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(19) Purification of the crude solid was not attempted as this might possibly have led to enrichment of one of the products.

Fluorene Derivatives: Friedel–Crafts Reaction of 2-Fluorenyl Basic Ethers

Winton D. Jones, Jr.,* William L. Albrecht, and Frank P. Palopoli

Department of Organic Chemistry, Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215

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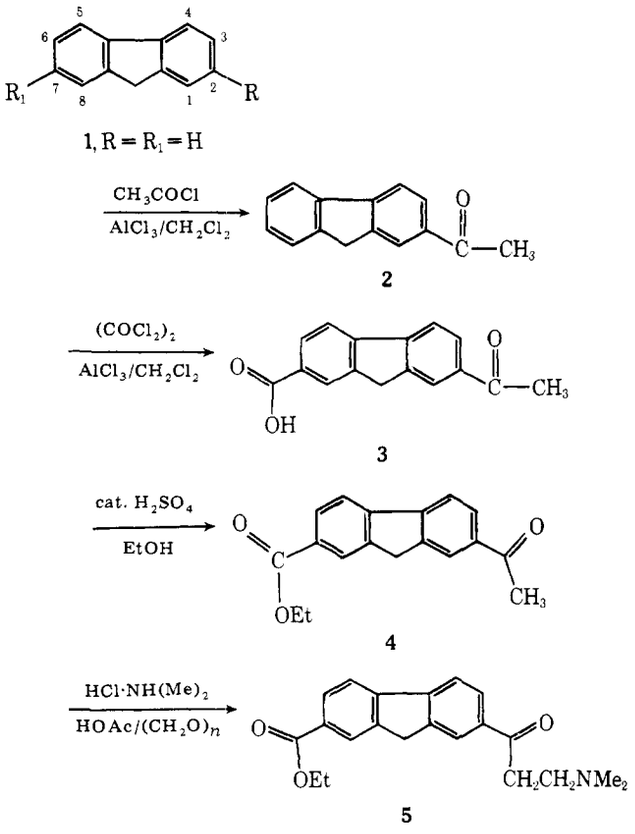
Fluorene 1 (R = R′ = H) has been reported to undergo bis-electrophilic substitution in the 2 and 7 positions.[1,2] While a great deal of synthetic effort has been concentrated on the preparation of symmetrically 2,7-disubstituted compounds, very little work has been done on derivatives of 1 in which R and R′ comprise different functional types.[3,4]

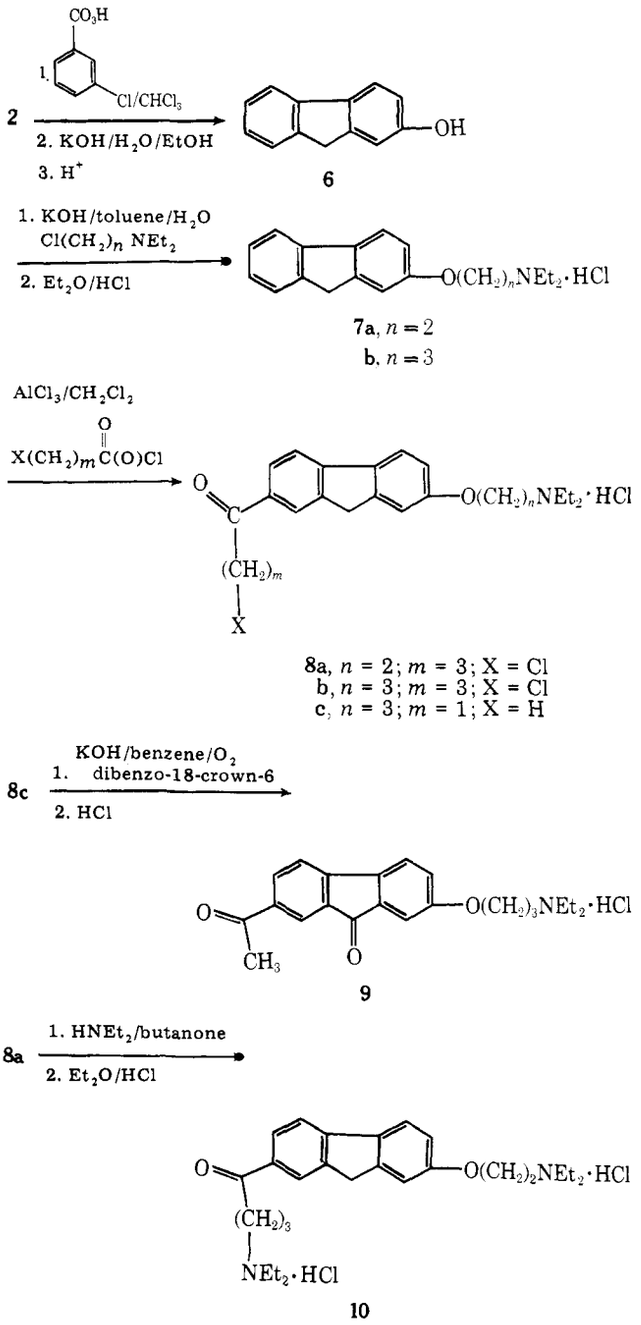
In connection with the synthesis of certain bis-basic derivatives of fluorene having antiviral activity, we were interested in devising synthetic routes to such disymmetric fluorenes. In particular we were interested in synthetic methods to compounds such as **4**, **8**, and **9**. These compounds would be valuable intermediates since simple chemical manipulations could lead to bis-basic fluorene and fluorenone derivatives having dissimilar substituents, e.g., **10**. The preparation and characterization of 2,7 disubstituted **1** compounds in which R and R′ comprise different functional types are described in this paper.

Treatment of 2-acetylfluorene (**2**) with oxalyl chloride led to the corresponding acid derivative **3**. Compound **3** was esterified to ester **4** and then converted to the base **5** (Scheme I). The ether analogues were prepared as shown in Scheme II. Baeyer-Villiger oxidation of **2** followed by hydrolysis of the intermediate acetate afforded **6**. Alkylation of **6** with the appropriate ω-halodialkylamine gave **7a** and **7b**. Although initial attempts to prepare compounds **8a–c** with BF_3·Et_2O used as the catalyst were unsuccessful, they were successfully prepared in good yield by acylation of **7** in methylene chloride with aluminum chloride used as the catalyst. Compounds of formula **8** were isolated as their hydrochloride salts by treatment of the reaction mixture with an aqueous hydrochloric

Scheme I



Scheme II



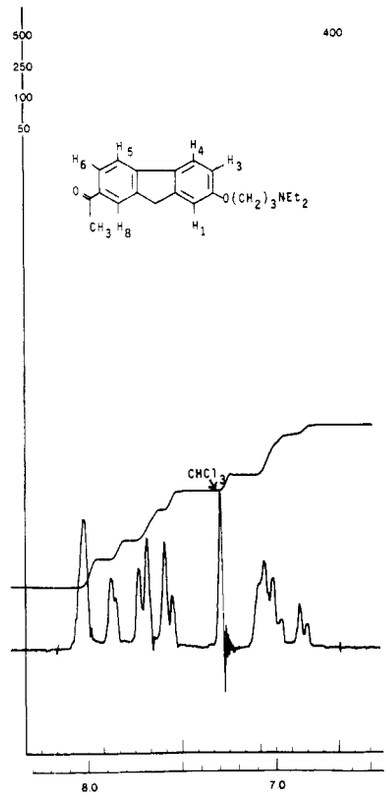


Figure 1. ^{1}H NMR spectrum (60 MHz) of **8c** in $CDCl_3$.

acid–sodium chloride solution. This procedure was convenient since it eliminated possible isolation problems resulting from intractable Lewis acid complexes and probable side reactions of **8a** or **8b** arising from treatment with strong base.[5,6] A survey of the literature revealed very few reports of Friedel–Crafts acylations of basic substrates.[7] None of these authors isolated the products directly as the hydrochloride salts. This reaction and the accompanying workup should be general for aromatic nuclei, the solubility characteristics for which allow them to be salted out of water.

The 2,7 substitution patterns of **8a, 8b,** and **8c** were determined by ^{1}H NMR. These compounds all exhibited a complex signal (2 H) at δ 7.1 to 7.0 and the A portion of an ABC multiplet (1 H) at δ 8.1 to 8.0. For example, in the ^{1}H NMR spectrum of **8c** (Figure 1) the signals due to aromatic protons showed a broad singlet (1 H) with fine structure at δ 8.1 and absorption for the A portion of an ABC multiplet (1 H) at δ 7.1 superimposed on a doublet of doublets (1 H) centered at δ 7.0 (J_{AB} = 9.0 Hz, J_{AC} = 2.0 Hz). The absorptions at δ 7.0 and 7.1 were assigned to H_3 and H_1, respectively. The complex absorptions between δ 7.5 and 7.9 (3 H) along with the deshielded peak at δ 8.1 were tentatively assigned to H_4, H_5, H_6, and H_8. This ^{1}H NMR pattern along with the well-documented regioselectivity exhibited by the Baeyer–Villiger oxidation[8-10] definitively established that the basic ether was located in the 2 position of the fluorene nucleus. Moreover, the two proton signals at δ 7.0 and 7.1 and their splitting patterns required that the acetyl group be situated on a different aromatic ring than the basic ether. The ^{1}H NMR of **8c** did not establish the position of the acetyl group since the spectrum in Figure 1 was consistent with either a 2,7- or a 2,6-disubstitution pattern. The signal at δ 8.1 was inconsistent with an acetyl function at either H_5 or H_8 since the exhibited J values were incorrect for these substitutions (see Experimental Section). The problem of the position of the acetyl group was resolved by oxidation of **8c** to the fluorenone **9**. This oxidation was carried out in 41% yield with a modification of

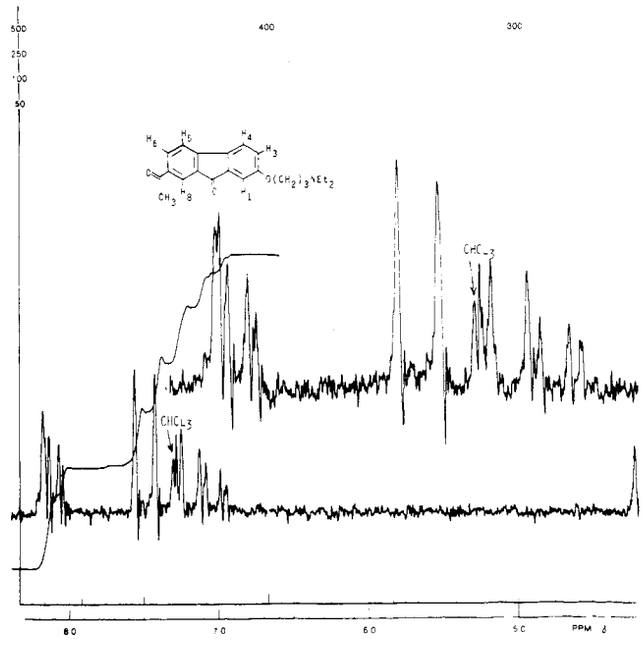


Figure 2. ^{1}H NMR spectrum (60 MHz) of **9** in $CDCl_3$.

the procedure of Gokel and Durst.[11] Fortuitously, a consideration of all of the signals due to the aromatic hydrogens of **9** permitted a structural assignment to be made (Figure 2). The doublet centered at δ 7.5 (J = 9.0 Hz, 2 H) was assigned to H_4 and H_5. Careful consideration of the theoretical pattern of 2,6 disubstitution vs. 2,7 disubstitution showed that only the latter was consistent with the observed doublet. In the 2,6-disubstituted fluorenone H_4 and H_8 would be expected to be part of ABC systems; however, one would not expect the chemical shifts of H_4 and H_8 to be equivalent with no further splitting. Additional support for 2,7 disubstitution was the expected downfield shift in the ABC multiplets that appeared at δ 8.1 (H_8) and 7.1 (H_1) in **8c** (Figure 1) to δ 8.2 and 7.3, respectively, in **9** (Figure 2). The doublet of doublets centered at δ 7.0 (J = 9.0, 2.0 Hz) was assigned to H_3 while the doublet of doublets superimposed on H_3 and centered at δ 8.1 (J = 9.0, 2.0 Hz) was assigned to H_6 (Figure 2). The two doublet of doublets added further support for the structural assignment since $J_{H_3H_4} = J_{H_5H_6}$ = 9.0 Hz. The assignment of the 2,7-disubstitution pattern to **8c** also necessitated the assignment of this pattern to all of the compounds of formula **8**.

Compounds **8a** and **8b** were especially valuable intermediates since they could be readily aminated to yield the desired bis-basic fluorene derivatives. For example, amination of **8a** with diethylamine in refluxing butanone gave **10**.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. The infrared and ultraviolet spectra were obtained on Perkin-Elmer 521 and Perkin-Elmer 350 recording spectrometers, respectively. Nuclear magnetic resonance spectra were obtained on a Varian A 60A spectrometer. Where analyses are indicated by symbols of the elements, results were within ±0.4% of the theoretical value.

7-Acetylfluorene-2-carboxylic Acid (3). To a stirred mixture of **2** (50.0 g, 0.24 mol) and $AlCl_3$ (101.0 g, 0.75 mol) in CH_2Cl_2 (1500 mL) chilled in a dry ice–acetone bath was added oxalyl chloride (64.0 g, 0.50 mol) dropwise over 45 min. The mixture was allowed to warm to room temperature, stirred for 3 days, and then heated at reflux for 5 h. The reaction mixture was hydrolyzed with cold aqueous HCl and the resulting emulsion was concentrated to remove CH_2Cl_2. Chilling and filtration gave a tan solid, 31.0 g (51%), mp 290–295 °C. Recrystallization of a small quantity of the acid from EtOH gave the analytical sample of **3**, mp 291–294 °C. Anal. C, H.

7-Acetylfluorene-2-carboxylic Acid Ethyl Ester (4). Com-

pound **3** was stirred and heated with absolute EtOH (400 mL) and H_2SO_4 (14.0 mL) for 2 days. After filtration of the hot dark-brown solution, the ester began to crystallize immediately and gave 25.6 g (78%) of a tan solid. Recrystallization (EtOH) gave tan needles of **4**: mp 141–143 °C; IR (KBr) 1695 (ester C=O), 1665 (unsaturated C=O), and 1600 cm^{-1} (aromatic CH); NMR ($CDCl_3$) δ 8.2–7.7 (m, 6 H), 4.4 (q, 2 H, J = 7.0 Hz), 3.8 (s, 2 H), 2.6 (s, 3 H), 1.4 (t, 3H, J = 7.0 Hz); UV_{max} 322 nm (ϵ 37 200). Anal. C, H.

7-[(3-Dimethylamino)propionyl)]7-fluorene-2-carboxylic Acid Ethyl Ester (5). Acetic acid (50 mL) was added to a mixture of **4** (11.3 g, 0.04 mol), paraformaldehyde (1.20 g, 0.04 mol), and dimethylamine hydrochloride (3.30 g, 0.04 mol). The mixture was stirred and heated on the steam bath for 3 h. Concentration in vacuo gave a solid that when recrystallized (CH_2Cl_2–EtOAc) gave 9.95 g (66%), mp 195–207 °C. A second recrystallization (CH_2Cl_2–butanone) gave the analytical sample of **5**: mp 206–207 °C; NMR ($CDCl_3$/TFA) δ 8.2–7.8 (m, 6 H), 4.5 (q, 2 H, J = 7.0 Hz), 3.9 (m, 2 H), 3.7 (m, 4 H), 3.1 (s, 3 H), 3.0 (s, 3 H), 1.4 (t, 3 H, J = 7.0 Hz); IR (KBr), 1712 (ester C=O) and 1670 cm^{-1} (broad unsaturated C=O). Anal. C, H, N.

2-Hydroxyfluorene (6). To a stirred solution of **2** (50.0 g, 0.24 mol) in hydrocarbon stabilized $CHCl_3$ (1 L) in a blackened flask (2 L)[14] was added *m*-chloroperbenzoic acid (30.3 g (82%), 0.24 mol) at 5 °C in divided portions. The reaction mixture was allowed to warm to room temperature and was then stirred at ambient temperature for 3 days. The resulting brown solution was extracted with saturated $NaHCO_3$, H_2O, and brine and then dried ($MgSO_4$), filtered, and concentrated to give a tan solid. The solid was hydrolyzed with a KOH (100.0 g), H_2O (2 L), EtOH (300 mL) mixture. Filtration and acidification (pH 2) gave 23.8 g (64%) of **6**, mp 169–170 °C (lit.[12] mp 171 °C).

3-(2-Fluorenyloxy)-*N,N*-diethylpropylamine Hydrochloride (7b). To a stirred solution of **6** (23.8 g, 0.13 mol) dissolved in 17% NaOH (300 ml) was added 3-diethylaminopropyl chloride (20.0 g, 0.13 mol) and toluene (300 mL). The two-phase reaction mixture was stirred and heated under reflux for 24 h. The organic layer was separated, washed with H_2O, and dried ($MgSO_4$). Filtration followed by acidification with gaseous HCl gave a tan precipitate. Recrystallization (MeOH–EtOAc) gave: 33.1 g (79%); mp 170–172 °C; IR (KBr) 2940, 2650, 2490, 1610, 1590, and 1450 cm^{-1}; NMR ($CDCl_3$) δ 7.7–7.1 (m, 5 H), 7.10 (m, 1 H), 6.8 (dd, 1 H, J = 8.0 Hz), 4.15 (t, 2 H, J = 7.0 Hz), 3.85 (s, 2 H), 3.4–2.9 (m, 6 H), 2.6–2.0 (m, 2 H), 1.4 (t, 6 H, J = 7.0 Hz); UV_{max} (EtOH) 272 nm (ϵ 20 700). Anal. C, H, N.

2-(2-Fluorenyloxy)-*N,N*-diethylaminoethane Hydrochloride (7a). This compound was prepared from **6** and β-diethylaminoethyl chloride in the same way as **7b**. The product was used in the next reaction without purification.

3-Chloropropyl-7-[2-(diethylamino)ethoxy]fluoren-2-yl Ketone Hydrochloride (8a). To a stirred solution of **7a** (50.0 g, 0.16 mol) and 4-chlorobutyryl chloride (45.6 g, 0.32 mol) in CH_2Cl_2 (2 L) cooled in a dry ice–acetone bath was added $AlCl_3$ (47.0 g, 0.35 mol) in divided portions over 20 min. The solution was allowed to slowly warm to room temperature and stirred for 3 days. The reaction mixture was poured onto cracked ice (1 L) and concentrated HCl (200 mL). The two-phase mixture was then stirred for 45 min. The CH_2Cl_2 layer was separated and washed with brine (2 L). The aqueous layer was extracted with CH_2Cl_2 (2 L) and the organic layers were combined and dried ($MgSO_4$). The resulting dark-brown solution was filtered and concentrated in vacuo to a dark oil. Crystallization of the oil gave 44.0 g (63%) of a solid mp 149–151 °C. Recrystallization (3.1 g charcoal MeOH–EtOAc) gave 19.7 g of **8a**, mp 168.5–170.5 °C. Anal. C, H, N.

3-Chloropropyl 7-[3-(Diethylamino)propoxy]fluoren-2-yl) Ketone Hydrochloride (8b). To a stirred solution of **7b** (18.9 g, 0.057 mol) and 4-chlorobutyryl chloride (16.0 g, 0.1 mol) in CH_2Cl_2 (1500 mL) chilled in a dry ice–acetone bath was added $AlCl_3$ (13.3 g, 0.1 mol). The reaction was then treated as above to give after recrystallization (MeOH–EtOAc): 15.8 g (63%) of **8b**; mp 175–177 °C; NMR ($CDCl_3$) δ 8.2 (m, 1 H), 7.9–7.7 (m, 3 H), 7.1 (m, 1 H), 7.0 (1 H, J = 9.0, 2.0 Hz), 4.7–4.5 (m, 2 H), 3.9–3.1 (m, 12 H), 2.3–2.1 (m, 2 H), 1.5 (t, 6 H, J = 7.0 Hz); IR (KBr) 2910, 2900, 2450, 1660, 1612, and 1550 cm^{-1}; UV_{max} (EtOH) 324 nm (ϵ 30 200). Anal. C, H, N.

Methyl 7-[3-(Diethylamino)propoxy]fluoren-2-yl Ketone Hydrochloride (8c). To a stirred solution of **7b** (7.07 g, 0.21 mol) and acetyl chloride (23.2 g, 0.30 mol) in CH_2Cl_2 2 L) chilled in a dry ice–acetone bath was added $AlCl_3$ (46.7 g, 0.35 mol) in divided portions over 30 min. The suspension was treated as in **8a**.[13] Recrystallization (MeOH–EtOAc) gave 52.0 g (65%) of **8c**; mp 173–175 °C; IR (KBr) 1670 cm^{-1} (unsaturated CO): UV_{max} (EtOH) 326 nm (ϵ 31 100); NMR ($CDCl_3$, free base) δ 8.1 (m, 1 H), 7.9–7.6 (m, 3 H), 7.1 (m, 1 H), 7.0 (m, 1 H), 4.1 (t, 2 H, J = 6.0 Hz), 3.9 (s, 2 H), 2.8–2.4 (m, 9 H), 2.1–1.8 (m, 2 H), 1.0 (t, 6 H, J = 7.0 Hz). Anal. C, H, N.

2-Acetyl-7-[3-(diethylamino)propoxy]-9*H*-fluoren-9-one (9). To a stirred mixture of **8c** free base (8.10 g, 0.024 mol) and dibenzo-18-crown-6 (420 mg, 0.0012 mol) in benzene (30.0 ml) was added KOH pellets (2.0 g, 0.036 mol) and the stirring rate was increased to the most rapid rate consistent with the solution remaining in the flask (125-mL Erlenmeyer). The suspension became dark red and then turned brown within 15 min. It was stirred open to the atmosphere for an additional 30 min and then poured into H_2O (200 mL)–CH_2Cl_2 (100 mL). The two-phase suspension was filtered and an orange solid was collected. The solid was acidified with dilute HCl and the resulting suspension was filtered. Recrystallization of the precipitate (MeOH–EtOAc) gave 3.8 g (41%) of **9** as an orange powder: mp 248–249 °C; IR (KBr) 2600, 2400 (amine hydrochloride), 1710 (9 carbonyl), 1655 cm^{-1} (acetyl carbonyl); NMR ($CDCl_3$ free base) δ 8.2 (m, 1 H, $J_{(m)}$ = 2.0 Hz, $J_{(p)}$ < 1.0 Hz), 8.1 (dd, 1 H, $J_{(o)}$ = 9.0 Hz, $J_{(m)}$ = 2.0 Hz), 7.5 (d, 2 H, $J_{(o)}$ = 9.0 Hz), 7.3 (m, 1 H, $J_{(m)}$ = 2.0 Hz, $J_{(p)}$ < 1.0 Hz), 7.0 (dd, 1 H, $J_{(o)}$ = 9.0 Hz, $J_{(m)}$ = 2.0 Hz), 4.1 (t, 2 H, J = 6.0 Hz), 2.7–2.3 (m, 9 H), 2.1–1.8 (m, 2 H), 1.1 (t, 6 H, J = 7.0 Hz). Anal. C, H, N.

3-Diethylaminopropyl 7-[2-(Diethylamino)ethoxy]fluoren-2-yl) Ketone Hydrochloride (10). To a stirred mixture of **8a** (21.2 g, 0.05 mol), KI (8.3 g, 0.05 mol), and K_2CO_3 (6.0 g, 0.043 mol) in butanone (300 mL) was added diethylamine (50.0 mL). The mixture was then heated and stirred at reflux for 24 h. An additional 50 mL of diethylamine was added and the burgundy colored solution was heated for an additional 4 h. The solution was allowed to cool, then filtered and concentrated in vacuo to a purple semisolid residue which was dissolved in dilute HCl, filtered, and made basic with NaOH in a two-phase Et_2O–H_2O mixture. The Et_2O layer was separated, washed with brine, separated, dried ($MgSO_4$), and filtered. Partial concentration of the filtrate gave a small amount of a yellow solid, which was filtered. The filtrate was further concentrated to a purple oil. The purple oil was dissolved in benzene (500 mL) and then concentrated in vacuo and the residue was dissolved in anhydrous Et_2O, which was then acidified with ethereal HCl. The resulting precipitate was washed with fresh Et_2O and then recrystallized (MeOH–butanone–charcoal) to give 9.0 g (36%) of **10** as a tan solid, mp 260–262 °C. Anal. Calcd for $C_{27}H_{38}N_2O_2 \cdot 2HCl \cdot 3H_2O$: C, 64.66; H, 8.17; N, 5.59; Cl, 14.14. Found: C, 64.91, H, 7.97; N, 5.24; Cl, 13.76; NE = 253.8.

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Registry No.—2, 781-73-7; **3,** 63715-82-2; **4,** 63715-83-3; **5,** 63715-84-4; **6,** 2443-58-5; **7a,** 63715-90-2; **7b,** 63715-85-5; **8a,** 63715-86-6; **8b,** 63715-87-7; **8c,** 63715-88-8; **8c** free base, 63715-92-4; **9,** 63715-89-9; **10,** 63715-91-3; dimethylamine HCl, 506-59-2; 3-diethylaminopropyl chloride, 104-77-8; β-diethylaminoethyl chloride, 100-35-6; 4-chlorobutyryl chloride, 4635-59-0; acetyl chloride, 75-36-5.

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(14) The blackened flask was prepared by covering a 2-L round-bottom flask with black epoxy paint.