New Methods of Introducing the Carbo-t-butoxy Amino-Protecting Group. Investigation of t-Alkyl Chloroformates Substituted with Electron-Withdrawing Substituents

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α-Bromo- and α,α-dibromo-t-butyl chloroformate have been synthesized and found to be significantly more stable than t-butyl chloroformate. On treatment with aniline and other amines the corresponding urethans were obtained although the acylation reaction was generally unsuccessful with amino acid derivatives. Catalytic reduction of the carbanilates over a palladium–carbon catalyst gave the corresponding carbo-t-butoxy derivatives although in low yields only. The α-bromo-t-butyl carbamates were found to undergo a unique "self-cleavage" reaction upon warming in ethanol, being converted to the corresponding ammonium bromide. The chloroformate of 2-methyl-3-butyn-2-ol was also synthesized and shown to be more stable than t-amyl chloroformate.

In addition to its use in peptide chemistry, the carbo-t-butoxy (BOC) group is of considerable importance to the nonpeptide synthetic organic chemist.[1,2] Although for the most part the problem of introducing this group onto an amino function has been solved, a wide variety of acylating agents[3] currently being available, there is still no reagent which is completely satisfactory with the more weakly basic amino compounds. We have therefore sought to develop reagents of this type which would approach acid chlorides in their reactivity. Although t-butyl chloroformate was first synthesized many years ago[4] and has in fact been used occasionally[5,6] to introduce the BOC group, it seems too unstable for general use under ordinary conditions.

In view of the well-known stability of formyl fluoride[7] relative to the corresponding chloride, it was assumed that the same relationship might hold for the related pair of haloformates. With this in mind, numerous methods were investigated for the conversion, at low temperatures, of the unstable chloroformate to the corresponding fluoride. Exchange reactions utilizing hydrogen fluoride[8] and various salts such as sodium[9,10] thallous,[11] and silver fluoride were examined without success. Eventually the fluoroformate (I) was obtained by direct reaction between t-butyl alcohol and carbonyl chlorofluoride[12,13] in methylene dichloride solution in the presence of pyridine. As expected, the fluoroformate proved to be sufficiently stable to be distilled at atmospheric pressure, bp 78–79°, and could be stored without difficulty under ordinary conditions. It showed typical haloformate reactivity toward a variety of amino compounds. Reaction with glycine and alanine in aqueous solution gave the BOC derivatives in a few minutes in 75–80% yield. During the course of our studies Schnabel and Ugi[14] and their associates described a similar method for the preparation of t-butyl fluoroformate and recommended it as a general-purpose carbo-t-butoxylating agent. Unfortunately, however, since carbonyl chlorofluoride is not generally available this would not seem to represent an ideal solution to the problem at hand. On the other hand, if more satisfactory routes to this compound could be devised or if carbonyl chlorofluoride became more readily accessible, I could eventually prove to be one of the carbo-t-butoxylating agents of choice.

A different approach to the problem posed by the instability of t-butyl chloroformate involved the idea of developing stable reagents which would allow introduction of an acyl group which, in a subsequent step, could

(1) For general reviews of amino-protecting groups, see (a) Y. Wolman in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 11. (b) J. F. W. McOmie in "Advances in Organic Chemistry, Methods and Results," Vol. 3, R. A. Raphael, Ed., Interscience, New York, N. Y., 1963, Chapter 4.

(2) For recent applications of the use of the BOC group in the synthesis of nonpeptide nitrogen compounds, see a–n. (a) Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *J. Chem. Soc. C*, 1547 (1969); (b) G. Zinner and M. Hitze, *Arch. Pharm. (Weinheim)*, **302**, 788 (1969). (c) H. O. House and F. A. Richey, Jr., *J. Org. Chem.*, **34**, 1430 (1969). (d) K. A. Jensen, U. Anthoni and A. Holm, *Acta Chem. Scand.*, **23**, 1916 (1969). (e) K. A. Jensen, G. Felbert, C. T. Pedersen, and V. Svanholm, *ibid.*, **20**, 278 (1966). (f) K. A. Jensen, U. Anthoni, B. Kägi, C. Larsen, and C. T. Pedersen, *ibid.*, **22**, 1 (1968). (g) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 395 (1969). (h) A. M. Felix and R. I. Fryer, *J. Heterocycl. Chem.*, **5**, 291 (1968). (i) T. Sheradsky, *ibid.*, **4**, 413 (1967). (j) C. G. Overberger and W. H. Daly, *J. Amer. Chem. Soc.*, **86**, 3402 (1964). (k) L. A. Carpino and D. E. Barr, *J. Org. Chem.*, **31**, 764 (1966). (l) L. A. Carpino, *ibid.*, **30**, 736 (1965). (m) L. A. Carpino, *J. Amer. Chem. Soc.*, **82**, 3133 (1960). (n) J. R. Bartels-Keith, *J. Chem. Soc. C*, 617 (1966).

(3) In spite of some disadvantages the most widely used reagent is still t-butyl azidoformate. Synthetic routes to this and other, more recently recommended reagents are listed. (a) t-Butyl azidoformate: L. A. Carpino, B. A. Carpino, P. J. Crowley, C. A. Giza and P. H. Terry, *Org. Syn.*, **44**, 15 (1964); K. P. Polzhofer, *Chimia (Aarau)*, **23**, 298 (1969); H. Yajima and H. Kawatani, *Chem. Pharm. Bull. (Tokyo)*, **16**, 182 (1968); M. Itoh and D. Morino, *Experientia*, **24**, 101 (1968); Y. A. Kiryushkin and A. I. Miroshnikov, *ibid.*, **21**, 418 (1965). K. Inouye, M. Kanayama, and H. Otsuka, *Nippon Kagaku Zasshi*, **85**, 599 (1964); D. S. Tarbell, *Accounts Chem. Res.*, **2**, 296 (1969), footnote 27; E. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967). (b) t-Butyl p-nitrophenyl carbonate: G. W. Anderson and A. C. McGregor, *J. Amer. Chem. Soc.*, **79**, 6180 (1957). (c) t-Butyl cyanoformate: L. A. Carpino, *ibid.*, **82**, 2725 (1960); L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964); M. Leplawy and W. Stec., *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, (6) **12**, 21 (1964). (d) N-(t-Butyloxycarbonyloxy)-succinimide: M. Frankel, D. Ladkany, C. Gilon and Y. Wolman, *Tetrahedron Lett.*, 4765 (1966); H. Gross and L. Bilk, *Justus Liebigs Ann. Chem.*, **725**, 212 (1969). (e) t-Butyl 8-quinolyl carbonate: B. Rzeszotarska and S. Wiejak, *ibid.*, **716**, 216 (1968). (f) t-Butylcarbonic diethylphosphoric anhydride: D. S. Tarbell and M. A. Insalaco, *Proc. Natl. Acad. Sci. U. S.*, **57**, 235 (1967); (g) t-Butyl 2,4,5-trichlorophenyl carbonate: W. Broadbent, J. S. Morley, and B. E. Stone, *J. Chem. Soc. C*, 2632 (1967); (h) t-Butyl pentachlorophenyl carbonate: M. Fujino and C. Hatanaka, *Chem. Pharm. Bull. (Tokyo)*, **15**, 2015 (1967).

(4) A. R. Choppin and J. W. Rogers, *J. Amer. Chem. Soc.*, **70**, 2967 (1948).

(5) R. B. Woodward, K. Heusler, H. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *ibid.*, **88**, 852 (1966); R. B. Woodward, *Angew. Chem.*, **78**, 557 (1966).

(6) S. Sakakibara, I. Honda, K. Takada, M. Miyoshi, T. Ohnishi, and K. Okumura, *Bull. Chem. Soc. Jap.*, **42**, 809 (1969).

(7) G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **82**, 2380 (1960).

(8) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 237 (1961).

(9) G. A. Olah and S. J. Kuhn, *Ber.*, **89**, 862 (1956).

(10) A. N. Nesmejanov and E. J. Kahn, *ibid.*, **67**, 370 (1934).

(11) S. Nakanishi, T. C. Myers, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 3099 (1955).

(12) H. J. Emeleus and J. F. Wood, *J. Chem. Soc.*, 2185 (1948).

(13) Carbonyl chlorofluoride was purchased from the Ozark-Mahoning Co., Tulsa, Okla.

(14) E. Schnabel, H. Herzog, P. Hoffmann, E. Klauke, and I. Ugi, *Justus Liebigs Ann. Chem.*, **716**, 175 (1968); *Angew. Chem.*, **80**, 396 (1968).

be converted to the BOC derivative. The instability of most carbo-*t*-butoxylating agents is a direct consequence of the same factors which promote the rapid acid-catalyzed cleavage of the BOC group, *i.e.*, the ease of formation of the *t*-butyl cation. The stability of alkyl cations can be decreased dramatically by the introduction of electron-withdrawing groups near the cationic center. The effect of α-halogen substitution can be judged from studies on the reactivity of appropriately substituted *t*-butyl chlorides in solvolytic reactions.[15] The effect is also evident in comparisons of the ease of cleavage of appropriate halo-substituted urethans (Table I). The differences are clearly substantial in the case of the bromo- and chlorourethans.

TABLE I

EASE OF CLEAVAGE OF $C_6H_5NHCOOCMe_2$ | CH_2X BY HCl-$MeNO_2$ (*ca.* 0.2 *M*)

X	Time[a]
H	1
I	2
Br	240
Cl	600

[a] Time in minutes required for initial appearance of the precipitate of aniline hydrochloride.

In order to make practical use of this stabilizing effect a clean method of reducing the α-halocarbo-*t*-butoxy group to the parent function was required. While it has been possible to effect this conversion the yields have not been high and this and other unforeseen complications have limited the usefulness of this technique. In spite of these other difficulties both α-chloro- and α-bromo-*t*-butyl chloroformates were prepared in fair yields and found to be distillable without difficulty at water aspirator pressure. Reaction with aniline gave the model carbamate derivatives. Although no method could be found by which the α-chlorourethans could be reduced to the BOC derivatives, hydrogenation of the α-bromo analogs proceeded in methanol solution over a palladium–carbon catalyst in the presence of ammonium acetate (eq 1). In the

$$RNHCOC(CH_3)_2 \xrightarrow[CH_3OH,\ NH_4OAc]{H_2,\ Pd\text{-}C} RNHCOC(CH_3)_3 \qquad (1)$$
(O; CH_2Br)

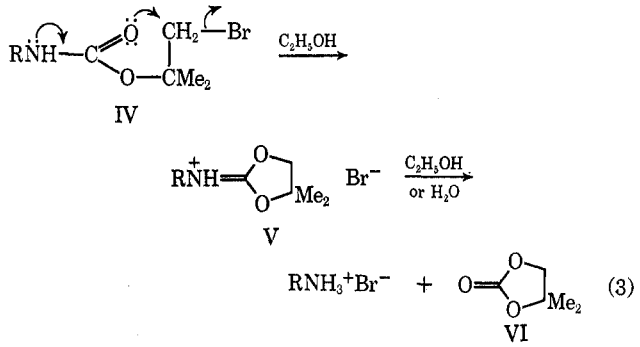
case of model compounds, yields in the reduction never exceeded about 40%. In addition two further difficulties were encountered in the use of α-bromo-*t*-butyl chloroformate. In the first place, although ammonia, aniline, and benzyl amine gave high yields of the corresponding urethans, amino acids, or esters failed to react normally with the chloroformate. Instead of the desired urethan there was isolated the amine hydrobromide (III) and/or the urea derivative (II) (eq 2).

$$ROCOCH_2NH_3^+Cl^- \xrightarrow[Et_3N]{ClCOOCMe_2,\ CH_2Br} (ROCOCH_2NH)_2CO + ROCOCH_2NH_3^+Br^- \qquad (2)$$
II III

R = C_2H_5 or $C_6H_5CH_2$

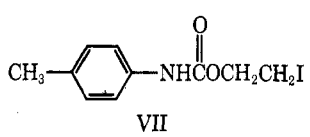
(15) A. Streitwieser, Jr., *J. Amer. Chem. Soc.*, **78**, 4935 (1956).

Urea formation in a related reaction involving *t*-amyl chloroformate has been described recently by Sakakibara and coworkers.[16] The amine hydrobromide III may have been derived from the initially formed bromourethan since subsequent experiments showed that the α-bromo-*t*-butyloxycarbonyl derivatives of simple amines such as aniline, while stable in solvents such as benzene and methylene dichloride, underwent conversion to the corresponding amine hydrobromide during attempted recrystallization from polar solvents such as ethanol. This unique reaction represents the "self cleavage" of a protective group and may be visualized as originating in the neighboring-group process pictured in eq 3.[17] Further hydrolysis or



(3)

solvolysis of intermediate V would lead to the formation of the amine hydrobromide and the cyclic carbonate VI which, in fact, could be isolated from the reaction mixture following filtration of the amine salt. The ease with which this self-cleavage reaction occurs is remarkable, particularly in view of the low solvolytic reactivity reported by Winstein[18,19] for β-bromoethyl carbanilates and the demonstrated stability[21] of the β-iodoethyl derivative VII toward refluxing ethanol.



VII

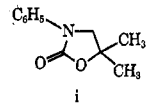
The enhanced solvolytic reactivity of carbanilates such as IV is a notable example of the "*gem*-dimethyl effect."[22] Pertinent data from a limited study of structural effects on this reaction are presented in Table II. The monomethyl derivative (VIII) oc-

(16) S. Sakakibara and M. Itoh, *Bull. Chem. Soc. Jap.*, **40**, 646 (1967).

(17) This represents the first example of a new type of protective group which is of considerable potential utility, namely one which is stable under a variety of conditions but subject to rapid cleavage simply by dissolving in an appropriate solvent. Further studies will deal with the development and possible practical applications of such novel protective groups.

(18) (a) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957). (b) B. Capon, *Quart. Rev. (London)*, **18**, 45 (1964).

(19) If the solvolysis is carried out in ethanolic alkali no carbonate (VI) or aniline is formed. Instead the 2-oxazolidinone (i) is obtained as expected on the basis of preferred N rather than O participation in alkaline solution.



i

Formation of i was first observed during attempted reduction of IV (R = C_6H_5) to *t*-butyl carbanilate by means of sodium borohydride.[20]

(20) H. C. Brown and H. M. Bell, *J. Org. Chem.*, **27**, 1928 (1962).

(21) J. Grimshaw, *J. Chem. Soc.*, 7136 (1965).

(22) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 196–202.

TABLE II
YIELD OF ANILINE HYDROHALIDE BY REFLUXING IN ETHANOL FOR VARIOUS PERIODS

Compd	Yield, % 15 min	1 hr	4 hr
$C_6H_5NHCOOCHCH_2Br$ (VIII)[a] (CH3)	12	27	
$C_6H_5NHCOOCMe_2CH_2Br$ (IX)[b]	63	92	
$C_6H_5NHCOOCMe_2CH_2Cl$ (X)[c]		16	27
$C_6H_5NHCOOCH_2CMe_2Cl$ (XI)[d]		0	
$C_6H_5NH(CH_2)_3Br$ (XII)[e]		0	

[a] T. Mukaiyama, T. Fujisawa, H. Nohira, and T. Hyugasi, *J. Org. Chem.*, **27**, 3337 (1962). [b] Reference 32. [c] Obtained from the corresponding alcohol and phenylisocyanate, mp 79–81° (benzene–ligroin). *Anal.* Calcd for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.09; H, 6.32; N, 6.02. [d] E. L. Eliel, C. Herrmann, and J. T. Traxler, *J. Amer. Chem. Soc.*, **78**, 1193 (1956). [e] Obtained as in *c*, mp 44–45.5° (benzene–ligroin, bp 30–50°). *Anal.* Calcd for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.70; H, 4.82; N, 5.48.

cupies an intermediate position. As expected the α-chloro-*t*-butyloxycarbonyl derivative (X) is considerably less reactive than the corresponding α-bromo derivative (IX). The position of the *gem*-dimethyl groups in IX appears to be optimum as shown by a comparison of the two chloro derivatives, X and XI. The tertiary chloride (XI) is completely unreactive under the conditions used presumably because of hindrance to internal attack at the tertiary center. Although prior ionization of the tertiary chloride might also be expected to result in self-cleavage of XI such an ionization would be inhibited by the inductive effect of the carbamoyloxy group.

Although interesting in themselves these self-cleavage reactions made it impractical to use the α-bromo-BOC group for the present purposes. In view of the relative stability of the corresponding α-chloro derivatives (*e.g.*, X) toward self-cleavage it is unfortunate that no method could be found for the reduction of the α-chloro-BOC to the BOC group.

An attempt was made to avoid the self-cleavage reaction in the case of the α-bromo-*t*-butyl derivatives by introduction of a second α-bromo substituent. As expected,[23] the presence of the second bromine atom markedly increased the stability of the corresponding chloroformate (XIII) and, in addition, the derived urethans (XIV) showed no tendency to undergo the

$ClCOOCMe_2(CHBr_2)$ XIII

$C_6H_5NHCOOCMe_2(CHBr_2)$ XIV

self-cleavage process. However, in spite of an expectation to the contrary,[24] reduction of the α,α-dibromo-BOC group by catalytic means was no more satisfactory than in the case of the monobromo derivative. Furthermore, the increased bulk around the carbonyl group in chloroformate XIII led to somewhat diminished reactivity toward amino compounds. In view of these difficulties and the various other problems associated with the use of both the α-bromo- and α,α-dibromo-*t*-butyl chloroformates neither of these reagents can be considered to be generally useful in connection with the problem at hand although in certain special circumstances they may prove to be of value, particularly the dibromo derivative.

A final method examined in order to provide appropriate stabilization of a chloroformate precursor to a BOC-like protective group involved replacement of the electronegative halogen atoms in the above series of compounds by a highly electronegative carbon atom. Again judging from solvolysis studies[25] it is clear that the 1,1-dimethyl-2-propynyl cation is considerably less stable than the *t*-amyl cation. In line with this difference the chloroformate (XV) derived from 2-methyl-

$Me_2CC{\equiv}CH$ (OCOCl) XV

$Me_2CC{\equiv}CH$ ($OCONHC_6H_5$) XVI

3-butyn-2-ol proved to be easy to obtain and handle under ordinary conditions. The chloroformate could be distilled without difficulty under water aspirator pressure although the pure material darkened on storage. Reaction with various amino compounds gave the corresponding urethans. It has already been shown that the carbanilate (XVI) may be reduced catalytically over a palladium–carbon catalyst in excellent yield to the *t*-amyloxycarbonyl (AOC) derivative.[26] As is well known that the AOC derivatives are cleaved by trifluoroacetic acid and related reagents as easily as the BOC analogs but heretofore have not offered any significant advantages over the latter, although Sakakibara and coworkers[27] have found that, in direct acylation reactions, *t*-amyl chloroformate is more conveniently handled than *t*-butyl chloroformate. Since the present method gives rather low yields of the chloroformate and requires an extra step its use can be justified only in special cases.

Experimental Section[28]

α,α-Dibromo-*t*-butyl Alcohol.[29]—To a slurry of 178 g of N-bromosuccinimide in 400 ml of water was added 131.1 g of 1-bromo-2-methylpropene;[30] the mixture was stirred vigorously for 75 min at room temperature. After treatment with $Na_2S_2O_3$ to destroy excess N-bromosuccinimide the mixture was extracted with ether, the ether extracts were dried over $MgSO_4$, and the solution was distilled to give 169 g (75%) of the alcohol: bp 76–78° (12 mm); nmr δ ($CDCl_3$) 1.50 (s, 6 H, CH_3), 2.74 (s, 1 H, OH), 5.72 (s, 1 H, CH).

Anal. Calcd for $C_4H_8Br_2O$: C, 20.71; H, 3.48; O, 6.90. Found: C, 21.00; H, 3.14; O, 6.95.

α,α-Dibromo-*t*-butyl Chloroformate.—Phosgene was passed into 850 ml of methylene dichloride cooled by means of an ice–salt bath until 138 g had been absorbed. To the phosgene solution was added dropwise with stirring 186 g of α,α-dibromo-*t*-butyl alcohol while maintaining the temperature between −15 and −10°. A solution of 70 g of pyridine in 480 ml of methylene dichloride was then dropped in at the same temperature and the mixture then stirred at −10° to 0° for 2 hr. After the mixture

(23) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 25–26.

(24) *Cf.* L. Horner, L. Schläfer, and H. Kämmerer, *Ber.*, **92**, 1700 (1959).

(25) G. F. Hennion and D. E. Maloney, *J. Amer. Chem. Soc.*, **73**, 4735 (1951).

(26) N. Shachat and J. J. Bagnell, Jr., *J. Org. Chem.*, **28**, 991 (1963).

(27) S. Sakakibara, M. Fujino, Y. Shimonishi, S. Inouye, and N. Inukai, *Bull. Chem. Soc. Jap.*, **38**, 1522 (1965). However, see ref 6.

(28) Elemental analyses are by A. Bernhardt, Mülheim (Ruhr), Germany and C. Meade and associates, University of Massachusetts Microanalytical Laboratory. All melting and boiling points are uncorrected. Infrared spectra were recorded on Beckman IR-5 and IR-10 and Perkin-Elmer 237B instruments. Nmr spectra were obtained on a Varian A-60 instrument using TMS as internal standard.

(29) The method was adapted from that of C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, **77**, 2549 (1955).

(30) (a) J. K. Farrell and G. B. Bachman, *ibid.*, **57**, 1281 (1935); (b) S. Hünig and M. Kiessel, *Ber.*, **91**, 380 (1958).

had stood overnight at room temperature the salt was separated by filtration and excess phosgene removed by passing nitrogen through the solution for 0.5 hr. The liquid was washed with ice water, 4% $NaHCO_3$ solution, and again with ice water, dried ($MgSO_4$), and distilled to give 173.1 g (74.5%) of the chloroformate: bp 64–67° (1 mm); ir ($CHCl_3$) 5.63 μ; nmr ($CHCl_3$) δ 1.81 (s, 6 H, CH_3), 6.26 (s, 1 H, CH).

Anal. Calcd for $C_5H_7Br_2ClO_2$: C, 20.40; H, 2.40. Found: C, 20.12; H, 2.52.

Treatment of the chloroformate with aniline in methylene dichloride gave the **carbanilate**, mp 58–59.5° (recrystallized from ligroin, bp 60–70°). A polymorphic modification, mp 75–77°, was sometimes obtained.

Anal. Calcd for $C_{11}H_{13}Br_2NO_2$: C, 37.63; H, 3.73; N, 3.99. Found: C, 37.55; H, 3.82; N, 4.16.

α-Bromo-*t*-butyl Chloroformate.—A solution of 79 g of phosgene in 300 ml of methylene dichloride was cooled to −10° and a solution of 68.9 g of α-bromo-*t*-butyl alcohol[31] in 100 ml of CH_2Cl_2 added dropwise over 0.5 hr. There was then added over 2 hr a solution of 35.7 g of pyridine in 250 ml of CH_2Cl_2 while maintaining the temperature between −15 and −10°. The mixture was stirred for an additional 1.5 hr at −10 to 0° and then at 0 to 20° for 12 hr (overnight). The salt was filtered, nitrogen passed through the filtrate for 0.5 hr, and the solution washed once with ice-cold water, once with ice-cold 4% $NaHCO_3$ solution, and again with water. Drying over $MgSO_4$ followed by removal of solvent gave 75.5 g (78%) of the crude chloroformate which was distilled to give 53.7 g (67%), bp 56–64° (6–7 mm). Redistillation gave an analytical sample: bp 54° (5.5 mm); ir ($CHCl_3$) 5.63 μ; nmr ($CDCl_3$) δ 1.62 (s, 6 H, CH_3), 3.63 (s, 2 H, CH_2).

Anal. Calcd for $C_5H_8BrClO_2$: C, 27.87; H, 3.74; Br, 37.09; Cl, 16.45. Found: C, 27.99; H, 3.64; Br, 37.08; Cl, 16.25.

With ammonia the chloroformate gave in 76% yield the **carbamate**, mp 108–110° (recrystallized from C_6H_6). Attempted recrystallization from ethanol gave ammonium bromide.

Anal. Calcd for $C_5H_{10}BrNO_2$: C, 30.62; H, 5.14; N, 7.14; Br, 40.75. Found: C, 30.84; H, 5.19; N, 7.23; Br, 40.65.

With aniline in benzene or methylene dichloride the chloroformate gave in 86% yield the **carbanilate**, mp 77–78° (C_6H_6–ligroin), lit.[32] mp 75.5–76.5°. Attempted recrystallization from ethanol gave aniline hydrobromide. With benzyl amine in methylene dichloride in the presence of triethylamine the chloroformate gave in 60% yield **α-bromo-*t*-butyl N-benzylcarbamate**, mp 75–77° ($CHCl_3$–petroleum ether).

Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.35; H, 5.64; N, 4.90; Br, 27.92. Found: C, 50.42; H, 5.91; N, 5.06; Br, 28.05.

Treatment of Benzyl Glycinate with α-Bromo-*t*-butyl Chloroformate.—To a suspension of 2.0 g of the hydrochloride of benzyl glycinate in 25 ml of methylene dichloride there was added 2.1 g of triethylamine and the solution was cooled in an ice bath and treated during 40 min with a solution of 2.37 g of α-bromo-*t*-butyl chloroformate in 50 ml of methylene dichloride. After the mixture had stood for 20 hr at room temperature it was washed in a separatory funnel with cold water, 0.5 *N* HCl, 2.5% $NaHCO_3$ solution, and finally with water and saturated NaCl solution. Removal of solvent from the dried ($MgSO_4$) solution followed by addition of petroleum ether gave an oil which solidified on cooling to give 0.085 g (6.7%) of the **urea**, $(C_6H_5CH_2OCOCH_2NH)_2CO$, mp 105–106° ($C_6H_6$–petroleum ether).

Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.85; H, 5.95; N, 8.22.

From the original petroleum ether filtrate, after removal of solvent, there was obtained 0.158 g (6.5%) of benzyl glycinate hydrobromide, mp 145–148°. With ethyl glycinate the results were similar; the corresponding urea, mp 150–152° (lit.[33] mp 148–150°) was isolated in 23% yield along with varying amounts of ethyl glycinate hydrobromide depending on the conditions.

Reduction of α-Bromo-*t*-butyl Carbanilate.—A solution of 1 g of the carbanilate and 0.5 g of dry NH_4OAc (dried in a desiccator over P_2O_5) in 20 ml of dry methanol [distilled over $Mg(OCH_3)_2$] was treated with 0.1 g of 10% palladium–carbon catalyst and the mixture hydrogenated in a Parr apparatus at 45–55 lb/in² for 8–24 hr. After filtration of the catalyst the filtrate was diluted with 100 ml of water and extracted five times with 15-ml portions of ether. The extracts were washed once with 10 ml of water and 10 ml of $NaHCO_3$ solution (1 *M*), dried ($MgSO_4$), and evaporated to give 0.25–0.31 g (36–44%) of *t*-butyl carbanilate, mp 135–137°, lit.[34] mp 135–137°, identified by comparison of its infrared spectrum with that of an authentic sample. Attempts to carry out the reduction in benzene or ethyl acetate in the presence of NH_4OAc, MgO, or triethylamine were unsuccessful. Similarly Raney nickel in MeOH–NH_4OAc was ineffective. Reduction of the corresponding dibromo urethan by the same method gave a comparable yield of *t*-butyl carbanilate. α-Chloro-*t*-butyl carbanilate was recovered unchanged.

2-Methyl-3-butyn-2-yl Chloroformate.—A solution of 39 g of phosgene in 180 ml of CH_2Cl_2 was stirred and cooled in an ice bath while a solution of 33.2 g of 2-methyl-3-butyn-2-ol and 31.2 g of pyridine in 55 ml of CH_2Cl_2 was dropped in over a period of 1.5 hr. The mixture was allowed to stir in the ice bath for an additional 2 hr and washed twice with 75-ml portions of ice-cold water. After drying ($MgSO_4$), most of the solvent was removed from an ice bath with the aid of a water aspirator. The residue was transferred to a water bath preheated to 50–55° and the chloroformate distilled at 41–44° (20 mm). The distillation was carried out in a large flask because of frothing. The colorless liquid, 19 g (33%), darkened on standing in a refrigerator for a few days: ir ($CHCl_3$) 4.72, 5.62 μ; nmr ($CDCl_3$) δ 1.77 (s, 6 H, CH_3), 2.66 (s, 1 H, ≡CH).

Anal. Calcd for $C_6H_7ClO_2$: C, 49.16; H, 4.81; Cl, 24.19. Found: C, 48.85; H, 4.76; Cl, 24.02.

Treatment of the chloroformate with aniline gave the **carbanilate**, mp 101.5–102.5° [C_6H_6–ligroin (40–70°), 1:10], lit.[26] mp 102–103°.

Self-Cleavage of α-Chloro-*t*-butyl Carbanilate.—A solution of 0.68 g of the urethan in 10 ml of commercial absolute ethanol was refluxed for 1 hr. The solution was allowed to evaporate and the residue triturated with ether, the remaining solid being filtered and washed with ether. There was obtained 0.06 g (15.5%) of aniline hydrochloride, mp 192–196°. The ether filtrates on evaporation gave 0.47 g (69% recovery) of the starting urethan, mp 76.5–77.5°. Related reactions were carried out with other urethans for various periods of time. The results are compared in Table II. The aniline hydrohalides and recovered urethans were identified by spectral comparison (ir, nmr) with authentic samples.

1,1-Dimethylethylene Carbonate.—A solution of 8.47 g of α-bromo-*t*-butyl carbanilate in 180 ml of freshly distilled commercial absolute ethanol was refluxed for 4 hr. Evaporation of the solution gave a semisolid material which was triturated with two 100-ml portions of ether. The filtered ether solutions and washings were combined, dried over $MgSO_4$, and evaporated from a water bath at 40° with the aid of a water aspirator. There was obtained 1.84 g (51%) of a dark oily residue which on distillation gave 0.44 g (12%) of the carbonate, bp 92–94° (10 mm). Repitition of this reaction followed by repeated distillation gave a center cut for analysis: bp 95° (11 mm); ir[35] ($CHCl_3$) 5.52 μ; nmr ($CDCl_3$) δ 1.43 (s, 6 H, CH_3), 4.10 (s, 2 H, CH_2).

Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.36; H, 7.03.

5,5-Dimethyl-3-phenyl-2-oxazolidinone.—To a solution of 1 g of KOH in 20 ml of methanol was added 1 g of α-chloro-*t*-butyl carbanilate. The solid dissolved and in a few minutes a dense white solid separated. After 5 hr the mixture was diluted with water to 50 ml and the white solid filtered and recrystallized from benzene–ligroin (bp 60–70°) (1:4) to give 0.7 g (83%) of tiny white needles: mp 98–99.5°; ir (Nujol mull) 5.76 μ; nmr ($CDCl_3$) δ 1.55 (s, 6 H, CH_3), 3.78 (s, 2 H, CH_2), 7.45 (m, 5 H, phenyl).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.23; H, 7.01; N, 7.45.

***t*-Butyl Chloroformate.**—The original procedure of Choppin and Rogers[4] was followed except that the tedious purification procedure involving thionyl chloride and bromine was omitted. In essence the method was the same as that developed independently by Michejda and Tarbell[36] except that *n*-butane was used as solvent, as in the Choppin–Rogers procedure, rather than ether, as recommended by Michejda and Tarbell. The yield was generally 50–60% after one distillation. The stability of the distilled material was tested by storage at various temperatures.

(31) C. M. Suter and H. D. Zook, *J. Amer. Chem. Soc.*, **66**, 738 (1944).
(32) H. O. House, *ibid.*, **77**, 5083 (1955).
(33) T. C. Frazier, E. D. Little, and B. E. Lloyd, *J. Org. Chem.*, **25**, 1944 (1960).
(34) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 4427 (1957).
(35) Ethylene carbonate is reported to show an absorption near 5.5 μ in nonpolar solvents. See C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y. 1963, p 234.
(36) C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964).

At −13° there was no decomposition after 1 week although slight decomposition was noted after 5 weeks. In a refrigerator at 6° no change was noted after 1 week. At room temperature complete decomposition occurred in a few days.

The method of Choppin and Rogers was also used to obtain a crude solution of *t*-**butyl bromoformate** from carbonyl bromide.[37] Upon storage of the bromoformate solution overnight at 6° complete decomposition occurred.

Treatment of *t*-Butyl Chloroformate with Thallous Fluoride.—A mixture of 27.3 g of *t*-butyl chloroformate and 48 g of thallous fluoride was stirred at 0° for 5 days. Distillation gave 16.4 g (89%) of *t*-butyl chloride, bp 52°. After only 10 hr the chloroformate could be recovered unchanged. Similar results were obtained in methylene dichloride and tetramethylene sulfone[38] as solvent or by substitution of alkali or silver fluorides for the thallous salt. In no case could *t*-butyl fluoroformate be obtained in this way.

***t*-Butyl Fluoroformate.**—Carbonyl chlorofluoride was passed into 50 ml of methylene dichloride while cooling in a Dry Ice–ethanol bath until 11 g had been absorbed. There was then dropped in with continued cooling in the same bath over a period of 15 min a solution of 7.4 g of *t*-butyl alcohol in 7.9 g of pyridine. The mixture was stirred in the Dry Ice–ethanol bath for 1 hr, at 0° for 3 hr, and at room temperature for 24 hr. The mixture was shaken in a separatory funnel twice with 25-ml portions of ice water (ice chips present), dried over $MgSO_4$, filtered, and distilled. After removal of the solvent there was obtained 4.6 g (38%) of the fluoroformate: bp[39] 78–79° [lit.[14] bp 4° (15 mm)]; ir (neat) 5.48 μ; nmr ($CDCl_3$) δ 1.27 (s, CH_3).

(37) H. J. Schumacher and S. Lehner, *Ber.*, **61**, 1671 (1928).
(38) C. W. Tullock and D. D. Coffman, *J. Org. Chem.*, **25**, 2016 (1960).

Registry No.—α,α-Dibromo-*t*-butyl alcohol, 24482-83-5; α,α-dibromo-*t*-butyl chloroformate, 25557-88-4; α,α-dibromo-*t*-butyl carbanilate, 25557-89-5; α-bromo-*t*-butyl chloroformate, 25557-90-8; α-bromo-*t*-butyl carbamate, 25557-91-9; α-bromo-*t*-butyl N-benzylcarbamate, 25557-92-0; $(C_6H_5CH_2OCOCH_2NH)_2CO$, 25557-93-1; 2-methyl-3-butyn-2-yl chloroformate, 25557-94-2; 1,1-dimethylethylene carbonate, 4437-69-8; 5,5-dimethyl-3-phenyl-2-oxazolidinone, 25557-96-4.

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(39) Distillation at atmospheric pressure is not recommended since some decomposition must have occurred at this point. Prior to distillation reaction of an aliquot of the crude solution with glycine gave BOC-glycine in 80% yield, mp 88–90°. Further examination of *t*-butyl fluoroformate was discontinued because of the timely appearance of the paper of Schnabel and Ugi and their collaborators[14] who provide detailed descriptions of a similar method for the large-scale synthesis of this compound

The Synthesis and Nuclear Magnetic Resonance Spectra of Some Disubstituted Derivatives of 2-Methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane[1]

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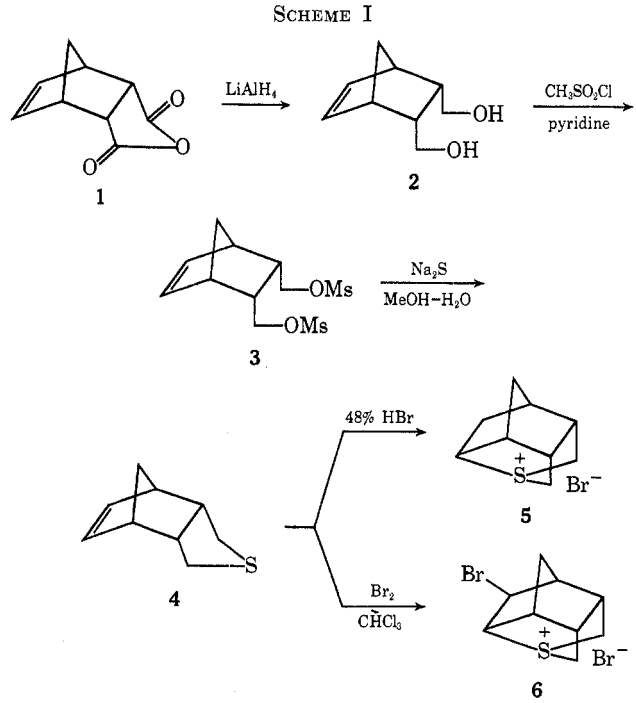
2-Methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**8**) has been prepared by reduction of sulfonium salt **5** with lithium aluminum hydride. A series of 4,10-disubstituted derivatives (**10a–e**) of **8** has been prepared by the reaction of several nucleophiles with bromosulfonium salt **6**. Nmr chemical shifts are presented for the tricyclic compounds, for sulfonium salts **5** and **6**, and for some symmetrical norbornene(ane) derivatives. Spin-decoupling techniques have been used on two of the compounds (**2** and **10a**) to confirm the assignment of chemical shifts. A mechanism for the formation of **10** *via* thiiranium ion **12** has been proposed.

The synthesis of 2-thia-1,2-dihydro-*endo*-dicyclopentadiene (**4**) from *endo-cis*-5-norbornene-2,3-dicarboxylic anhydride (**1**) *via* diol **2** and dimesylate **3** has previously been described.[2] The facile cyclization of **4** to the sulfonium salts **5** and **6** with 48% hydrobromic acid and bromine in chloroform, respectively, has also been reported from this laboratory.[2,3] These reactions are summarized in Scheme I.

The sulfonium salt **5** has been found to react with various nucleophilic reagents to yield monosubstituted products,[4] and the bromosulfonium salt **6** has been reported to react with aqueous lithium carbonate to yield *exo-cis*-2-thiatetrahydro-*endo*-dicyclopentadiene-9,10-diol (**7a**).[3]

At this time we wish to report the preparation and nmr spectrum of 2-methyl-6-thiatricyclo[3.2.1.1^{3,8}]-

SCHEME I



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(2) P. Wilder, Jr., and L. A. Feliu-Otero, *J. Org. Chem.*, **30**, 2560 (1965).
(3) P. Wilder, Jr., and L. A. Feliu-Otero, *ibid.*, **31**, 4264 (1966).
(4) L. A. Feliu-Otero, Ph.D. Thesis, Duke University, Durham, N. C., 1965.