate invariably resulted in large losses of product.

The crude product was generally isolated in good yield (60–90%), as listed in Table I, in a good state of purity; however, large losses were generally observed during further purification due to the volatility and the thermal and hydrolytic instability of many of the carbamates. The yields in parenthesis in Table I are after further purification.

In most of the experiments described subsequently, no attempt was made to determine the optimum experimental conditions.

As a typical preparation, the synthesis of *t*-butyl carbamate is given in detail.

***t*-Butyl Carbamate (2).**—Trifluoroacetic acid (15.5 ml., 0.21 mole) was added (hood!) slowly to a stirred mixture of *t*-butyl alcohol (7.4 g., 0.1 mole) and sodium cyanate (13 g., 0.2 mole) in 25–100 ml. of benzene (volumes of solvent significantly larger than this decreased the yield). A mildly exothermic reaction occurred and some gas bubbled out of the system. The container was loosely stoppered, and the reaction mixture was stirred for 3 hr. (or overnight, the yield was the same). Fifteen milliliters of water was added and the organic layer was separated and dried; the solvent was removed *in vacuo* at a pot temperature of 40–50°. The residue solidified, 92% yield, m.p. 98–101°. Recrystallization from water gave an analytically pure product, 8 g. (69% yield), m.p. 107–108° (lit.[21] m.p. 108°).

The preparation of the other compounds was essentially identical to that described for the preparation of *t*-butyl carbamate. The specific reaction conditions are listed in Table I.

Further details of the work-up, where these are not obvious from the table, are given as follows.

***dl*-Menthol Carbamate (6).**—The product also was obtained, although in lower yield than listed in the table, when tetrahydrofuran was used as solvent. When the sodium cyanate was omitted from the reaction, menthol was quantitatively recovered showing that menthol did not undergo any rearrangement under these reaction conditions.

4-Chloro-17α-methyl-19-nortestosterone Carbamate (7).—At the conclusion of the reaction period (Table I), the tetrahydrofuran was distilled from the reaction mixture *in vacuo*, and the semisolid residue was treated with water. The resulting solid was treated with acetone and the insoluble material discarded. The filtrate, on concentration, left an oil which was dissolved in benzene and chromatographed using neutral alumina. The crystalline fractions that were isolated were combined and recrystallized from ethanol–water.

2,2,4,4-Tetramethyl-1,3-bis(carbamyloxy)cyclobutane (12).—The starting glycol was obtained from Eastman Chemical Products; it is a mixture of the *cis* and *trans* glycols and was used as such.

At the end of the reaction period the ether was removed and the residual slurry was neutralized with sodium bicarbonate. On dilution with water, the solid dicarbamate (mixture of *cis* and *trans* isomers) separated. This was recrystallized from water.

When the reaction was carried out using tetrahydrofuran as solvent and worked up as before, some ether-insoluble material was isolated, which proved to be the monocarbamate (mixture of *cis* and *trans* isomers), m.p. 160–170° (10% yield).

Terpin Biscarbamate (14).—At the end of the reaction period the solvent was removed *in vacuo* and the residue was diluted with water, then extracted with ethyl acetate. Concentration of this extract gave an oil which was chromatographed over neutral alumina to give the biscarbamate as a solid (45% yield), and some oil that analyzed as slightly impure monocarbamate.

2-Methyl-2-pentanethiol.—A mixture of 1 equiv. of 2-methyl-2-pentanol (K and K Laboratories), 1.1 equiv. of thiourea, and 1.3 equiv. of concentrated hydrobromic acid was stirred at room temperature for 18 hr.[27] At the end of this time, two layers were present. Addition of an aqueous solution of *p*-toluenesulfonic acid to a portion of this two-phase system gave the thiouronium *p*-toluenesulfonate, m.p. 124–127° dec. (from methanol–ether).

Anal. Calcd. for $C_{14}H_{24}N_2O_3S_2$: C, 50.27; H, 7.21; N, 8.42. Found: C, 50.14; H, 7.19; N, 8.37.

The balance of the two-phase system was treated with 2 equiv. of sodium hydroxide (keeping the system under nitrogen) at 35–40°. A large oily layer separated. This was steam distilled directly from the reaction mixture. The distillate was separated and extracted with some ether and distilled. The mercaptan distilled, b.p. 129–130°, $n^{25}D$ 1.4470 (lit.[27] b.p. 122–123°, $n^{20}D$ 1.4389), 52% over-all yield.

2-Methyl-2-propylpropane-1,3-dithiol Dicarbamate (18). A. 2-Methyl-2-propyl-1,3-dibromopropane.—A mixture of 2-methyl-2-propylpropane-1,3-diol (132 g., 1.0 mole) and sufficient phosphorus tribromide to form a paste was stirred and warmed to 65°. The balance of the bromide (271 g., 1.0 mole total) was slowly added, maintaining the reaction temperature at 80–90° by cooling or warming as required. After the addition was completed, the orange mixture was kept at 145–150° for 20 hr. The

(22) T. Kempf, *J. prakt. Chem.*, [2]**1**, 405 (1870).

(23) Bayer and Co., German Patent 318,803 (1919).

(24) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

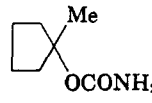
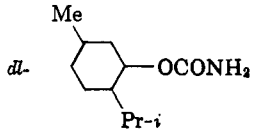
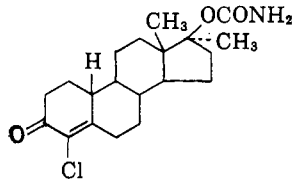
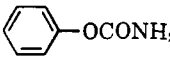
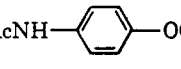
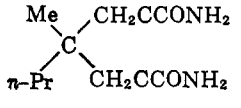
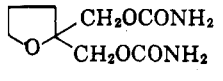
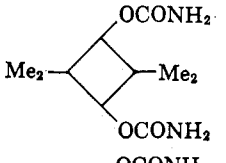
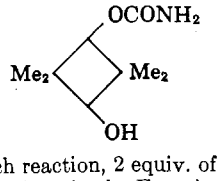
(25) R. Riemschneider and G. Orlick, *Monatsh.*, **84**, 313 (1953).

(26) All melting points are corrected. The microanalyses were performed by Mrs. D. Rolston and her staff of these laboratories.

(27) Procedure of D. F. Lee, *et al.*, *Chem. Ind.* (London), **27**, 868 (1960).

TABLE I

SYNTHESES OF CARBAMATES

No.	Compound	Conditions[a]	M.p., °C.	Recrystallization solvent	Yield,[m] %	Analysis: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	*n*-BuOCONH$_2$	Benzene, 2 hr., 30°	53–54[b]	Water	(73)						
2	*t*-BuOCONH$_2$	Benzene, 2 hr., 30°	107–108[c]	Hexane	92	51.26	9.47		51.00	9.47	
3	Et$_2$C(Me)—OCONH$_2$	No solvent, 4 hr., 45°	55–56[d]	Hexane	(39)						
4		CH_2Cl_2, 18 hr., 30°	108–109	Cyclohexane	78	58.72	9.15	9.78	58.84	9.08	10.02
5	HC≡CCH$_2$OCONH$_2$	Ether, 3 hr., 30°	47–50[e]	Benzene	60	48.48	5.09	14.14	48.42	5.15	14.22
6		AcOH, 3 hr., 30°	164–166[f]	Ethanol	87	66.29	10.62	7.03	66.24	10.74	6.77
7		THF, 18 hr., 30°	213–216	Ethanol–water	25	65.65	7.71	3.83	65.64	7.54	3.79
8		Ether, 48 hr., 30°	145–148[g]	Water	62						
9	AcNH— 	CH_2Cl_2, 18 hr., 30°	200–202[h]	Water	35	55.67	5.19	14.43	55.66	5.21	14.72
10		THF, 2 hr., 30°	102–103[i]	Water	75						
11		THF, 18 hr., 40°	194–196	Ethanol	57	44.03	6.47	12.84	44.11	6.38	12.92
12		Ether, 18 hr., 30°	175–185[j]	Water	(45)	52.16	7.88	12.17	52.24	7.79	11.90
13		THF, 18 hr., 30°	160–170[j]	Water	10	57.72	9.17	7.48	57.71	8.93	8.10

[a] In each reaction, 2 equiv. of sodium cyanate and 2 equiv. of trifluoroacetic acid were used for each hydroxyl group present. Other details are given in the Experimental section. [b] Ref. 20, m.p. 54°. [c] Ref. 21, m.p. 108°. [d] Emylcamate, ref. 2, m.p. 55–56°. [e] B.p. 95–100 (1.5 mm.); ref. 9, m.p. 43–44°. [f] Ref. 11, m.p. 165–166°. [g] Ref. 22, m.p. 141°. [h] After recrystallization from water, the compound melted at 165–167°; after drying, m.p. 200–202° (shrinking at 182°); lit.[23] m.p. 181°. [i] Meprobamate, ref. 24, m.p. 105–

mixture was poured into water and then steam distilled. The distillate was extracted with ether and dried; the solvent was removed and the dibromide distilled, b.p. 96–97° (7 mm.), n^{27}D 1.4995, 35% yield.

Anal. Calcd. for $C_7H_{14}Br_2$: Br, 61.9. Found: Br, 61.6.

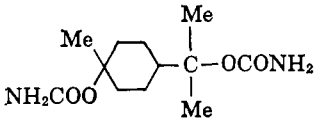
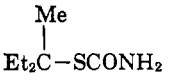
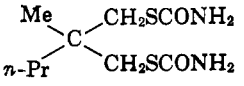
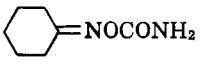
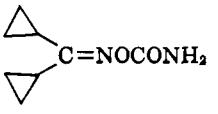
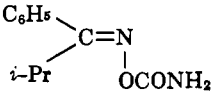
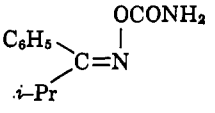
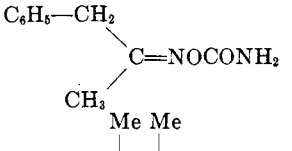
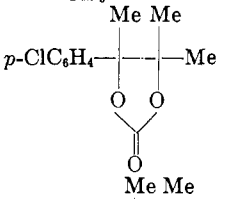
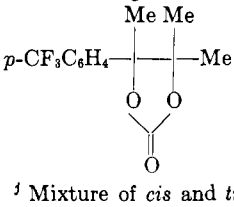
B. 2-Methyl-2-propyl-1,3-propanedithiol.—A solution of sodium polysulfide was prepared by bubbling hydrogen sulfide into 40 ml. of 40% aqueous sodium hydroxide until the solution was saturated, then adding this solution to a suspension of 18 g. of sulfur in 35 ml. of ethanol.[28] A vigorous reaction occurred with hydrogen sulfide evolution. When the reaction subsided, the solution was heated on a steam bath for 0.5 hr. The solution was diluted with 300 ml. ethanol, 17 g. of the dibromide was added, and the solution was refluxed for 24 hr. Most of the alcohol was distilled, and a large volume of water was added to the residue. The polysulfide was isolated as an oil, 12 g. This was added dropwise to a solution of 9.2 g. of sodium in 350 ml. of liquid ammonia. The ammonia was allowed to evaporate, and the residue was treated with ether and a little ethanol, then diluted with water. The system was made acidic with dilute sulfuric acid; then the ether extracts were dried and concentrated giving 9.1 g. oil, n^{25}D 1.5095. The dimercaptan was distilled, 7.5 g., n^{25}D 1.5095, b.p. 57° (0.7 mm.).

Anal. Calcd. for $C_7H_{16}S_2$: C, 51.16; H, 9.81. Found: C, 51.19; H, 9.88.

C. Preparation of the Bisthiolcarbamate.—The reaction was carried out according to our standard procedure. The reaction mixture was rinsed with water, dried, and concentrated. A

(28) H. J. Backer and N. Evenhuis, *Rec. trav. chim.*, **56**, 174 (1937).

TABLE I
(*continued*)

No.	Compound	Conditions[a]	M.p., °C.	Recrystallization solvent	Yield,[m] %	Analyses—Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
14		THF, 18 hr., 30°[c]	203–205	Ethanol–water	(45)	55.80	8.58	10.85	56.10	8.82	10.93
15	*n*-BuSCONH$_2$	Ether, 3 hr., 30°	98–100[k]	Hexane	65	45.08	8.32	10.52	45.25	8.21	10.68
16	*t*-BuSCONH$_2$	Ether, 4 hr., 30°	92–95[l]	Hexane	50	45.08	8.32	10.52	45.23	8.31	10.67
17		CH_2Cl_2, 18 hr., 30°	45–47	Hexane	(25)	52.13	9.38	8.69	52.21	9.70	8.81
18		CH_2Cl_2, 18 hr., 30°	102–104	Isopropyl ether–hexane	50	43.17	7.25	11.19	43.10	7.36	11.02
19		CH_2Cl_2, 18 hr., 30°	94–96	Water	90	53.83	7.74	17.94	54.18	7.79	17.79
20		Ether, 18 hr., 30°	114–116	Water	77	57.13	7.19	16.66	57.15	7.33	16.74
21		CH_2Cl_2, 4 hr., 30°	114–116	Cyclohexane–hexane	(40)	64.06	6.84	13.58	64.34	7.08	13.67
22		CH_2Cl_2, 3 hr., 30°	94–96	Cyclohexane	(31)	64.06	6.84	13.58	63.87	6.77	13.65
23	*p*-ClC$_6$H$_4$CH=NOCONH$_2$	CH_2Cl_2, 18 hr., 30°	157–158	Benzene	80	48.38	3.55	14.11	48.44	3.70	13.88
24		CH_2Cl_2, 5 hr., 30°	87–89°	Chloroform–hexane	(13)	62.48	6.29	14.57	62.68	6.52	14.66
25		Ether, 3 hr., 30°	73–75	Water	(56)	59.9	5.42		60.0	5.54	
26		CH_2Cl_2, 18 hr., 30°	71–74	Cyclohexane	(20)	56.94	4.78		56.81	4.91	

106°. [j] Mixture of *cis* and *trans* isomers; see Experimental. [k] Ref. 25, m.p. 102°. [l] B.p. 110–112° (2 mm.). [m] The yields listed are based on a single run; no attempt was made to determine the optimum conditions for highest yield; the figures in parentheses are the yields after several recrystallizations during which time serious losses due to hydrolysis resulted.

white solid formed, 50% yield, m.p. 85–90°. It was recrystallized first from methanol–water, then from isopropyl ether–hexane, giving an 11% yield of analytically pure product. The combined filtrates appeared to contain some monocarbamate and some cyclic dithiocarbamate.

syn-**Isobuty ophenone Oxime**.—A mixture of isobutyrophenone (74 g., 0.5 mole), hydroxylamine hydrochloride (52.15 g., 0.75 mole), and anhydrous sodium acetate (82 g., 1.0 mole) in ethanol was heated at reflux for 4 hr. The suspension was filtered and the filtrate was concentrated *in vacuo* to yield an oil which solidified to a crystalline material, m.p. 58–63°, corresponding to a mixture of *syn* and *anti* isomers[19]; yield, 80 g. (98%).

Some of this material was dissolved in ether and treated with excess ethereal hydrogen chloride; a white solid separated immediately. The suspension was heated at reflux for 1 hr. and the solid then isolated. The melting point of this oxime hydrochloride was 113–117° dec. No attempt was made to purify it since on treatment with water, the free base separated, m.p. 85–90°. It was recrystallized several times from hexane, m.p. 89.5–92° (lit.[19] m.p. 89–90°).

All attempts to separate the original mixture of oximes (m.p. 58–63°) by fractional crystallization or thin-layer chromatography failed.

anti-**Isobutyrophenone Oxime**.—The reaction was carried out as described for the preparation of the *syn* isomer, except that the mixture was maintained *at room temperature* for 8 hr. If continued for longer periods, isomerization started to occur and an inseparable mixture resulted.

The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* keeping the pot temperature below 40°. The residual oil crystallized. On recrystallization from cyclohexane, 33 g. of pure *anti*-isobutyrophenone oxime was obtained, m.p. 97–100[29] (lit.[19] m.p. 95–96°), m.m.p. 56–60° with the *syn* isomer.

Attempts to prepare the *anti* isomer by ultraviolet light isomerization in ethanol or benzene for varying lengths of time led only to an inseparable mixture of *syn* and *anti* forms. Brief warming with dilute alcoholic hydrochloric acid also gave an inseparable mixture of isomers, m.p. 56–60°.

Evidence obtained from thin layer chromatography experiments indicate that the mixture of *carbamates* prepared from the *syn–anti* oxime mixture could be separated on alumina using methylene chloride as eluate.

p-Chlorobenzaldoxime Carbamate (22).—*syn-* and *anti-p*-chlorobenzaldoximes were prepared as described by Erdmann.[30] The same carbamate was obtained regardless of which isomer was used as starting material.

Benzyl Methyl Ketoxime Carbamate (23).—The ketoxime, b.p. 106° (1.5 mm.), was prepared as described by Neber.[31] No isomer of this oxime is known.

At the end of the reaction period, the reaction mixture was treated with water, and the aqueous suspension was extracted with methylene chloride. The organic solution was dried and concentrated to give an oil which slowly solidified. The semisolid material was chromatographed in ethyl acetate solution using alumina (Fisher chromatographic alumina), and the crystalline eluates were further purified by recrystallization from a mixture of chloroform and hexane.

2-(*p*-Chlorophenyl)-3-methyl-2,3-butanediol Cyclic Carbonate (25).—The starting diol[32] was treated in the standard manner. After removal of the solvent, a little water was added; then the solution was neutralized with bicarbonate, extracted with ether, dried, and concentrated to an oil that slowly set to a semisolid. The oil was dissolved in benzene and chromatographed over neutral alumina. The fractions that crystallized were combined and recrystallized from methanol, 56% yield. The infrared spectra show no –NH absorption and thus agree with the elemental analysis, which corresponds to the cyclic carbonate.

Some of the other chromatographic fractions crystallized after prolonged standing. Inspection of the infrared spectra indicates that a mixture of mono- and dicarbamates was probably present.

2-(*p*-Trifluoromethylphenyl)-3-methyl-2,3-butanediol Cyclic Carbonate (26). **A. 2-(*p*-Trifluoromethylphenyl)-3-methyl-2,3-butanediol.**[33]—To the Grignard reagent prepared from 113 g. (0.454 mole) of *p*-bromobenzotrifluoride and 12.5 g. (0.51 mole) of magnesium turnings in 1000 ml. of ether was added 21 g. (0.205 mole) of 2-methyl-2-hydroxy-3-butanone (K and K Laboratories) in 50 ml. of ether at such a rate that refluxing proceeded slowly. The mixture was stirred overnight and treated first with 100 ml. of a saturated ammonium chloride solution and then with 100 ml. of 2 *N* hydrochloric acid. After stirring for 30 min., the ethereal layer was separated and concentrated *in vacuo* to give a solid. This was recrystallized from cyclohexane, a mixture of methanol–water, and a mixture of cyclohexane and benzene. White needles were obtained, m.p. 98–99°; yield, 30 g. (59%).

Anal. Calcd. for $C_{12}H_{15}F_3O_2$: C, 58.06; H, 6.09. Found: C, 58.48; H, 6.51.

B. Preparation of the Cyclic Carbonate.—The starting diol was treated in the standard manner. The resulting oil was chromatographed over neutral alumina. The fractions that crystallized were combined and recrystallized from cyclohexane, 20% yield.

Acknowledgment.—We wish to thank Mr. Kenneth Snader for experimental assistance.

(29) We are indebted to Dr. Robert Lyle for providing us with a sample of *anti*-isobutyrophenone oxime (isolated by manual separation of crystals). It proved to be identical by mixture melting point and infrared comparisons with our material.

(30) H. Erdmann and E. Schwechten, *Ann.*, **260**, 53 (1890).

(31) P. W. Neber and A. V. Friedolsheim, *ibid.*, **449**, 109 (1926).

(32) Phenglycodol, J. Mills, *et al.*, *Proc. Soc. Exptl. Biol. Med.*, **96**, 100 (1957).

(33) The preparation of this material was carried out by Dr. Irwin Pachter of our laboratories.

Sulfonyl Fluorides as Intermediates in Organic Synthesis. I. The Synthesis of Aminobenzenesulfonyl Fluorides and Their Condensation with β-Ketonic Esters

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Aminobenzenesulfonyl fluorides have been synthesized by deacylation of acetylaminobenzenesulfonyl fluorides or by catalytic hydrogenation of nitrobenzenesulfonyl fluorides over Raney nickel catalyst. They can be condensed in the usual way with β-ketonic esters to give N-acylacetylaminobenzenesulfonyl fluorides which can be converted into the corresponding sulfonates by alkaline hydrolysis.

The condensation of β-ketonic esters with substituted anilines to give acylacetylanilides is generally conducted in boiling xylene. Aminobenzenesulfonic acids or their salts, however, possessing very low basicity and negligible solubility in this reaction medium, fail to react. Since this excluded one-step synthesis of N-acylacetylaminobenzenesulfonates III, indirect synthetic routes had to be investigated.

Esters of N-acylacetylaminobenzenesulfonic acids IIa and IIb were expected to be interesting intermediates for the preparation of N-acylacetylaminobenzenesulfonates of type III.

However, condensation of β-ketonic esters with methyl aminobenzenesulfonates Ia gave only low yields of the expected compounds IIa, along with rather large amounts of methylaminobenzenesulfonic acids resulting from autoalkylation of methyl aminobenzenesulfonates Ia. Phenyl acylacetylaminobenzenesulfonates IIb could be obtained in high yields, but were found too resistant to alkaline hydrolysis.

Finally, the condensation of β-ketonic esters with aminobenzenesulfonyl fluorides Ic, and the subsequent alkaline hydrolysis of the resulting N-acylacetylaminobenzenesulfonyl fluorides IIc proved to be a successful

$$\mathrm{RCOCH_2COOC_2H_5} + \mathrm{H_2NArSO_2X} \xrightarrow[\text{xylene}]{\text{boiling}}$$

Ia, X = $-OCH_3$
b, X = $-OC_6H_5$
c, X = $-F$

$$\mathrm{RCOCH_2CONHArSO_2X} \xrightarrow{\text{NaOH}} \mathrm{RCOCH_2CONHArSO_2ONa}$$

IIa, X = $-OCH_3$
b, X = $-OC_6H_5$
c, X = $-F$

III

R = an aliphatic, aromatic, or heterocyclic substituent