(0.50 g-atom) of magnesium, and 300 ml of anhydrous ether, and a solution of 39 g (0.20 mol) of xanthone in 500 ml of warm benzene was added to it as rapidly as possible. The mixture was stirred overnight, and was poured into an excess of ammonium chloride solution. The benzene layer was separated, washed, dried (Na_2SO_4), and concentrated. The residue was taken up in benzene and passed through 600 g of Florisil. The first benzene fractions contained the desired alcohol **13a**, which was recrystallized from methylcyclohexane to give 13 g (26%): mp 106–107°; nmr (CCl_4) τ 2.0–2.2 (m, 2, aromatic), 2.4–2.9 (m, 6, aromatic), 8.00 (s, 1, exchangeable with D_2O, hydroxyl), and 9.20 (s, 9, *tert*-butyl); mass spectrum *m/e* (rel intensity) 254 (0.3, parent), 239 (1), 197 (100), 168 (3), and 152 (6).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.2; H, 7.2.

Treatment of 9-*tert*-Butyl-9-hydroxyxanthene with Thionyl Chloride and DMF.—A mixture of 1.0 g (0.0039 mol) of alcohol **13a**, 6 ml of thionyl chloride, and 2 drops of DMF was heated at reflux for 30 min. The solvent was removed and the residue was washed with acetonitrile to give 1.0 g (93%) of chloride **13b**, mp 86–88°. The nmr spectrum of the residue showed no other components. An analytical sample was prepared by recrystallization from acetonitrile: mp 88–89°; nmr (CCl_4) τ 1.8–2.0 (m, 2, aromatic), 2.4–2.9 (m, 6, aromatic), and 9.00 (s, 9, *tert*-butyl; mass spectrum *m/e* (rel intensity) 272 (1, parent), 257 (2), 237 (2), 215 (100), 197 (7), 181 (4), and 152 (6).

Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.9; H, 6.3; Cl, 13.0. Found: C, 74.7; H, 6.4; Cl, 12.9.

Registry No.—**3a**, 35666-50-3; **4**, 35666-51-4; **5**, 35666-52-5; **6**, 35666-53-6; **7**, 35666-54-7; **10**, 35666-55-8; **12b**, 20685-15-8; **13a**, 35666-57-0; **13b**, 35666-58-1.

The 9-Fluorenylmethoxycarbonyl Amino-Protecting Group

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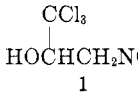
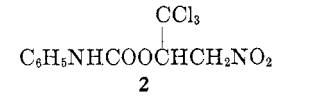
A new amino-protecting group, the 9-fluorenylmethyloxycarbonyl group (FMOC), which is stable toward acids and catalytic hydrogenation but readily cleaved under mildly basic, nonhydrolytic conditions, is reported. The FMOC group may be introduced by reaction of the amine with 9-fluorenylmethyl chloroformate. A number of protected amino acid derivatives were coupled with other amino acids or esters by use of the corresponding *N*-hydroxypiperidine esters. Deblocking of the FMOC group was carried out with liquid ammonia or at room temperature with piperidine, morpholine, ethanolamine, etc.

The amino-protecting groups which are most commonly used are those which are deblocked under various acidic conditions.[1] Heretofore no amide or urethane function has been available which could be rapidly cleaved under mild, alkaline, nonhydrolytic conditions, although several protective groups are known to be cleaved by basic reagents. The phthaloyl group[2] is removed by hydrazine in ethanol[2a] (or more recently by the use of aqueous methylamine[2b]), and the trifluoroacetyl group by dilute aqueous alkali.[3] Strong aqueous alkali or sodium ethoxide has been used to cleave the β-tosylethyloxycarbonyl group,[4] a cleavage process the nature of which anticipates to some extent the method described in the present paper. This work originated in the observation of Crowley[6] that the carbanilate **2** derived from 3,3,3-trichloro-1-nitro-2-propanol (**1**)[7]

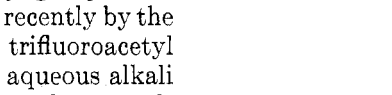


1



2

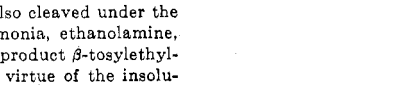
upon treatment with ammonia in benzene was converted to aniline in good yield. This result had been anticipated on the basis of Chattaway's work[8] on the base-induced reactions of simple esters of alcohol **1**, reactions which clearly involve β eliminations followed by conjugate addition to the intermediate α,β-unsaturated nitro compound **3**. Since this process might



3

conceivably be the basis for a new type of amino-protective group, it has been further examined. The same idea was pursued independently by Wieland,[9] and the related β elimination involving the corresponding sulfone analogs has already been recommended by Stirling[4] as a deblocking procedure for the β-tosylethyloxycarbonyl group.

In our work it early became apparent that the simple β-nitroethyloxycarbonyl group could probably not be developed into a practical, generally useful protective group since the sensitivity toward cleavage by basic reagents is too high. We have used stability toward pyridine as a criterion, as we wished to achieve development of a group stable at least to such a mild base since pyridine represents a common solvent for a number of functional group transformations. For special purposes there may of course be need for a protective group cleavable by such a base or one even milder. Neither **2** nor **4a** was stable toward standing in



4a, R = H
b, R = CH_3

(1) For reviews see (a) E. Schröder and K. Lübke, "The Peptides," Vol. 1, Academic Press, New York, N. Y., 1965, pp 3–51; (b) Y. Wolman in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 11.

(2) (a) D. A. Kidd and F. E. King, *Nature (London)*, **162**, 776 (1948); *J. Chem. Soc.*, 3315 (1949); J. C. Sheehan and V. S. Franck, *J. Amer. Chem. Soc.*, **71**, 1856 (1949); (b) S. Wolfe and S. K. Hasan, *Can. J. Chem.*, **48**, 3572 (1970).

(3) F. Weygand and E. Csendes, *Angew. Chem.*, **64**, 136 (1952). For an alkyl-type protective group which is cleaved by methanolic ammonia, see M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).

(4) A. T. Kader and C. J. M. Stirling, *J. Chem. Soc.*, 258 (1964). We have now found that the β-tosylethyloxycarbonyl group is also cleaved under the conditions described in the present paper (liquid ammonia, ethanolamine, etc.). In the case of liquid ammonia cleavage the by-product β-tosylethylamine[5] is easily separated from the desired amine by virtue of the insolubility of the former in ether.

(5) J. Madinaveita, A. R. Martin, F. L. Rose, and G. Swain, *Biochem. J.*, **39**, 85 (1945).

(6) P. J. Crowley, M. S. Thesis, University of Massachusetts, Amherst, 1958.

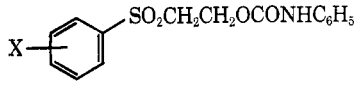
(7) F. D. Chattaway and P. Witherington, *J. Chem. Soc.*, 1178 (1935).

(8) F. D. Chattaway, *ibid.*, 355 (1936).

(9) T. Wieland, G. J. Schmitt, and P. Pfaender, *Justus Liebigs Ann. Chem.*, **694**, 38 (1966).

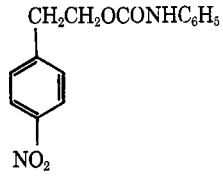
pyridine at room temperature for 4 hr. While the stability toward pyridine could be increased by substitution of a methyl group on the α carbon atom, *e.g.*, **4b** was stable in pyridine under the above conditions and was only partially cleaved after 24 hr, this system has the disadvantage of incorporating an asymmetric carbon, a possible disadvantage in the protection of optically active compounds.

Much less sensitive to basic reagents were the sulfone analogs, **5**. The *o*- and *p*-nitro derivatives (**5b**, **5c**) of Stirling's compounds did not appear to offer any advantages over the parent substance **5a**. All of these



5a, X = H
b, X = *o*-NO_2
c, X = *p*-NO_2

compounds were found to be cleaved to aniline by means of ethanolamine at room temperature. Other systems of potential interest which were examined but shown not to be cleaved by ethanolamine were the carbanilates **6–8**.



6

$Cl_2CHCH_2OCONHC_6H_5$

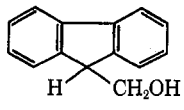
7

$Cl_2CHCH_2SCONHC_6H_5$

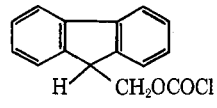
8

On the basis of some clues derived from a consideration of theoretical studies relating to β-elimination reactions of benzhydryl and 9-fluorenyl thiocyanates[10,11] we were led to investigate the 9-fluorenylmethyloxycarbonyl (FMOC) group. The results have proved the FMOC group to be eminently successful as a protective group for the purpose at hand. A preliminary report has outlined the results.[12] In the present paper we provide experimental details for the synthesis of key intermediates useful for introduction of the FMOC group, descriptions of acylation procedures, and examples of useful deblocking conditions. In addition it is shown that peptide coupling reactions and cleavages can be carried out with FMOC protection, thus demonstrating the potential utility of this blocking group in peptide synthesis.

9-Fluorenylmethanol **9**, which has been reported by Brown and Bluestein,[13] was used as the basis for the new protective system. Treatment of **9** with phosgene gave the chloroformate **10**, a stable compound which



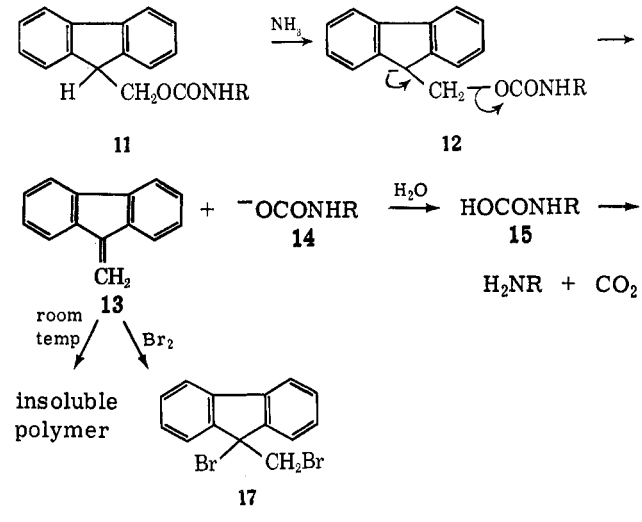
9



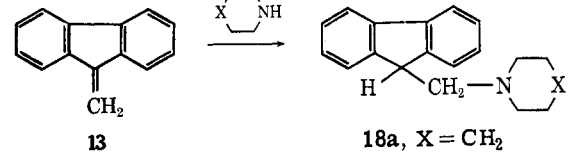
10

reacts normally with amino compounds to give the carbamates in yields of 88–97%.

A variety of basic, nonhydrolytic cleavage techniques for the FMOC group was examined, the mildest of which involves allowing a solution or suspension of the protected derivative to stand in contact with liquid ammonia for several hours. Work-up with water leads to the formation of the free amine without the necessity of acidification and rebasification.[4,14] Although no mechanistic studies were carried out, the reaction probably represents an ElcB-type elimination process activated by the aromaticity effect of the dibenzocyclopentadienyl anion. In contrast to the case of the β-tosylethyloxycarbonyl group, which on treatment with potassium hydroxide or sodium ethoxide gives the stable carbamate salt thereby requiring subsequent acidification to free the amine,[4] the present method leads to the direct formation of the free amino compound. This considerably simplifies the work-up technique. A by-product under these conditions is dibenzofulvene[15] (**13**), which can be isolated if desired.



In addition some dibenzofulvene polymer often accompanies the monomeric species. In fact, by choosing appropriate work-up conditions it is possible to effect complete conversion to the polymer, thus further simplifying the isolation technique. The polymer is insoluble in solvents which can be used to extract the desired amine. Ammonia shows no tendency to add to dibenzofulvene under the conditions of the reaction. On the other hand, if a secondary amine such as morpholine or piperidine is used as cleavage reagent, the amine subsequently adds to the initially formed dibenzofulvene to give adducts of type **18** in good yield. Authentic dibenzofulvene[15] was shown to react with piperidine and morpholine to give the same compounds. In many cases these adducts will have solubility and other properties which differ greatly from those of the



13

18a, X = CH_2
b, X = O

(10) (a) A. Ceccon, U. Miotti, U. Tonellato, and M. Padovan, *J. Chem. Soc. B*, 1084 (1969); (b) U. Miotti, A. Sinico, and A. Ceccon, *Chem. Commun.*, 724 (1968).

(11) *Cf.* (a) R. A. More O'Ferrall and S. Slae, *J. Chem. Soc. B*, 260 (1970); (b) R. A. More O'Ferrall, *ibid.*, 268, 274 (1970). See also T. A. Spencer, M. C. R. Kendall, and I. D. Reingold, *J. Amer. Chem. Soc.*, **94**, 1250 (1972).

(12) L. A. Carpino and G. Y. Han, *ibid.*, **92**, 5748 (1970).

(13) W. G. Brown and B. A. Bluestein, *ibid.*, **65**, 1082 (1943).

(14) Compare S. L. Johnson and D. L. Morrison, *ibid.*, **94**, 1323 (1972).

(15) A. Sieglitz and H. Jassoy, *Ber.*, **55**, 2032 (1922).

TABLE I
FMOC AMINO ACIDS AND ESTERS

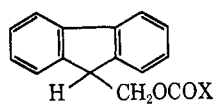
Compd	Registry no.	Mp, °C	Recrystn solvent	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	α^t_D (t, c, solvent)
FMOC-DL-ala	35661-38-2	176–178	$MeNO_2$	88	69.45	5.47	4.50	69.44	5.67	4.48	
FMOC-L-ala	35661-39-3	144–145	EtOAc-Et_2O	94	69.45	5.47	4.50	69.40	5.40	4.38	−3.48 (28.6, 2.5, EtOAc)
FMOC-β-ala	35737-10-1	145–147	EtOAc	91	69.45	5.47	4.50	69.46	5.38	4.54	
FMOC-L-phe	35661-40-6	183–185	EtOAc	92	74.52	5.43	3.62	74.31	5.45	3.73	+11.6 (28.2, 1.2, EtOAc)
FMOC-gly-OEt	35661-41-7	109–110	Ligroin (bp 60–70°)	91	70.15	5.85	4.31	70.20	5.91	4.08	
FMOC-gly-OBu-t	35661-42-8	79–81	Et_2O–hexane	90	71.38	6.52	3.97	71.40	6.58	4.02	

desired amine. Curiously, diethylamine effected cleavage of **11** (R = C_6H_5) as shown by the isolation of aniline in good yield, but only dibenzofulvene and its polymer were observed as by-products rather than the diethyl analog of **18**. This may be due to the influence of steric effects in the addition to **13**. Ethanolamine was also routinely used to cleave the FMOC group and, in this case also, monomeric dibenzofulvene was the by-product formed, although the work-up procedure could undoubtedly be modified in such a way that the corresponding polymer would be the sole by-product (see above).

For a protective group to be most useful in the synthesis of multifunctional compounds it should be removable selectively under conditions which leave untouched other commonly used functions. Many of the common protective groups are cleaved by acidic reagents of various strengths.[1] Under such conditions, *e.g.*, treatment with trifluoroacetic acid or hydrogen bromide in acetic acid or nitromethane for periods of 1–2 days at room temperature, there was no attack on the FMOC group. In addition the FMOC derivative of ethyl glycinate could be hydrolyzed to FMOC-glycine in quantitative yield by refluxing the ester in a mixture of acetic and hydrochloric acids for 10 hr. Catalytic hydrogenation over a palladium catalyst in a Parr apparatus in methanol with a little added acetic acid for 24 hr led to complete recovery of starting material. The activity of the catalyst under these conditions was checked by hydrogenation of a 1:1 mixture of FMOC-aniline and benzyl carbanilate, whereby the latter was completely converted[1] to aniline whereas the former was recovered unchanged. With 85% hydrazine[1] in ethanol at room temperature for 12 hr or at 50° for 8 hr there was no observable cleavage, although after 5 hr at 65° aniline was liberated in over 80% yield. FMOC-aniline could be recovered, completely unaffected, from its solution in pyridine after 48 hr at room temperature.

Because of their potential special utility to the synthetic organonitrogen chemist,[16] we have synthesized and report here the properties of several hydrazine and related derivatives protected by the FMOC group. These include the carbazate (**19a**), azide (**19b**), and the hydrazo- (**20**) and azodiformates (**21**).

Introduction of the FMOC group onto the amino group of a simple amine such as benzylamine was carried out by slowly adding a solution of the amine to a cold solution of FMOC–Cl in benzene, ether, or other solvent. This order of addition avoids the presence of an excess of a basic amino compound, which might conceivably lead to premature degradation of the chloroformate or the desired FMOC derivative. In the case of amino acid derivatives a solution of FMOC-Cl in dioxane was added slowly to a solution of the amino acid in dilute sodium carbonate. For both techniques the yields were high (88–98%).



19a, X = $NHNH_2$
b, X = N_3

FMOC—NHNH—FMOC
20

FMOC—N=N—FMOC
21

Using the protected amino acid derivatives, no difficulties were encountered in forming peptide linkages by the usual classical techniques involving active ester formation followed by condensation with another amino acid or amino acid ester. For convenience *N*-piperidyl esters[17] were chosen as active ester components. In one case the 8-hydroxyquinoline ester[18] was used successfully and presumably other active esters would serve as well. Since the main thrust of this work is not related to the synthesis of long-chain peptides, we leave this elaboration to others who may be interested in this area and see some value in our technique. Among the dipeptides synthesized as models were the FMOC derivatives of methyl glycyl-L-leucinate, ethyl L-alanylglycinate, ethyl L-leucylglycinate, and benzyl and *tert*-butyl L-tryptophylglycinate. In addition to studying the cleavage of FMOC-aniline, deblocking of the following models was carried out (yields 95–100%): FMOC-gly-gly-OH, by piperidine: FMOC-gly-OEt, FMOC-gly, FMOC-DL-ala, FMOC-gly-gly-OH, FMOC-L-Try-OH, and FMOC-L-phe-OH by liquid ammonia. In the last case the L-phenylalanine obtained after cleavage showed essentially the same optical rotation as the material from which the FMOC derivative was prepared. This suggests that neither introduction nor removal of the FMOC group leads to racemization. More refined techniques will have to be examined in order to detect whether minor amounts of racemization are taking place.[19] Amino acid derivatives not described in the Experimental Section are collected in Tables I–III.

(16) For related BOC derivatives see (a) L. A. Carpino, P. H. Terry, and P. J. Crowley, *J. Org. Chem.*, **26**, 4336 (1961); (b) L. A. Carpino, B. A. Carpino, P. J. Crowley, C. A. Giza, and P. H. Terry, *Org. Syn.*, **44**, 15 (1964); (c) L. A. Carpino, D. Collins, S. Göwecke, J. Mayo, S. D. Thatte, and F. Tibbetts, *ibid.*, **44**, 20 (1964).

(17) B. O. Handford, J. H. Jones, G. T. Young, and T. F. N. Johnson, *J. Chem. Soc.*, 6814 (1965).

(18) H.-D. Jakubke and A. Voight, *Ber.*, **99**, 2419 (1966).

(19) Compare D. S. Kemp, S. W. Wang, G. Busby, III, and G. Hugel, *J. Amer. Chem. Soc.*, **92**, 1043 (1970).

TABLE II
FMOC AMINO ACID *N*-PIPERIDYL ESTERS[a]

Compd	Registry no.	Mp, °C	Recrystn solvent	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	α^t_D (*t*, *c*, solvent)
FMOC-L-phe-ONC_5H_{10}	35737-11-2	60–62 dec	Et_2O	98	74.04	6.38	5.96	73.95	6.43	6.00	−2.68 (28.2, 2.5, EtOAc)
FMOC-L-ala-ONC_5H_{10}	35820-67-8	48–50	Et_2O–ligroin (bp 60–70°)	96	70.05	6.60	7.11	70.10	6.71	7.10	+4.65 (27.4, 2.5, EtOAc)
FMOC-L-leu-ONC_5H_{10}	35661-43-9	55–56 (dec)	Et_2O–ligroin (bp 60–70°)	91	71.56	7.34	6.42	71.27	7.66	6.12	−3.45 (27.8, 2.5, EtOAc)
FMOC-β-ala-ONC_5H_{10}	35661-44-0	111–113	EtOAc–Et_2O	87	70.05	6.60	7.11	70.10	6.67	7.15	
FMOC-L-Try-ONC_5H_{10}	35661-45-1	134–135 dec	EtOAc–Et_2O	99	73.08	6.09	8.25	72.90	6.31	8.24	+56.27 (25.4, 1.1, $CHCl_3$)

[a] The reaction time varied between 5 and 23 hr.

TABLE III
FMOC DIPEPTIDES[a]

Compd	Registry no.	Mp, °C	Recrystn solvent	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	α^t_D (*t*, *c*, solvent)
FMOC-gly-L-leu-OMe	35661-46-2	135–136.5 dec	EtOAc–ligroin (bp 60–70°)	100	67.92	6.60	6.60	67.84	6.69	6.44	+16.55 (2.5, $CHCl_3$)
FMOC-L-ala-gly-OEt	35737-12-3	153–155 dec	EtOAc–ligroin (bp 60–70°)	100	66.67	6.06	7.07	66.86	6.20	7.01	−20.84 (27.7, 2.5, $CHCl_3$)
FMOC-L-leu-gly-OEt	35661-47-3	138–140 dec	Et_2O	100	68.49	6.85	6.39	68.48	6.81	6.52	−59.8 (28.8, 2.5, 95% EtOH)
FMOC-L-Try-gly-$OCH_2C_6H_5$	35737-13-4	169.5–171 dec	EtOAc–ligroin (bp 60–70°)	100	73.30	5.41	7.33	73.04	5.47	7.24	+12.5 (29, 2, $CHCl_3$)

[a] The reaction time varied between 17 and 24 hr.

Experimental Section[20]

9-Fluorenylmethyl Chloroformate.—A solution of 7.12 g of phosgene in 75 ml of CH_2Cl_2 was cooled in an ice bath, and 12.8 g of 9-fluorenylmethanol[13] was added slowly with stirring. The solution was stirred for 1 hr in the ice bath and then let stand for 4 hr at ice-bath temperature. Removal of solvent and excess phosgene under reduced pressure gave an oil which crystallized after several hours to give 16 g (95%) of the crude chloroformate, mp 61.5–63°. Recrystallization twice from ether gave 14.5 g (86%) of the chloroformate as colorless crystals: mp 61.5–63°; ir ($CHCl_3$) 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4–4.6 (m, 3, $CHCH_2$), 7.1–7.8 (m, 8, aryl).

Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.63; H, 4.26. Found: C, 69.59; H, 4.26.

9-Fluorenylmethyl Azidoformate. A.—To an ice-cold, stirred solution of 0.52 g of NaN_3 in 2 ml of H_2O was added slowly a solution of 1.35 g of 9-fluorenylmethyl chloroformate in 2.5 ml of acetone. The mixture was stirred in the ice bath for 2 hr and at room temperature for 2 hr, and the solid was filtered, washed with water, and recrystallized from acetone to give 1.13 g (82%) of the azide as colorless crystals, mp 83–85°. The analytical sample, from hexane, had mp 89–90°: ir ($CHCl_3$) 2135 (N_3), 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4–4.5 (m, 3, $CHCH_2$), 7.1–7.9 (m, 8, aryl).

Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.15; N, 15.85. Found: C, 67.87; H, 4.17; N, 15.80.

B.—Treatment of 9-fluorenylmethyl carbazate with $NaNO_2$ in HOAc–H_2O followed by the usual work-up and recrystallization from hexane gave the azidoformate, mp 89–90°, in 88% yield.

9-Fluorenylmethyl Carbazate.—To a mixture of 0.39 g of 95% N_2H_4 and 20 ml of ether was added slowly with stirring and ice-bath cooling a solution of 1 g of 9-fluorenylmethyl chloroformate in 20 ml of ether. The mixture was stirred at room temperature for 12 hr and evaporated to dryness, and 50 ml of H_2O was added. The residual solid was filtered and washed with H_2O to give 0.95 g (97%) of the crude carbazate, mp 170° dec. Recrystallization from nitromethane gave 0.94 g (96%) of the pure hydrazide: mp 171° dec; ir (KBr) 3310, 3202 (NH), 1686 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.67; H, 5.65; N, 11.00.

9-Fluorenylmethyl Hydrazodiformate.—To a solution of 1 g of 9-fluorenylmethyl chloroformate in 20 ml of benzene was added dropwise with stirring at ice bath temperatures 0.065 g of 95% N_2H_4. The mixture was stirred in the ice bath for 30 min and at room temperature for 10 min and then treated slowly with 5 ml of pyridine. The resulting clear solution was stirred at room temperature for 2 hr and poured into 200 ml of H_2O, and the organic layer was collected and washed with H_2O, 5% HCl, and H_2O again. Evaporation of the solvent left a solid which was recrystallized from nitromethane to give 0.91 g (99%) of the hydrazide: mp 202° dec; ir (KBr) 3307, 3290 (NH), 1720, 1710 cm^{-1} (C=O); nmr ($CDCl_3$–DMSO-d_6) δ 3.95–4.70 (m, 6, $CHCH_2$), 6.95–7.85 (m, 16, aryl), 7.90–8.40 (broad s, 2, NH).

Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.63; H, 5.04; N, 5.88. Found: C, 75.31; H, 5.08; N, 5.90.

9-Fluorenylmethyl Azodiformate.—A suspension of 2.0 g of 9-fluorenylmethyl hydrazodiformate and 0.332 g of pyridine in 200 ml of CH_2Cl_2 was treated slowly with 0.747 g of *N*-bromosuccinimide and the yellow solution was refluxed for 24 hr. The resulting solution was washed with H_2O, 10% Na_2CO_3, and again with H_2O and finally dried ($MgSO_4$) and evaporated to dryness. The residue was boiled with 200 ml of ether, the solution was filtered while hot to remove some unreacted hydrazo compound, and the filtrate was concentrated until orange crystals began to separate. Storage in a refrigerator overnight gave 1.85 g (94%) of the azo compound, mp 148–151° dec. Recrystallization from ether gave 1.83 g (93%): mp 149.5–151° dec; ir (KBr) 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.0–4.8 (m, 6, $CHCH_2$), 6.95–7.85 (m, 16, aryl).

Anal. Calcd for $C_{30}H_{22}N_2O_4$: C, 75.95; H, 4.64; N, 5.91. Found: C, 76.11; H, 4.78; N, 5.80.

9-Fluorenylmethyl Carbanilate.—To a solution of 2 g of 9-fluorenylmethyl chloroformate in 10 ml of benzene was added dropwise with stirring in an ice bath 1.02 g of aniline. The mixture was stirred in an ice bath for 20 min and at room temperature for 1 hr, and 0.5 ml of H_2O was added. After the solution was stirred for 10 min, filtration gave 2.4 g (98%) of the crude carbanilate, mp 182–184°. Recrystallization from $CHCl_3$ gave 2.3 g (94%) of the pure ester, mp 188–190°. The same compound was obtained by treatment of 9-fluorenylmethanol with phenyl isocyanate in refluxing benzene: ir (KBr) 3335 (NH), 1700 cm^{-1} (C=O); nmr (DMSO-d_6–$CDCl_3$) δ 4.1–4.58 (m, 3, $CHCH_2$), 6.67–7.91 (m, 13, aryl), 9.55 (s, 1, NH).

(20) Melting and boiling points are uncorrected. Infrared spectra were obtained on a Beckman IR-10 instrument and nmr spectra on a Varian A-60 unit with TMS as internal standard. Elemental analyses were carried out by Charles Meade and associates, University of Massachusetts Microanalytical Laboratory and Galbraith Laboratories, Inc., Knoxville, Tenn.

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 80.00; H, 5.40; N, 4.44. Found: C, 79.81; H, 5.63; N, 4.34.

9-Fluorenylmethyl *N*-Cyclohexylcarbamate.—A solution of 1 g of 9-fluorenylmethyl chloroformate in 200 ml of ether was cooled in an ice bath and 0.769 g of cyclohexylamine in 100 ml of ether was added slowly. The mixture was stirred in the ice bath for 20 min and at room temperature for 20 min. After filtration to remove the amine salt, the ether solution was washed with H_2O, dried ($MgSO_4$), and evaporated and the residue was recrystallized from ether to give 1.2 g (97%) of the carbamate, mp 158.5–161° dec. Further recrystallization from ether gave the pure ester as colorless needles: mp 165–167° dec; ir (KBr) 3330 (NH), 1679 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.7–2.2 (m, 11, cyclohexyl), 3.27–3.80 (broad s, 1, NH), 4.18–4.95 (m, 3, $CHCH_2$), 7.3–8.2 (m, 8, aryl).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.50; H, 7.17; N, 4.36. Found: C, 78.59; H, 7.24; N, 4.35.

9-Fluorenylmethoxycarbonyl-L-tryptophan.—To a solution of 1.58 g of L-tryptophan in 10 ml of dioxane and 20.5 ml of 10% Na_2CO_3 was added slowly with stirring and ice bath cooling a solution of 2 g of 9-fluorenylmethyl chloroformate in 20 ml of dioxane. The mixture was stirred in the ice bath for 4 hr and at room temperature for 8 hr, poured into 450 ml of H_2O, and extracted with ether. The aqueous layer was cooled in an ice bath, acidified with concentrated HCl to congo red paper, and stored in a refrigerator overnight. Filtration gave 3.1 g (94%) of the protected amino acid, mp 182–185° dec. Recrystallization from $MeNO_2$ followed by $CHCl_3$–hexane gave 3.0 g (91%) of the pure material, mp 185–187°, $[\alpha]^{23.5}D$ +6.4° (*c* 1, EtOAc).

Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.24; H, 5.16; N, 6.57. Found: C, 73.54; H, 5.22; N, 6.10.

9-Fluorenylmethoxycarbonylglycine. A. From FMOC-Cl.—To a solution of 0.57 g of glycine dissolved in 20.2 ml of 10% Na_2CO_3 was added with stirring and cooling in an ice bath a solution of 1.96 g of FMOC-Cl. The mixture was stirred at room temperature for 2 hr, poured into 400 ml of H_2O, and extracted twice with ether to remove small amounts of 9-fluorenylmethanol and the high-melting polymer of dibenzofulvene. The aqueous layer was cooled in an ice bath and acidified with concentrated HCl to congo red paper. The white precipitate was extracted with ethyl acetate, the extracts were washed with water, dried ($MgSO_4$), and evaporated, and the white residue, mp 173–176°, which amounted to 2 g (89%), was recrystallized from $MeNO_2$ to give 1.98 g (88%) of the pure acid: mp 174–175°; nmr (DMSO-d_6) δ 3.64–3.85 (d, 2, CH_2), 4.2–4.5 (m, 3, $CHCH_2$), 7.25–8.05 (m, 8, aryl).

B. From FMOC-N_3.—The reaction was carried out as described above except that the mixture was stirred for 64 hr at room temperature. The ether extracts yield some recovered FMOC-N_3 as well as the alcohol. Work-up as described gave 1.35 g (60%) of the protected derivative, mp 174–175°.

Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.69; H, 5.05; N, 4.71. Found: C, 68.45; H, 5.08; N, 4.85.

Hydrolysis of Ethyl 9-Fluorenylmethoxycarbonylglycinate.—A solution of 0.1 g of FMOC-gly-OEt in 10 ml of HOAc and 0.5 ml of concentrated HCl was refluxed for 10 hr and poured into 200 ml of H_2O, and the gelatinous precipitate was filtered, washed with H_2O, and dried in air to give 0.091 g (100%) of FMOC-gly-OH, mp 173–175°. The infrared spectrum was identical with that of an authentic sample and a mixture melting point showed no depression.

9-Fluorenylmethoxycarbonyl-L-leucine.—A solution of 0.993 g of L-leucine in 20.2 ml of 10% Na_2CO_3 and 10 ml of dioxane was treated as described for FMOC-gly with a solution of 1.96 g of FMOC-Cl in 15 ml of dioxane. Upon evaporation of the ethyl acetate extracts after acidification a syrup was obtained which solidified in a Dry Ice–acetone bath to give 2.4 g (90%) of colorless crystals, mp 155–156° dec after recrystallization from ether, $[\alpha]^{28.3}D$ −4.44 (*c* 2.5, EtOAc).

***N*-Piperidyl 9-Fluorenylmethoxycarbonylglycinate.**—To a solution of 0.5 g of FMOC-gly-OH and 0.187 g of *N*-hydroxypiperidine in 10 ml of anhydrous ethyl acetate was added 0.347 g of dicyclohexylcarbodiimide (DCCD). The mixture was stirred at room temperature for 1 hr and then for 5 min longer after the addition of a few drops of HOAc. The urea was removed by filtration and the filtrate was washed in order as follows: twice with 5% HCl, once with H_2O, twice with 5% Na_2CO_3, once with NaCl solution, and once with H_2O. After drying ($MgSO_4$), evaporation under reduced pressure and recrystallization from ether or ethyl acetate–ligroin (bp 60–70°) gave 0.55 g (86%) of the active ester: mp 123.5° dec; nmr ($CDCl_3$) δ 0.9–2.3 (m, 6, $CH_2CH_2CH_2$), 2.3–2.6 (m, 4, NCH_2CH_2), 3.9–4.2 (d, 2, $NHCH_2$), 4.2–4.7 (m, 3, $CHCH_2$), 5.6–6.0 (broad s, 1, NH), 7.0–8.3 (m, 8, aryl).

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.47; H, 6.32; N, 7.37. Found: C, 69.44; H, 6.45; N, 7.35.

8-Quinolyl 9-Fluorenylmethoxycarbonylglycinate.—A solution of 1 g of FMOC-gly-OH and 0.538 g of 8-hydroxyquinoline in 125 ml of ethyl acetate was treated with 0.693 g of DCCD and the mixture was stirred at room temperature for 5 hr. After the addition of a few drops of HOAc and work-up as described for the corresponding *N*-piperidyl ester there was obtained 1.09 g (76%) of the active ester: mp 162–164° dec (acetone–ligroin); nmr ($CDCl_3$) δ 4.4–4.7 (m, 5, CH_2, $CHCH_2$), 5.7–6.1 (broad s, 1, NH), 7.4–8.2 (m, 14, aryl).

Anal. Calcd for $C_{26}H_{20}N_2O_4$: C, 73.58; H, 4.72; N, 6.00. Found: C, 73.55; H, 4.82; N, 6.58.

Ethyl 9-Fluorenylmethoxycarbonylglycylglycinate.—A mixture of 0.36 g of FMOC-gly-ONC_5H_{10}, 0.159 g of gly-OEt·HCl, 0.155 g of NaOAc·$3H_2O$, and 2 ml of dioxane was stirred at room temperature for 24 hr and poured into 100 ml of cold H_2O. The precipitated white solid was recrystallized from EtOAc–Et_2O to give 0.3 g (83%) of the dipeptide ester, mp 131.5–132.5°. By a similar technique the same compound was obtained in 77% yield from FMOC-gly-ONC_3H_6.

Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.97; H, 5.76; N, 7.33. Found: C, 65.94; H, 5.69; N, 7.34.

9-Fluorenylmethoxycarbonylglycylglycine.—To a solution of 2 g of FMOC-gly-ONC_5H_{10} in 25 ml of dioxane was added at room temperature a solution of 0.474 g of glycine in 6.31 ml of 1 *N* NaOH. The solution was stirred for 1 hr, 20 ml of H_2O was added, and stirring was continued for 1 hr. After pouring into 500 ml of H_2O and extraction with ethyl acetate the aqueous layer was cooled and acidified with concentrated HCl to congo red paper. The precipitate was dried in air and recrystallized from CH_3CN to give 1.44 g (77%) of the dipeptide, mp 176–177°. The same compound was obtained in 92% yield by acylation of gly-gly-OH by means of FMOC-Cl.

Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.41; H, 5.08; N, 7.91. Found: C, 64.47; H, 5.10; N, 7.67.

***tert*-Butyl 9-Fluorenylmethoxycarbonyl-L-tryptophylglycinate.**—To a solution of 2.2 g of FMOC-L-Try-ONC_5H_{10} in 55 ml of dioxane was added at room temperature a solution of 0.679 g of *tert*-butyl glycinate in 0.312 g of HOAc. After stirring for 24 hr the solution was poured into 1000 ml of H_2O and the mixture was cooled in an ice box for 2 hr. Filtration and recrystallization from ether–hexane gave 2.18 g (94%) of the ester, mp 146.5–148.5° dec, $[\alpha]^{23.2}D$ −18.9 (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{32}H_{33}N_3O_5$: C, 71.24; H, 6.12; N, 7.79. Found: C, 71.12; H, 6.17; N, 7.69.

Liquid Ammonia Cleavage of 9-Fluorenylmethyl Carbanilate.—A solution of 1 g of FMOC-NHC_6H_5 in 250 ml of liquid ammonia was stirred for 10 hr and evaporated to dryness and the residue was treated with 100 ml of ligroin. Filtration removed a small amount of dibenzofulvene polymer. The filtrate was concentrated to about 10 ml and cooled in a refrigerator, which caused the separation of dibenzofulvene as colorless needles. Evaporation of the filtrate, dissolution of the residue in benzene, and passage of HCl gas gave 0.33 g (80%) of aniline hydrochloride, mp 195–197°. The dibenzofulvene was characterized by treatment with bromine in ether solution. Recrystallization from ligroin gave 0.91 g (85%) of the dibromide, mp 139–141° dec (lit.[21] mp 143° dec).

Liquid Ammonia Cleavage of 9-Fluorenylmethoxycarbonyl-L-phenylalanine.—A solution of 1.55 g of FMOC-L-Phe-OH in 250 ml of liquid ammonia was stirred for 10 hr and evaporated to dryness, and 200 ml of ether was added to the residue. Dibenzofulvene could be isolated from the ether solution in 95% yield as the dibromide. The insoluble portion was filtered and dissolved in the minimum amount of H_2O. Filtration removed a trace amount of dibenzofulvene polymer and evaporation of the filtrate gave 0.66 g (100%) of L-phenylalanine, $[\alpha]^{27}D$ −33.2 (1.992, H_2O), identified by comparison of its infrared spectrum with that of an authentic sample. The L-phenylalanine from which the above FMOC derivative was prepared had $[\alpha]^{26.7}D$ −33.24 (1.962, H_2O). By a similar method glycine (100%), DL-alanine (100%), glycylglycine (98%), and L-tryptophan [94%, $[\alpha]^{24.5}D$

(21) H. Wieland, F. Reindel, and J. Ferrer, *Ber.*, **55**, 3313 (1922).

-35.3 (c 1, H_2O)] were obtained from the corresponding FMOC derivatives.

Liquid Ammonia Cleavage of Ethyl 9-Fluorenylmethoxycarbonylglycinate. A.—A solution of 1 g of FMOC-gly-OEt in 150 ml of liquid ammonia was stirred for 6 hr and evaporated to dryness, and the residue was treated with 200 ml of ether. Ethyl glycinate was precipitated from the ether solution as the hydrochloride [0.39 g (90%), mp 135° dec] by treatment with dry HCl. The salt was identified by mixture melting point and comparison of infrared spectra with that of an authentic sample.

B.—The cleavage was repeated as above except that 0.1 g of the protected derivative was used and after evaporation of the liquid ammonia 250 ml of water was added and the mixture was stirred under ordinary diffuse daylight and incandescent room lighting for about 18 hr. After filtration of the dibenzofulvene polymer, extraction with ether and precipitation with HCl gave ethyl glycinate hydrochloride in 70–80% yield. Conversion of dibenzofulvene to its polymer under fluorescent room lighting appeared to require a considerably longer period.

Liquid Ammonia Cleavage of *tert*-Butyl 9-Fluorenylmethoxycarbonyl-L-tryptophylglycinate.—A solution of 1.0 g of FMOC-L-Try-gly-OBu-*t* in 150 ml of liquid ammonia was stirred for 10 hr and evaporated to dryness, and the yellow residue was extracted with six 50-ml portions of ligroin to remove dibenzofulvene. The insoluble residue was dissolved in 50 ml of warm ethyl acetate, the solution was filtered to remove a trace of dibenzofulvene polymer and evaporated, and the residue was recrystallized from ethyl acetate–ligroin. There was obtained 0.476 g (81%) of L-Try-gly-OBu-*t*, mp 95–97.5° (lit.[22] mp 94–97°), identified by comparison of the ir and nmr spectra with those of an authentic sample prepared by the hydrogenolysis of the carbobenzoxy derivative.[22]

Piperidine Cleavage of 9-Fluorenylmethyl Carbanilate.—A solution of 0.5 g of FMOC-NHC_6H_5 in 15 ml of piperidine was stirred at room temperature for 40 min and poured into 250 ml of cold H_2O. The precipitated solid was removed by filtration and the filtrate was extracted with ether. The dried ($MgSO_4$) ether extracts were evaporated, 2 ml of benzene added and the aniline derivatized by the addition of benzoyl chloride which gave 0.28 g (90%) of the benzamide derivative, mp 161–161.5°, after recrystallization from ethanol.

The solid (0.4 g, 96%, mp 117.5–119°) precipitated from the original solution by the addition of H_2O was recrystallized from ligroin to give 0.35 g (84%) of *N*-(**9-fluorenylmethyl**)**piperidine**: mp 116–117°; nmr ($CDCl_3$) δ 1.35–2.25 (m, 6, $CH_2CH_2CH_2$), 2.4–3.1 (m, 6, CH_2N), 3.84–4.18 (t, 1, $CHCH_2$), 7.12–8.06 (m, 8, aryl).

Anal. Calcd for $C_{19}H_{21}N$: C, 86.69; H, 7.98; N, 5.32. Found: C, 86.70; H, 7.92; N, 5.40.

N-(**9-Fluorenylmethyl**)**morpholine.**—Cleavage of FMOC-NH-C_6H_5 by means of morpholine (room temperature, 25 min) by a method analogous to that described for piperidine gave aniline in 96% yield (as the benzoyl derivative) and in 95% yield the adduct of dibenzofulvene and morpholine, mp 172.5–174° (95% ethanol).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.79; H, 7.46; N, 5.13.

Dibenzofulvene.—A solution of 0.5 g of FMOC-NHC_6H_5 in 15 ml of β-methoxyethyl amine was stirred at room temperature for 30 min and poured into 250 ml of H_2O, and the turbid mixture was extracted with ether. The dried ($MgSO_4$) ether layer was evaporated and the residue was washed with ligroin to give 0.26 g (93%) of dibenzofulvene: mp 49–51° (lit.[15] mp 46–48°); nmr ($CDCl_3$) δ 5.82 (s, 2, CH_2), 7.0–7.8 (m, 8, aryl). The dibromide had mp 141° dec (lit.[21] mp 143°) and caused no depression of melting point of an authentic sample. On standing the dibenzofulvene was converted to a high melting polymer.[21,23]

From the orginal ligroin-soluble portion there was obtained aniline in 80% yield (as the benzoyl derivative).

Piperidine Cleavage of 9-Fluorenylmethoxycarbonylglycylglycine.—A solution of 1.3 g of FMOC-gly-gly-OH in 10 ml of piperidine was stirred at room temperature for 30 min and then poured into 200 ml of cold H_2O. The filtrate, after removal of 0.96 g (100%) of the piperidine–dibenzofulvene adduct, was evaporated by a current of air and the residue was recrystallized from ethanol–H_2O (10:1) to give 0.4 g (83%) of glycylglycine, mp >200°, identified by comparison of its infrared spectrum with that of an authentic sample.

2-(*o*-Nitrophenylsulfonyl)ethyl Carbanilate.—Treatment of the corresponding alcohol[24] with phenyl isocyanate in benzene in the presence of a few drops of triethylamine gave the urethane, mp 130–132°, after recrystallization from benzene.

Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00. Found: C, 51.52; H, 4.10; N, 8.00.

2-(*p*-Nitrophenylsulfonyl)ethyl carbanilate was prepared[25] as described for the corresponding ortho isomer and recrystallized from C_6H_6–nitroethane (1:1), mp 167–169° dec.

Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00. Found: C, 51.60; H, 4.17; N, 7.90.

2,2-Dichloroethyl carbanilate was prepared as described for the *o*- and *p*-nitrophenylsulfonylethyl derivatives and recrystallized from benzene–ligroin (1:1), mp 68–69°.

Anal. Calcd for $C_9H_9Cl_2NO_2$: C, 46.18; H, 3.87; N, 5.98. Found: C, 46.00; H, 3.66; N, 5.98.

S-(**2,2-Dichloroethyl**)**thiocarbanilate** was prepared as described for the corresponding oxygen analog by substitution of 2,2-dichloroethanthiol for the alcohol and recrystallized from benzene–ligroin (bp 40–70°) (1:1), mp 86.5–87.5°.

Anal. Calcd for $C_9H_9Cl_2NOS$: C, 43.21; H, 3.63; N, 5.60. Found: C, 43.20; H, 3.56; N, 5.60.

Registry No.—**5b,** 35661-54-2; **5c,** 35661-55-3; **7,** 35661-56-4; **8,** 35661-57-5; **10,** 28920-43-6; **11** (R = Ph), 28991-69-7; **11** (R = cyclohexyl), 35661-50-8; **18a,** 35661-58-6; **18b,** 28991-70-0; **19a,** 35661-51-9; **19b,** 28920-44-7; **20,** 35737-14-5; **21,** 35661-53-1; 9-fluorenylmethoxycarbonyl-L-tryptophan, 35737-15-6; 9-fluorenylmethoxycarbonylglycine, 29022-11-5; 9-fluorenylmethoxycarbonyl-L-leucine, 35661-60-0; *N*-piperidyl 9-fluorenylmethoxycarbonylglycinate, 35661-61-1; 8-quinolyl 9-fluorenylmethoxycarbonylglycinate, 35661-62-2; ethyl 9-fluorenylmethoxycarbonylglycylglycinate, 35665-37-3; 9-fluorenylmethoxycarbonylglycylglycine, 35665-38-4; *tert*-butyl 9-fluorenylmethoxycarbonyl-L-tryptophenylglycinate, 35665-39-5.

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