naphthalene (**13**), mp 134.5–135.5 °C (lit.[19] mp 136 °C, 135–136 °C).

Reaction with *tert*-Butyl Halides. Treatment of a solution of **2** (1.85 mmol) with 0.35 g (3.8 mmol) of *tert*-butyl chloride resulted in only limited reaction at −70 °C (little color change). Warming the solution to ambient temperature resulted in a color change from blue to light orange. The crude product (oil, 0.60 g) was analyzed by gas chromatography using column A and an initial column temperature of 180 °C for 10 min, then heating at 3 °C/min to 210 °C, and holding isothermally at the upper limit. The compounds which eluted had the following retention times relative to **17** [normalized percent peak area, identity (if known)]: 0.63 (1, **18**), 0.77 (32, **16**), 0.85 (4), 1.0 (51, **17**), 1.08 (4), 1.19 (3, *o*-dibenzoylbenzene),[20] 1.27 (1, **1**),[20] 1.37 (2), 1.46 (2). The crude product was chromatographed, using petroleum ether (bp 30–60 °C) containing 10% benzene as eluant. The first fraction contained 0.15 g (21%) of 1,3-di-*tert*-butyl-1,3-diphenylphthalan, **17**: mp (from ethanol) 213–214 °C; NMR 0.70 (s, 18 H), 7.0–7.55 (m, 8 H), 7.55–8.0 (m, 6 H); IR ($CHCl_3$) 1480, 1445, 1395, 1360, 1160, 1025, 1005, 995, 900, 695 cm^{-1}; mass spectrum, *m/e* (relative intensity) 369 (1, $M^+ - CH_3$), 328 (14), 327 (49, $M^+ - t$-Bu), 272 (15), 271 (100), 270 (36), 193 (14), 119 (13). Anal. Calcd for $C_{28}H_{32}O$: C, 87.45; H, 8.39. Found: C, 87.31; H, 8.51.

The second fraction was identified as 1-*tert*-butyl-1,3-diphenylphthalan (**16**): 0.10 g (16%); an oil; NMR 1.13 (s, 9 H), 5.79 (s, 1 H), 6.7–8.2 (m, 14 H); mass spectrum, *m/e* (relative intensity) 313 (1, $M^+ - CH_3$), 272 (19), 271 (100, $M^+ - t$-Bu), 194 (11), 193 (24), 165 (42), 105 (18), 77 (24). Rechromatographing **16** and collecting the central fraction provided an analytical sample. Anal. Calcd for $C_{24}H_{24}O$: C, 87.75; H, 7.38. Found: C, 87.44; H, 7.03.

The third fraction contained *o*-(α-phenylneopentyl)benzophenone (**18**): 0.05 g (8%); mp (from methanol) 65–65.5 °C; NMR 0.97 (s, 9 H), 4.07 (s, 1 H), 7.0–8.1 (m, 14 H); IR (KBr) 1660, 1595, 1580, 1475, 1445, 1365, 1275, 1150, 925, 765, 735, 715, 700, 655, 635; mass spectrum, *m/e* (relative intensity) 313 (3, $M^+ - CH_3$), 273 (14), 272 (92), 271 (100, $M^+ - t$-Bu), 270 (17), 253 (17), 194 (39), 193 (47), 165 (44), 105 (19), 91 (20). Anal. Calcd for $C_{24}H_{24}O$: C, 87.76; H, 7.37. Found: C, 88.00; H, 7.48.

Repeating the preceding reaction using 0.51 g (3.72 mmol) of *tert*-butyl bromide resulted in a marked color change at −70 °C. The crude product was analyzed by gas chromatography as before, with the following retention times relative to **14** (normalized percent peak area, identity): 0.31 (4), 0.53 (1), 0.63 (3, **18**), 0.76 (23, **16**), 0.85 (6), 1.0 (25, **17**), 1.11 (4), 1.21 (13, *o*-dibenzoylbenzene),[20] 1.28 (11, **1**),[20] 1.42 (10).

Repeating the preceding experiment using 0.26 g (1.90 mmol) of *tert*-butyl bromide resulted in a color change from blue to red-brown at −70 °C, but decolorization did not occur on warming. Chromatography of the crude product (0.56 g) as before gave, in order of elution, 0.13 g of a fraction containing three *tert*-butylated compounds (attempts to resolve this mixture were not successful), 0.22 g (36%) of **10**, 0.03 g (6%) of *o*-dibenzoylbenzene, and finally 0.10 g (16%) of **19**: mp (from ethanol) 140–141 °C; NMR 1.32 (s, 9 H), 7.1–7.9 (m, 13 H); IR ($CHCl_3$) 1650, 1605, 1450, 1410, 1365, 1315, 1280, 935, 845 cm^{-1}; mass spectrum, *m/e* (relative intensity) 342 (73 M^+), 286 (21), 265 (14), 209 (100), 152 (20), 105 (12). Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48. Found: C, 84.40; H, 6.39.

Acknowledgment. This research was financially supported by the National Science and Engineering Research Council of Canada. I thank the Centre National de la Recherche Scientifique, Thiais, France, and especially Dr. Z. Welvart both for helpful discussions and for providing me with the time and facilities to prepare this manuscript.

Registry No. **1**, 5471-63-6; **2** (M = Li), 74563-16-9; **2** (M = Na), 74563-17-0; **2** (M = K), 74563-18-1; *cis*-**3**, 21596-49-6; *trans*-**2**, 74563-19-2; *trans*-**4**, 74563-20-5; *cis*-**4**, 74563-21-6; *cis*-**5**, 71176-48-2; *trans*-**5**, 74563-22-7; *cis*-**6**, 74563-23-8; *trans*-**6**, 74563-24-9; **7** (*n* = 2), 74563-25-0; **7** (*n* = 3), 74563-26-1; **7** (*n* = 4), 74563-27-2; **8**, 74577-81-4; **10**, 74563-28-3; **13**, 796-30-5; **16**, 74563-29-4; **17**, 74563-30-7; **18**, 74563-31-8; **19**, 74577-82-5; *o*-dibenzoylbenzene, 1159-86-0; 1,3-diphenyl-4,5,6,7-tetrahydroisobenzofuran, 74563-32-9; $Cl(CH_2)_2Cl$, 107-06-2; $Br(CH_2)_2Br$, 106-93-4; $Cl(CH_2)_3Cl$, 142-28-9; $Br(CH_2)_3Br$, 109-64-8; $Cl(CH_2)_4Cl$, 110-56-5; $Br(CH_2)_4Br$, 110-52-1.

(19) (a) A. Mustafa and M. Kamel, *J. Org. Chem.*, **22**, 157 (1957); (b) C. Dufraisse and R. Priou, *Bull. Soc. Chim. Fr.*, **5**, 502 (1938).

(20) Identified by GC/MS comparison with standards conducted on a Hewlett-Packard HP 5992A instrument using a 1.8 m × 2 mm i.d. glass column packed with 100/120 mesh Aue packing.[21]

(21) F. Karasek and H. Hill, Jr., *Res./Dev.*, **26**, 30 (1975).

Reaction of Ortho Esters with Secondary Amines

Roy A. Swaringen, Jr.,* John F. Eaddy, and Thomas R. Henderson

Wellcome Development Laboratories, Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

Received April 15, 1980

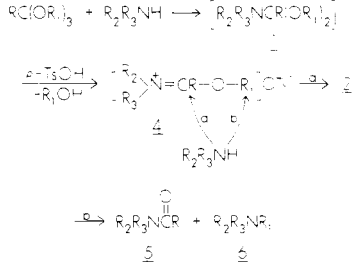
The scope of the reaction of ortho esters with secondary amines has been explored. With *p*-toluenesulfonic acid as catalyst, *N*-alkylanilines and orthoformates gave high yields of *N*-alkylformanilides and *N,N*-dialkylanilines in contrast to previous work with other acid catalysts where ortho amides were produced in low yield. Aliphatic cyclic amines (e.g., morpholine, piperidine) and orthoformates gave the corresponding ortho amides. This constitutes a new convenient synthesis of these useful reagents.

In theory the acid-catalyzed reaction of secondary amines with ortho esters could yield the amide acetals **1**, the ester aminals **2**, or the ortho amides **3**. To date the

$RC(OR_1)_2NR_2R_3$ $RC(OR_1)(NR_2R_3)_2$ $RC(NR_2R_3)_3$
1 **2** **3**

only examples have yielded the ortho amides, and these few examples have been limited to *N*-alkylanilines and orthoformates[1-6] (ortho amides of higher ortho carboxylic acids are unknown[7]). We have attempted to react a variety of secondary amines with ortho esters to explore the

Scheme I



(1) Clemens, D. H.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 2588.

(2) Clemens, D. H.; Shropshire, E. Y.; Emmons, W. D. *J. Org. Chem.* **1962**, *27*, 3664.

(3) Hagedorn, I.; Lichtel, K. E.; Winkelmann, H. D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 702.

(4) Hagedorn, I.; Lichtel, K. E. *Chem. Ber.* **1966**, *99*, 524.

0022-3263/80/1945-3986$01.00/0

Table I. Reactions of *N*-Alkylanilines and Ortho Esters with *p*-Toluenesulfonic Acid as Catalyst[a]

$RC(OR_1)_3$		R_2R_3NH		R_2R_3NCOR		$R_2R_3NR_1$	
R	R_1	R_2	R_3	% conversion	% yield	% conversion	% yield
H	CH_3	CH_3	C_6H_5	63[b]	92	68[b]	98
H	C_2H_5	CH_3	C_6H_5	82	94	84	96
H	CH_3	C_2H_5	C_6H_5	56[b]	91.5	52[b]	85
CH_3	CH_3	CH_3	C_6H_5	80	97.5	81	99

[a] Conversions and yields are estimated on the basis of the integration of the NMR spectrum. [b] Lower conversions with trimethyl orthoformate are believed to be due to loss of the reagent from the steam-jacketed condenser.

Table II. Ortho Amides from Amines and Orthoformates

amine (mol)	orthoformate (mol)	acid (mol)	final temperature, °C	reaction time, h	% yield of ortho amide	method
piperidine (2.0)	triethyl (0.50)	acetic (0.05)	158	22	49	*d*
piperidine (0.64)	triisopropyl (0.16)	acetic (0.016)	123	22	62	*d*
piperidine (1.80)	triethyl (0.90)	acetic (0.06)	144	29.5	44	*b*
piperidine (2.0)	triethyl (0.50)	pivalic (0.05)	140	23	51	*d*
morpholine (0.60)	triethyl (0.40)	pivalic (0.02)	170	1.5	66	*a*
morpholine (0.60)	triethyl (0.40)	KH_2PO_4 (0.02)	170	21.5	57	*a*
morpholine (0.60)	triethyl (0.40)	4-chlorobenzoic (0.02)	156	22	52	*a*
morpholine (0.60)	trimethyl (0.40)	acetic (0.02)	142	24	45	*f*
morpholine (0.30)	triethyl (0.20)	pivalic (0.01)	114	6	62	*e*
2,6-dimethylmorpholine (1.20)	triethyl (0.80)	acetic (0.04)	142	4	52	*c*
morpholine (1.0)	triethyl (0.50)	*p*-toluenesulfonic (0.005)	165	18	57	*a*
morpholine (1.0)	triethyl (0.50)	acetic (0.05)	180	2	63	*a*
N-methylpiperazine (1.0)	triethyl (0.50)	acetic (0.05)	180	2	71	*c*

[a] Straight-bore steam-jacketed condenser. Crystalline product filtered from reaction mixture. [b] Straight-bore steam-jacketed condenser. Product distilled under vacuum. [c] Straight-bore steam-jacketed condenser. Product isolated as pot residue after vacuum distillation. [d] Steam-jacketed condenser packed with glass helices. Product isolated as pot residue after vacuum distillation. [e] Continuous azeotropic distillation of toluene solvent. Crystalline product filtered from reaction mixture. [f] Soxhlet extractor filled with 3-A molecular sieves. Crystalline product filtered from reaction mixture.

scope of this reaction.

N-Alkylanilines. We have confirmed that the reaction of *N*-alkylanilines with orthoformates without catalyst or with hydrochloric or acetic acid as catalyst produced ortho amides in low yields. However, when *p*-toluenesulfonic acid was used as catalyst, the reaction gave high yields of *N*-alkylformanilides **5** (R = H) and *N,N*-dialkylanilines **6**. The essentially equal yields of products **5** and **6** (Table I) suggested that they were formed simultaneously. A possible rationale is offered in Scheme I. The lower nucleophilicity of *p*-toluenesulfonate relative to chloride or acetate may alter the structure of the intermediate **4** so that pathway b is favored. Trimethyl orthoacetate and *N*-methylaniline reacted similarly (Table I).

Aliphatic Secondary Amines. Trimethyl orthoacetate and morpholine gave *N*-acetylmorpholine (46%) and *N*-methylmorpholine (34%). Literature references to reactions of aliphatic amines and ortho esters are limited; however, McElvain and Tate reported obtaining *N*-ethyldibutylamine (22%) and *N,N*-dibutylacetamide (99%) from the reaction of dibutylamine and triethyl orthoacetate at 200–220 °C.[8] They considered the amide product to have arisen by aminolysis of ethyl acetate produced in the reaction. Such a mechanism is considered unlikely in the present work since the steam-jacketed condenser used to remove alcohol would also remove the ester and presumably lower the yield of amide product.

The reaction of morpholine with triethyl orthoformate with either *p*-toluenesulfonic or acetic acid as catalyst gave trimorpholinomethane, **7**, as the major product.[9] This appears to be the first example of the preparation of an aliphatic ortho amide by this method.[10] Trimorpholinomethane had previously been prepared from morpholine and *N,N*-dimethylformamide dimethyl acetal,[5,11] from morpholine, chloroform, and sodium methoxide,[5] and from morpholine and the adduct from *N*-formylmorpholine and dimethyl sulfate.[12] The current synthesis affords modest (45–65%) yields of trimorpholinomethane and offers advantages of convenience and economy over previous methods. The synthesis of ortho amides by this method appears to be limited to cyclic, six-membered-ring amines (e.g., morpholine, piperidine, *N*-methylpiperazine) except for the *N*-alkylanilines mentioned earlier. No ortho amides were isolated or detected in reactions with pyrrolidine or

(5) Scheeren, J. W.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 289.
(6) Wanmaker, W. L. Dissertation, Groningen, 1949.
(7) DeWolfe, R. H. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970; p 448.
(8) McElvain, S. M.; Tate, B. E. *J. Am. Chem. Soc.* **1945**, *67*, 202.
(9) Analysis of the mother liquors by gas chromatography showed the presence of *N*-formylmorpholine, *N*-ethylmorphine, and additional trimorpholinomethane.
(10) Tsuge, O.; Yanagi, K.; Horie, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2171. The authors claimed to have formed an ortho amide from morpholine and triethyl orthoformate; however, no conditions or yields were reported.
(11) Winberg, H. E.; Carnahan, J. E.; Coffmann, D. D.; Brown, M. *J. Am. Chem. Soc.* **1965**, *87*, 2055.
(12) Bredereck, H.; Simchen, G.; Beck, G. *Justus Liebigs Ann. Chem.* **1972**, *762*, 62.

Scheme II

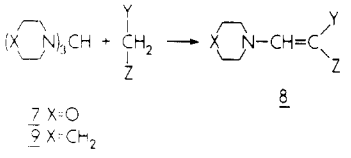


Table III. Reactions of Ortho Amides 7 and 9 with Acidic Methylenes

X	Y	Z	% yield of 8	mp, °C
O	CN	CO_2Et	90	137-138 (lit.[a] 140-141)
O	CN	$CONH_2$	91	169-173 (lit.[b] 173-175)
O	CO_2Et	CO_2Et	71	62-64 (lit.[c] 64-66)
O	p-ClC_6H_4	CN	49	116-117
CH_2	CN	$CONH_2$	71	159-161
O	3,4,5-$(OMe)_3C_6H_2CH_2$	CN	38	105-107 (lit.[d] 115-117)
CH_2	3,4,5-$(OMe)_3C_6H_2CH_2$	CN	68	100-101.5 (lit.[d] 92-93)

[a] A. A. Santilli, W. F. Bruce, and T. S. Osdene, *J. Med. Chem.*, 7, 68 (1974). [b] R. M. Cresswell, J. W. Mentha, and R. Seaman, U.S. Patent 3 864 341 (1974). [c] C. D. Hurd and L. T. Sherwood, *J. Org. Chem.*, 13, 471 (1948). [d] R. M. Cresswell, J. W. Mentha, and R. L. Seaman, British Patent 1 261 455 (1972).

hexamethyleneimine (homopiperidine). Acyclic secondary amines (e.g., dipropylamine, diisobutylamine, and bis(2-ethoxyethyl)amine) likewise did not yield detectable amounts of ortho amides. *N*-Methylbenzylamine and triethyl orthoformate with *p*-toluenesulfonic acid as catalyst gave *N*-benzyl-*N*-methylformamide (56%) and *N*-ethyl-*N*-methylbenzylamine (41%), the same product pattern as seen with the *N*-alkylanilines and this catalyst. The reaction requires removal of the alcohol byproduct which is routinely effected by distillation. Table II summarizes a number of reactions using different acid catalysts and reaction/isolation procedures.

Reactions of Ortho Amides. Ortho amides are useful synthons for introducing a disubstituted aminomethylene group (masked aldehyde equivalent) onto acidic methylene compounds (Scheme II).[13,14] As a class the aliphatic ortho amides are more reactive than orthoformates. Among the ortho amides, reactivity seems to parallel the basicity of the amine. Reactions of trimorpholinomethane, **7**, and tripiperidinomethane, **9**, with acidic methylenes are summarized in Table III.

Experimental Section

Nuclear magnetic resonance spectra (NMR) were recorded on a Varian T60 spectrometer using Me_4Si as an internal standard. Mass spectra were recorded with a Varian MAT CH5 double-focusing spectrometer. Microanalyses were performed in house or by Atlantic Microlabs. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. *N*-Alkylanilines were purified by vacuum distillation. Commercial morpholine, piperidine, and the various ortho esters were used as obtained.

Reaction of *N*-Methylaniline and Triethyl Orthoformate. *N*-Methylaniline (69.4 g, 0.648 mol), triethyl orthoformate (48 g, 0.324 mol), and *p*-toluenesulfonic acid monohydrate (0.6 g, 0.003 mol) were combined and heated to reflux, using a steam-jacketed condenser for continuous removal of ethanol. After 1 h the pot temperature had risen from 127 to 235 °C. The mixture was allowed to cool and stand overnight. Vacuum distillation gave two fractions: bp 42–60 °C (0.15 mm) and bp 62 °C (0.10 mm). The first fraction, 53.7 g, was assayed by NMR spectrometry as 69% (by weight) *N*-ethyl-*N*-methylaniline, 16% *N*-methylaniline, and 15% *N*-methylformanilide. The second fraction, 27.9 g, was essentially pure *N*-methylformanilide.

Trimorpholinomethane (7). Morpholine (87 g, 1.0 mol), triethyl orthoformate (74 g, 0.5 mol), and *p*-toluenesulfonic acid monohydrate (1 g, 0.005 mol) were combined and heated to reflux, using a steam-jacketed condenser for continuous removal of ethanol. After 20 h at reflux the internal temperature had risen to 165 °C, and heating was terminated. The mixture was allowed to cool and stand at room temperature for several hours. The resulting crystals were collected by filtration, washed with ether, and dried in vacuo to yield 58.8 g (65.1%) of **7** as pale yellow crystals: mp 145–151 °C (lit.[5] mp 160–162 °C); NMR ($CDCl_3$) δ 2.75 (t, 12, CH_2N), 3.27 (s, 1, $HC(N)_3$), and 3.65 (t, 12, CH_2O); mass spectrum, *m/e* 270 (M − 1, 0.6%), 185 ($(OC_4H_8N)_2CH^+$, 100%).

A similar preparation from morpholine (54.9 g, 0.63 mol), triethyl orthoformate (62.2 g, 0.42 mol), and glacial acetic acid (1.26 g, 0.021 mol) was complete in 2 h and gave 35.2 g (61.8%) of **7**, mp 137–153 °C.[15]

Ethyl 2-Cyano-3-morpholinoacrylate. Ethyl cyanoacetate (22.6 g, 0.2 mol) was added to a solution of trimorpholinomethane (59.7 g, 0.22 mol) in ethanol at 50 °C. After a mild exotherm (to 54 °C) the solution was allowed to stir for several minutes without external heating or cooling. When the temperature had dropped to 35 °C, the mixture was filtered, and the crystals were washed with ether and dried to yield 30.3 g (72%) of ethyl 2-cyano-3-morpholinoacrylate: mp 137–138 °C (lit.[16] mp 140–141 °C); NMR ($CDCl_3$) δ 1.3 (t, 3, CH_3CH_2O), 3.8 (br, 8, OC_4H_8N), 4.2 (q, 2, CH_3CH_2O), 7.7 (s, 1, CH=).

Concentration of the mother liquor gave a second crop of 7.5 g (18%) melting at 138–139 °C.

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.73; N, 13.33. Found: C, 57.01; H, 6.93; N, 13.21.

2-(3,4,5-Trimethoxybenzyl)-3-morpholinoacrylonitrile. 3-(3,4,5-Trimethoxyphenyl)propionitrile (4.4 g, 20 mmol) was melted in a 250-mL flask equipped with a mechanical stirrer, thermometer, and gas-inlet tube. Trimorpholinomethane (5.4 g, 20 mmol) was added, and a nitrogen atmosphere was established. The temperature was raised to 150 °C and maintained for 3 h. After the mixture was cooled to room temperature, the solid was washed thoroughly with ether and filtered. The crude product was purified by treatment with a warm mixture of chloroform–hexane (1:1) and filtration to remove a small amount of insolubles. Evaporation of the solvent gave 2.4 g (38%) of 2-(3,4,5-trimethoxybenzyl)-3-morpholinoacrylonitrile, mp 105–107 °C, identified by TLC and NMR.

2-(*p*-Chlorophenyl)-3-morpholinoacrylonitrile. A solution of 29.9 g (0.11 mol) of trimorpholinomethane and 15.2 g (0.10 mol) of (*p*-chlorophenyl)acetonitrile in 175 mL of dry ethanol was heated at reflux for 26 h. The mixture was cooled and the solvent was removed in vacuo. The residual solid was washed with water to remove morpholine. The crude product was taken up in acetone (300 mL) and crystallized by adding water and cooling to yield 12.1 g (48.8%) of yellow crystals: mp 116–117 °C; NMR ($CDCl_3$) δ 3.73 (br, 8, OC_4H_8N), 6.83 (s, 1, HC=), 7.27 (s, 4, p-ClC_6H_4).

Anal. Calcd for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26. Found: C, 62.47; H, 5.36; N, 11.20.

Tripiperidinomethane (9). Piperidine (153.3 g, 1.80 mol), triethyl orthoformate (133.4 g, 0.90 mol), and acetic acid (3.6 g, 0.06 mol) were combined in a 500-mL three-neck round-bottom flask equipped with a thermometer and a steam-jacketed condenser. The reactants were heated to a gentle reflux (initial pot temperature ~112 °C). The heat input was gradually increased during 29.5 h of relux; the final pot temperature was 144 °C. The reaction solution was allowed to cool and stand overnight and then

(13) Bredereck, H.; Effenberger, F.; Brendle, T. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 132.
(14) Weingarten, H.; Edelman, N. K. *J. Org. Chem.* **1967**, *32*, 3293.
(15) Despite the wide range in the melting point the product appeared to be quite pure on the basis of a 100-MHz NMR spectrum.
(16) Santilli, A. A.; Bruce, W. F.; Osdene, T. S. *J. Med. Chem.* **1974**, *7*, 68.

was concentrated in vacuo. High-vacuum distillation of the crude product gave 19.3 g of *N*-formylpiperidine, bp ~60–70 °C (0.1–0.2 mmHg), and 69.6 g (43.7% yield) of tripiperidinomethane, bp 98–106 °C (0.05–0.1 mmHg) [lit.[5] bp 107–110 °C (0.1 mm)]; NMR ($CDCl_3$) δ 1.43 (br s, 18, $(CH_2)_3$), 2.58 (br s, 12, CH_2N), 3.12 (s, 1, $HC(N)_3$).

2-Cyano-3-piperidinoacrylamide. Tripiperidinomethane (58.4 g, 0.22 mol) and cyanoacetamide (16.8 g, 0.20 mol) were combined in 200 mL of ethanol and stirred for 4.5 h at room temperature. After the mixture cooled, the crystals were filtered, washed, and dried to give 25.3 g (71%) of 2-cyano-3-piperidinoacrylamide: mp 159–161 °C; NMR ($CDCl_3$) δ 1.70 (s, 6, $(CH_2)_3$), 3.50 and 3.90 (2 br s, 4, $N(CH_2)_2$), 5.95 (br s, exchanges with D_2O, 2, NH_2), 7.90 (s, 1, =CH).

Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.39; H, 7.39; N, 23.53.

2-(3,4,5-Trimethoxybenzyl)-3-piperidinoacrylonitrile. Tripiperidinomethane (1.86 g, 7 mmol) and 3-(3,4,5-trimethoxyphenyl)propionitrile (1.11 g, 5 mmol) were combined quickly and heated for 18 h at 135 °C (pot temperature) under house vacuum (125 mmHg). The resultant brown oil was taken up in ether (3 mL) and placed on a short silica gel column. The column was washed with dichloromethane and the washings were concentrated to an oil which solidified on standing. The product was washed with ether (3 × 10 mL) and dried to yield 0.88 g (55.5%) of a beige solid (mp 100–101.5 °C), whose NMR spectrum was consistent with the desired structure. A second crop of light yellow solid (mp 86–92 °C) was isolated from the combined ether washings. NMR analysis showed the second crop to be an 85:15 mixture of expected product and starting nitrile. The combined assayed yield for the two crops was 1.075 g (68.0%).

Acknowledgment. We express our appreciation to Dr. David A. Yeowell for his support of this work and for useful comments and suggestions. The competent technical assistance of Mr. Steven L. Cook and Miss Eddie M. Lyon is also gratefully acknowledged.

Registry No. 5 (R = H, R_2 = CH_3, R_3 = C_6H_5), 93-61-8; **5** (R = H, R_2 = C_2H_5, R_3 = C_6H_5), 5461-49-4; **5** (R = CH_3, R_2 = CH_3, R_3 = C_6H_5), 579-10-2; **6** (R_1 = CH_3, R_2 = CH_3, R_3 = C_6H_5), 121-69-7; **6** (R_1 = C_2H_5, R_2 = CH_3, R_3 = C_6H_5), 613-97-8; **7**, 22630-09-7; **8** (X = O, Y = CN, Z = CO_2Et), 6630-64-4; **8** (X = O, Y = CN, Z = $CONH_2$), 25229-97-4; **8** (X = O, Y = CO_2Et, Z = CO_2Et), 62648-61-7; **8** (X = O, Y = *p*-ClC_6H_4, Z = CN), 74552-29-7; **8** (X = CH_2, Y = CN, Z = $CONH_2$), 72915-03-8; **8** (X = O, Y = 3,4,5-$(OMe)_3C_6H_2CH_2$, Z = CN), 30077-81-7; **8** (X = CH_2, Y = 3,4,5-$(OMe)_3C_6H_2CH_2$, Z = CN, 30077-83-9; **9**, 22630-08-6; tris(2,6-dimethylmorpholino)methane, 72915-01-6; tris(*N*-methylpiperazino)methane, 22630-10-0; *N*-methylaniline, 100-61-8; *N*-formylpiperidine, 2591-86-8; *N*-formylmorpholine, 4394-85-8; *N*-ethylmorpholine, 100-74-3; $HC(OCH_3)_3$, 149-73-5; $HC(OC_2H_5)_3$, 122-51-0; $CH_3C(OCH_3)_3$, 1445-45-0; $CH_3(C_6H_5)NH$, 100-61-8; $C_2H_5(C_6H_5)NH$, 103-69-5; piperidine, 110-89-4; morpholine, 110-91-8; 2,6-dimethylmorpholine, 141-91-3; *N*-methylpiperazine, 109-01-3; $HC(O\text{-}i\text{-}Pr)_3$, 4447-60-3; $CH_2(CN)CO_2Et$, 105-56-6; $CH_2(CN)CONH_2$, 107-91-5; $CH_2(p\text{-}ClC_6H_4)CN$, 140-53-4; $CH_2(3,4,5\text{-}(OMe)_3C_6H_2CH_2)CN$, 49621-50-3; $CH_2(CO_2Et)_2$, 105-53-3.

Preparation and Rearrangement of Trichothecane-Like Compounds. Synthesis of Aplysin and Filiformin

David J. Goldsmith,* Thottathil K. John, Cecil D. Kwong, and George R. Painter III

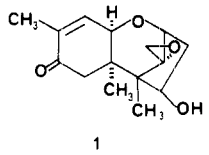
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received March 21, 1980

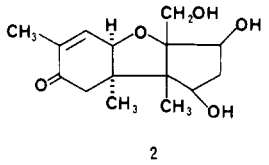
The preparation of three trichothecane-like compounds, olefin **9** and epoxides **10** and **23**, is reported. Subjection of **9** to conditions of acid-catalyzed rearrangement followed by hydrogenation leads to (±)-aplysin. The anti epoxide **10** also undergoes rearrangement but with migration of the aryl group rather than the pyranyl oxygen to give **26**. Syn epoxide **23** does not undergo skeletal rearrangement. Hydrogenation of olefin **9** affords (±)-filiformin.

Introduction

The trichothecane group of sesquiterpenoid fungal metabolites undergoes a variety of acid-catalyzed rearrangements.[1] Trichothecolone, **1**, for example, when treated with aqueous acid affords the rearranged apotrichothecane triol **2**.[2] The ring system and the substituents

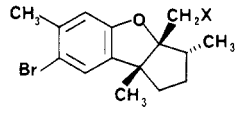


1

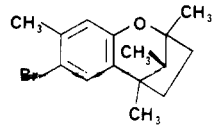


2

at the junction positions of the two five-membered rings of this apotrichothecane bear a striking resemblance to the structural features of several members of the laurane class of marine natural products.[3,4] In particular, the relationship can be seen between rearrangement product **2** and aplysin, **3**,[5] and aplysinol, **4**.[5,6] In addition, the bridged ring system of **1** is mirrored in the structure of another laurane substance, filiformin, **5** (a compound of somewhat dubious natural parentage).[7]



3, X = H
4, X = OH



5

(1) (a) Tamm, Ch. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 64. (b) Schumacher, R.; Gutzwiller, J.; Tamm, Ch. *Helv. Chim. Acta* **1971**, *54*, 2080. (c) Godtfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1965**, *19*, 1088. (d) Adams, P. M.; Hanson, J. R.; *J. Chem. Soc., Perkin Trans. 1* **1972**, 2783.

(2) Gutzwiller, J.; Mauli, R.; Sigg, H. P.; Tamm, Chm. *Helv. Chim. Acta* **1964**, 47, 2234.

(3) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. "Natural Products Chemistry"; Academic Press: New York, 1974; Vol. 1., pp 154–161.

(4) Schuer, P. J. "Chemistry of Marine Natural Products"; Academic Press: New York, 1973.

(5) Yamamura, S.; Hirata, Yi; *Tetrahedron* **1963**, *19*, 1963.

(6) McMillan, J. A.; Paul, I. C.; Caccamese, S.; Rinehart, K. L. *Tetrahedron Lett.* **1976**, 4219.

0022-3263/80/1945-3989$01.00/0