were evaporated *in vacuo* and the residue was recrystallized from acetone to give **5** (572 mg, 21%), mp 218–220°.

*Anal.* Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 56.91; H, 5.07; N, 15.62.

The pooled fractions containing the slower moving band were also evaporated *in vacuo*. The residue was recrystallized from ethanol–water to give **6** (385 mg, 14%), mp 219–221°.

*Anal.* Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 57.17; H, 5.06; N, 15.48.

**2′-*O*-Benzylguanosine (8) and 3′-*O*-Benzylguanosine (9).**—Guanosine (1.0 g, 3.5 mmmol) was benzylated by the general method. The column was washed with $CHCl_3$ (1 l.) and EtOAc (2 l.). The benzylated nucleosides were eluted with EtOAc:MeOH (95:5). The solvent was removed *in vacuo* and the residue was dissolved in 1.5 *N* $NH_4OH$. The solution was applied to a column containing 500 g of DE-52 (Whatman DEAE cellulose) preequilibrated with 1.5 *N* $NH_4OH$. Elution with the same solvent gave two bands. The combined fractions corresponding to the first band were evaporated *in vacuo* and the residue was crystallized from ammonia–water to give **8** (207 mg, 16%), mp >310°, darkens at 270°.

*Anal.* Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C, 54.81; H, 5.24; N, 18.89.

The material from the second band was treated in the same manner to give **9** (233 mg, 18%), mp >310°, darkens above 260°.

*Anal.* Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C, 54.39; H, 5.16; N, 18.62.

**2′-*O*-Benzyluridine (11) and 3′-*O*-Benzyluridine (12).**—Uridine (5.0 g, 20.5 mmol) was benzylated. The column was washed with $CHCl_3$ (2 l.) and $CHCl_3$:EtOAc (1:3, 2 l.) and the isomers were eluted with EtOAc (4 l.). The solvent was removed *in vacuo* and the residue was crystallized from EtOAc:$Me_2CO$ to give a mixture of **11** and **12** (4.17 g, 56%). Separation of the isomers was accomplished by fractional crystallization from EtOH. Isomeric purity of the fractions was evaluated using tlc (SilicAR 7 GF, 3% aqueous $NH_4Cl$). The total yield of **11** was 1.52 g (20.3%), mp 177–179°. Analytical samples were obtained by recrystallization from EtOH.

*Anal.* Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.47; H, 5.47; N, 8.48.

The total yield of **12** was 1.08 g (14.5%), mp 205–207°.

*Anal.* Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.47; H, 5.71; N, 8.46.

**2′-*O*-Benzylcytidine (14) and 3′-*O*-Benzylcytidine (15).**—Cytidine (**13**, 6.0 g, 24.7 mmol) was benzylated as described above. The column was washed with $CHCl_3$ (2 l.), EtOAc (3 l.), and EtOAc:MeOH (95:5, 3 l.). The isomeric mixture was eluted with EtOAc:MeOH (85:15). The solvent was removed *in vacuo* to give **14** and **15** as a solid foam (5.33 g, 65%).

The above mixture (1.0 g) was dissolved in a solution of MeOH (14 ml) and $H_2O$ (28 ml). The solution was applied to a column containing Dowex 1 × 8 ($OH^-$) and eluted with 30% aqueous MeOH. The fractions corresponding to the first major band were combined and evaporated. The residue was recrystallized from $H_2O$ to give **14** (530 mg, 34% from **13**), mp 160–161°.

*Anal.* Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.74; N, 12.61. Found: C, 57.49; H, 5.94; N, 12.46.

The combined fractions corresponding to the second major band were evaporated to dryness *in vacuo*. The residue was dissolved in $H_2O$ and lyophilized to give **15** (287 mg, 19% from **13**).

*Anal.* Calcd for $C_{16}H_{19}N_3O_5 \cdot 0.5H_2O$: C, 56.13; H, 5.89; N, 12.27. Found: C, 56.01; H, 5.86; N, 12.28.

**Debenzylation Procedure for *O*-Benzyl Purine Ribonucleosides.**—*O*-Benzyl nucleoside (50 mg) was dissolved in EtOH (25 ml) containing 1 *N* NaOH (0.5 ml). The solution was added to 5% Pd/C. The mixture was shaken under hydrogen (45 psi). After 3.5 hr, debenzylation was complete as judged by tlc (SilicAR 7 GF, EtOAc:$H_2O$:*n*-PrOH, 4:2:1 upper phase).

**Debenzylation Procedure for *O*-Benzylpyrimidine Ribonucleosides.**—2′-*O*-Benzyluridine (50 mg) was dissolved in EtOH (25 ml) containing $H_2O$ (10 ml) and 1 *N* NaOH (2 ml). The solution was added to 10% Pd/C (25 mg) and stirred under hydrogen (1 atm). After 1 hr debenzylation was complete as judged by tlc (as above); quantitative uv evaluation showed better than 95% recovery of uridine.

Treatment of 2′-*O*-benzylcytidine (**14**) under these conditions led to complete debenzylation, but about 10–25% reduction to dihydrocytidine occurred.

**Registry No.**—**1**, 58-61-7; **2**, 35638-82-5; **3**, 35638-83-6; **4**, 58-63-9; **5**, 35638-84-7; **6**, 35638-85-8; **7**, 118-00-3; **8**, 35687-58-2; **9**, 35638-86-9; **10**, 58-96-8; **11**, 6554-02-5; **12**, 4710-74-1; **13**, 65-46-3; **14**, 22423-30-9; **15**, 35687-60-6.

# An Unusual Spirane Synthesis

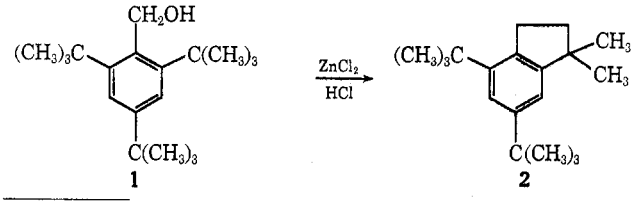
J. J. LOOKER,* D. P. MAIER, AND T. H. REGAN

*Research Laboratories, Eastman Kodak Company, Rochester, New York 14650*

*Received April 27, 1972*

The structure of the spirane formed by the cyclodehydration of the alcohol 5-*tert*-butyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (**3a**) has been established. The method used was to demonstrate the existence of a more stable isomer by lowering the barrier to ring inversion, and then to thermally isomerize the first to the second. The nmr spectra of the isomers are in agreement with the chemical results. Attempts to extend the cyclization reaction to five- and six-membered rings were unsuccessful. Two possible mechanisms for the cyclization are presented.

An unexpected cyclization is sometimes observed when a positive charge is formed near a crowded *tert*-butyl group. The positive carbon atom appears to insert itself into a carbon–hydrogen bond of one of the methyl groups of the *tert*-butyl substituent. The first example[1] of this reaction to be reported was the formation of indan **2** from alcohol **1**. Since no indan is formed when one of the ortho *tert*-butyl groups is replaced by methyl, some crowding is necessary for cyclization to occur. Other examples have subsequently appeared which include indans,[2] a benzocyclobutene,[3] and a cyclopropane.[4] We wish to report another example of this type of cyclization in which a three-membered ring is closed to form spirononatriene **4** in good yield (75%).




**1** **2**

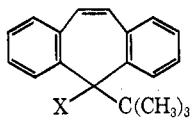
While attempting to prepare chloride **3b** for another problem, alcohol **3a** was synthesized by treating di-

(1) L. R. C. Barclay and M. C. MacDonald, *Tetrahedron Lett.*, 881 (1968).

(2) P. Martinson, *Acta Chem. Scand.*, **22**, 1357 (1968).

(3) M. H. Knight, T. Putkey, and H. S. Mosher, *J. Org. Chem.*, **36**, 1483 (1971).

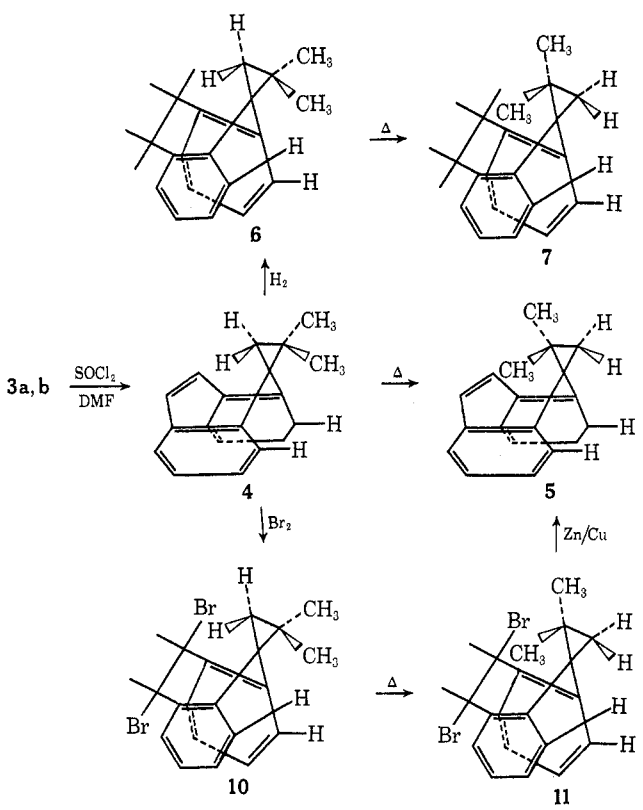
(4) G. J. Abruscato and T. T. Tidwell, *J. Amer. Chem. Soc.*, **92**, 4125 (1970).



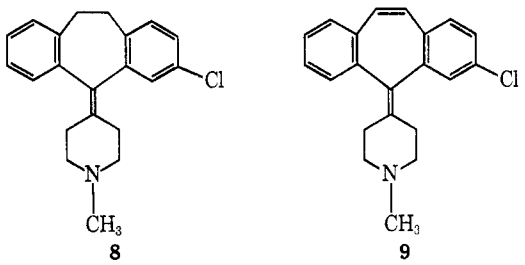
3a, X = OH
b, X = Cl

benzotropone with *tert*-butylmagnesium chloride. When the alcohol is treated with thionyl chloride and dimethylformamide (DMF), the only product isolated is a hydrocarbon, which differs from the starting alcohol by the loss of water. It no longer has a *tert*-butyl group (mass spectrum, nmr), but has a *gem*-dimethyl group (singlet, $\tau$ 8.69) and two cyclopropyl protons (singlet, $\tau$ 9.70). The most probable structures for this compound are **4** and **5**. Since its spectral properties do not allow a choice to be made between them, the chemical behavior of the spirane was examined.

Catalytic hydrogenation of the spirane occurs smoothly and, if care is taken to avoid heat, a thermally labile dihydrospirane is obtained. When this hydrocarbon is heated on a steam bath, it is isomerized to a new dihydrospirane. Based on the nmr spectra and molecular models of the two dihydrospiranes, structure **6** is assigned to the less stable and structure **7** to the more stable isomer. Isomerization causes the methyl groups to move out of the deshielding plane of the aromatic rings and away from the peri hydrogen atoms. The result is an upfield shift ($\tau$ 8.58 → 9.08) of the methyl signal. The cyclopropyl protons move into this deshielding area vacated by the methyl groups, and are shifted downfield ($\tau$ 8.91 → 8.71). Molecular models show that a steric interaction between the methyl groups and the peri hydrogen atoms is relieved by isomerization of **6** to **7**.



Our interpretation of these findings is that the spirane has the thermodynamically less stable structure **4**, in which there is a steric interaction identical with that proposed for dihydrospirane **6**. Isomerization to the more stable spirane **5** does not occur because of a high energy barrier to ring inversion. When the vinyl group is reduced, the less stable isomer **6** is formed, but the energy barrier has been lowered so that isomerization to the more stable form **7** can readily occur at 100°. The barrier to inversion is known to be significantly lower for the dihydro system. For example, the activation energy for the inversion[5] (racemization) of **8** is 9 kcal/mol lower than that of **9**. Models



**8** **9**

show that dihydrospirane **6** undergoes ring inversion with only a slight twist of the ethano bridge and aromatic rings. Spirane **4** must turn itself inside out to effect isomerization.

If this interpretation is correct, isomerization of spirane **4** to **5** should be possible if the temperature is raised high enough. The expected isomerization does occur at 210°, and is complete after 5 days. It can also be effected in refluxing quinoline (bp 238°) in 13 hr. The more stable spirane **5** has also been prepared by an alternative method. Bromination of the less stable spirane **4** produces the thermally labile dibromospirane **10** which, upon heating at near 100°, readily isomerizes to **11**. Debromination of **11** with zinc–copper couple gives the more stable spirane **5**.

The behavior of 9-*tert*-butyl-9-hydroxyfluorene (**12a**) and 9-*tert*-butyl-9-hydroxyxanthene (**13a**) toward thionyl chloride and DMF was examined to see if spirane formation could be extended to the five- and six-membered rings. Both alcohols are converted to the corresponding chlorides, **12b** and **13b**, in high yield under these conditions.

**12a**, X = OH
b, X = Cl



**13a**, X = OH
b, X = Cl

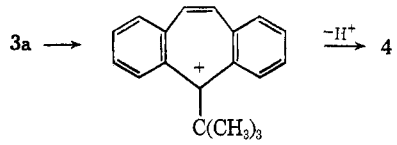
Alcohol **12a** has recently been found to undergo rearrangement when treated with strong acid,[6] but spirane formation was not observed. The difference in behavior between alcohol **3a** and alcohols **12a** and **13a** is probably due to the planarity of the central five- and six-membered rings. The boat-shaped seven-membered ring in **3a** causes a steric interaction between the equatorial substituent at carbon 5 and the peri hydrogen atoms. Relief of this interaction is probably the driving force for cyclization. Models show that the two substituents at carbon 9 in alcohols

(5) A. Ebnöther, E. Jucker, and A. Stoll, *Helv. Chim. Acta*, **48**, 1237 (1965).

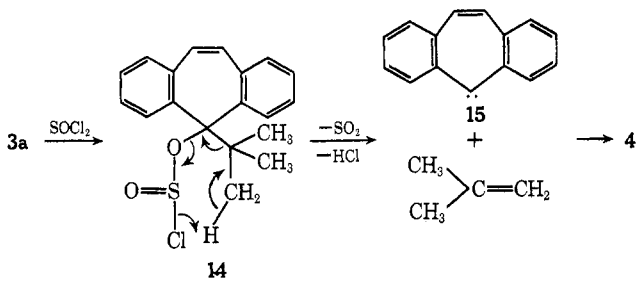
(6) H. Volz, G. Zimmermann, and B. Schelberger, *Tetrahedron Lett.*, 2429 (1970).

**12a** and **13a** occupy positions with nearly identical relationships to the rest of the molecule, and neither experiences any steric crowding.

Two mechanisms appear reasonable for the cyclization process. The first is the carbonium ion path suggested by Barclay and MacDonald,[1] which involves attack of the cation center by an $sp^3$ carbon orbital.




The second mechanism is the stepwise or concerted formation of carbene **15** and isobutylene from ester **14**.




14

Subsequent addition of the carbene to the olefin within the solvent cage would give spirane **4**. No evidence has been obtained which allows a distinction to be made between these two possibilities.

## Experimental Section

**5-*tert*-Butyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (3a).**—A Grignard reagent was prepared from 18.5 g (0.20 mol) of *tert*-butyl chloride, 4.8 g (0.20 g-atom) of magnesium, and 300 ml of anhydrous ether, and a solution of 25 g (0.12 mol) of 5*H*-dibenzo-[*a*,*d*]cyclohepten-5-one in 100 ml of dry benzene was added rapidly with stirring. Aftr 2 hr the mixture was poured into excess saturated ammonium chloride solution, and the organic layer was separated, washed, dried, and concentrated. The residue was chromatographed on Florisil with 20% benzene in ligroin (bp 63–75°). The first fractions solidified and were recrystallized from ligroin to give alcohol **3a**: yield 6.5 g (20%); mp 145–146°; ir (KBr) 3500 $cm^{-1}$ (OH); nmr ($DCCl_3$) $\tau$ 9.20 (s, 9, *tert*-butyl), 7.80 (s, 1, exchanges with $D_2O$, OH), 3.20 (s, 2, olefinic), 2.4–2.7 (m, 6, aromatic), 1.7–1.9 (m, 2, aromatic); mass spectrum *m/e* (rel intensity) 264 (0.4, parent), 249 (0.3), 207 (100), 179 (14), and 178 (26).

*Anal.* Calcd for $C_{19}H_{20}O$: C, 86.3; H, 7.6. Found: C, 86.1; H, 7.7.

The use of *tert*-butyllithium in place of the Grignard reagent gave the same yield of product.

**Reaction of 5-*tert*-Butyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (3a) with Thionyl Chloride and DMF.**—A mixture of 2.0 g (0.0076 mol) of alcohol **3a**, 6 ml of thionyl chloride, and 4 drops of DMF was heated at reflux for 30 min. The solvent was distilled and the solid residue was washed with water and recrystallized from ethanol: yield 1.4 g (75%) of spirane **4**; mp 104–105°; nmr ($DCCl_3$) $\tau$ 9.79 (s, 2, cyclopropyl), 8.69 (s, 6, methyl), and 2.4–2.9 (m, 10, aromatic and vinyl); uv $\lambda_{max}$ (EtOH) 282 nm (log $\epsilon$ 4.08); mass spectrum *m/e* (rel intensity) 246 (100, parent), 245 (77), 231 (61), 216 (30), 215 (36), and 189 (39).

*Anal.* Calcd for $C_{19}H_{18}$: C, 92.6; H, 7.4. Found: C, 92.4; H, 7.1.

**Reduction of Spirane 4.**—A mixture of 2.1 g (0.085 mol) of spirane **4**, 150 ml of ethanol, and 0.1 g of 10% palladium on charcoal was treated with hydrogen at 50 psi for 15 hr. The catalyst was removed by filtration and the solvent was distilled, care being taken not to heat the solution above room temperature. The product, dihydrospirane **6**, was recrystallized from methanol in such a manner as to minimize exposure to heat: yield 1.8 g (86%); mp 87–88°; nmr ($DCCl_3$) $\tau$ 8.91 (s, 2, cyclopropyl), 8.58 (s, 6, methyl), 6.1–7.4 (m, 4, benzyl), 2.95–3.03 (m, 6, aromatic), and 2.6–2.9 (m, 2, aromatic); mass spectrum *m/e* (rel intensity) 248 (79, parent), 247 (39), 283 (100), 191 (21), 189 (21), and 91 (16).

*Anal.* Calcd for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 91.8; H, 8.1.

**Isomerization of Dihydrospirane 6.**—Heating 1.0 g of dihydrospirane **6** on a steam bath for 20 min caused it to isomerize to compound **7** quantitatively: mp 56–58° (recrystallized from methanol, mp 58–59°); nmr ($DCCl_3$) $\tau$ 9.08 (s, 6, methyl), 8.71 (s, 2, cyclopropyl), 6.3–7.5 (m, 4, benzyl), 3.10 (s, 8, aromatic); mass spectrum identical with that of isomer **6**.

*Anal.* Calcd for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 91.7; H, 7.9.

**Thermal Isomerization of Spirane 4.**—A 0.050-g sample of spirane **4** was dissolved in 0.3 ml of hexachlorobutadiene and heated in an nmr tube at 206° for 26 hr. Nmr spectra were measured at intervals during this time and showed a decrease in the methyl ($\tau$ 8.69) and cyclopropyl ($\tau$ 9.79) peaks of spirane **4** and the appearance of the methyl ($\tau$ 9.32), cyclopropyl ($\tau$ 8.70), and vinyl ($\tau$ 2.97) peaks of spirane **5**. Integration showed that isomerization was 60% complete after 26 hr. When spirane **4** was sealed in an ampoule and heated at 210° for 5 days, the nmr spectrum of the product was that of spirane **5**.

A solution of 0.10 g of spirane **4** in 0.3 ml of quinoline was heated at 240° for 13 hr. The nmr spectrum showed complete isomerization to **5**. The solution was poured into dilute hydrochloric acid and the solid was collected and recrystallized from acetonitrile to give 0.060 g (60%) of spirane **5**: m 97–98°; nmr ($DCCl_3$) $\tau$ 2.65 (m, 3, aromatic), 2.97 (s, 2, olefinic), 8.70 (s, 2, cyclopropyl), 9.32 (s, 6, methyls); mass spectrum is identical with that of spirane **4**.

*Anal.* Calcd for $C_{19}H_{18}$: C, 92.6; H, 7.4. Found: C, 92.6; H, 7.7.

**Bromination of Spirane 4.**—A mixture of 1.0 g (0.0040 mol) of spirane **4**, 0.65 g (0.0040 mol) of bromine, and 1 ml of carbon tetrachloride was wrapped in aluminum foil and left at room temperature for 15 hr. The solvent was removed and the solid was washed with 3 ml of ethanol to give 1.2 g (74%) of dibromide **10**: mp 143–144°; nmr ($DCCl_3$) $\tau$ 8.97, 8.90, 8.25, 8.18 (AB quartet, 2, cyclopropyl), 8.46 (s, 3, methyl), 8.60 (s, 3, methyl), 3.18, 3.33, 4.34, 4.48 (AB quartet, 2, benzylic), 2.6–3.0 (m, 7, aromatic), and 2.0–2.2 (m, 1, aromatic); mass spectrum *m/e* (rel intensity) 404 (0.3, parent), 325 (40), 269 (18), 246 (43), 245 (100), and 215 (32).

*Anal.* Calcd for $C_{19}H_{18}Br_2$: C, 56.2; H, 4.5; Br, 39.4. Found: C, 56.4; H, 4.4; Br, 39.4.

**Isomerization of Dibromide 10.**—A solution of 1.2 g of dibromide **10** in 10 ml of toluene was heated on a steam bath for 1 hr and the solvent was distilled. Recrystallization of the residue from methylcyclohexane gave 1.05 g (88%) of the isomeric dibromide **11**: mp 165–166°; nmr ($DCCl_3$) $\tau$ 8.92 (s, 3, methyl), 8.63 (s, 3, methyl), 8.37, 8.47, 8.70, 8.80 (AB quartet, 2, cyclopropyl), 3.55, 3.75, 4.27, 4.47 (AB quartet, 2, benzyl), 2.6–3.1 (m, 7, aromatic), and 1.9–2.1 (m, 1, aromatic); mass spectrum identical with that of dibromide **10**.

*Anal.* Calcd for $C_{19}H_{18}Br_2$: C, 56.2; H, 4.5; Br, 39.4. Found: C, 56.4; H, 4.4; Br, 39.1.

**Debromination of Dibromospirane 11.**—A mixture of 0.90 g (0.0022 mol) of dibromospirane **11**, 1 g of zinc–copper couple, 2 drops of DMF, and 20 ml of 1,2-dimethoxyethane was heated at reflux with stirring for 1 hr. The solid was separated and the filtrate was concentrated to a solid, which was dissolved in benzene and passed through a small amount of Florisil. The benzene was removed and the product was recrystallized from acetonitrile to give 0.49 g (90%) of spirane **5**, mp 97–98°.

**Treatment of 9-*tert*-Butyl-9-hydroxyfluorene with Thionyl Chloride and DMF.**—A mixture of 2.0 g (0.0084 mol) of alcohol **12a**,[7] 6 ml of thionyl chloride, and 1 drop of DMF was heated at reflux for 30 min. The solvent was removed, leaving 2.15 g (100%) of chloride **12b**: mp 101–103° (reported[8] mp 104–105°); nmr ($DCCl_3$) $\tau$ 2.26–2.83 (m, 8, aromatic) and 8.90 (s, 9, *tert*-butyl); mass spectrum *m/e* (rel intensity) 256 (24, parent), 241 (4), 221 (3), 206 (13), 200 (24), 199 (50), 165 (25), and 57 (100).

**9-*tert*-Butyl-9-hydroxyxanthene (13a).**—A Grignard reagent was prepared from 45 g (0.50 mol) of *tert*-butyl chloride, 12 g

(7) C. L. Arcus and E. A. Lucken, *J. Chem. Soc.*, 1634 (1955).

(8) R. C. Fuson, H. A. DeWald, and R. Gaertner, *J. Org. Chem.*, **16**, 21 (1951).

(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 ($CCl_4$) $\tau$ 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 ($CCl_4$) $\tau$ 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

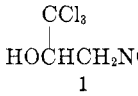
LOUIS A. CARPINO* AND GRACE Y. HAN

*Department of Chemistry, University of Massachusetts at Amherst, Amherst, Massachusetts 01002*

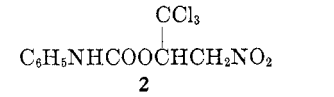
*Received April 10, 1972*

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 $\beta$-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]

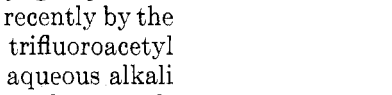


**1**



**2**

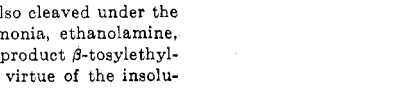
upon treatment with ammonia in benzene was converted to aniline in good yield. This result had been anticipated on the basis of Chattaway's work[8] on the base-induced reactions of simple esters of alcohol **1**, reactions which clearly involve $\beta$ eliminations followed by conjugate addition to the intermediate $\alpha,\beta$-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 $\beta$ elimination involving the corresponding sulfone analogs has already been recommended by Stirling[4] as a deblocking procedure for the $\beta$-tosylethyloxycarbonyl group.

In our work it early became apparent that the simple $\beta$-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 $\beta$-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 $\beta$-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).