Another sample of **5a** (1 g) was fused at 120 °C for about 0.5 h during which time an equivalent amount of water was liberated, and the melt resolidified as a white solid. The solid was recrystallized to give **4a** in the form of white flakes (0.9 g, mp 147–148 °C).

The aniline solution, from which **5a** was removed by filtration, was evaporated to dryness at <1 mmHg pressure and 80 °C. The residue was digested with 10% aqueous HCl, leaving a white, saltlike residue (15 g) which was recrystallized from hot water to give the hydrochloride of **4a** in the form of pearl-white platelets (mp 275–277 °C; no depression with an authentic sample). The aqueous acid extract was neutralized with NaOH. A yellowish-white powder precipitated and was removed by filtration. This powder (2.5 g) was recrystallized from heptane to give *N,N'*-diphenylacetamidine (**7**) in the form of white crystals (mp 126–127 °C; no depression with an authentic sample).[9] The compound was also identified by its ir spectrum, identical with that of an authentic sample.

When 0.16 mol of **1a** was made to react with **2a** as solvent, 54% of **1a** was isolated as **5a**, 30% as **4a**, and 15% as **7**.

2. In *p*-Toluidine (2b) to Give 5b. Acetylanthranil (0.1 mol) was dissolved in **2b** (0.6 mol) to give a clear solution which became turbid soon thereafter as the product began to precipitate from solution. Precipitation appeared to be complete after 4 h. The precipitate (mp 119–120 °C) was collected by filtration and washed with Et_2O. The mother liquor containing the excess aniline was diluted 20-fold with ether and additional precipitate (mp 119–120 °C) formed which was also collected by filtration. The combined precipitates represented a 95% yield of *N*-(2-carboxyphenyl)-*N'*-(*p*-tolyl)acetamidine (**5b**), identified by its ir spectrum and its elemental analysis.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 72.0; H, 6.1; N, 10.3.

A sample of **5b** (1.0 g) was dissolved in 0.5% aqueous base to give a clear solution. A few minutes thereafter, the solution became cloudy with the formation of the quinazolone, which precipitated as a white powder. Precipitation appeared to be complete within 1 h, and the product (0.9 g) was collected by filtration, dried, and recrystallized from heptane to give *N*-(*p*-tolyl)-2-methylquinazol-4-one (**4b**) in the form of long, flat needles (mp 151–152 °C). The assigned structure of **4b** was verified by its ir spectrum.

3. In *p*-(Dimethylamino)aniline (2c) to Give 5c. Acetylanthranil (0.1 mol) was dissolved at room temperature in **2c** (0.2 mol) to give a clear solution, which became a semisolid mixture within 4 h. The mixture was diluted with Et_2O and separated by filtration. The amount isolated represented 96% of the expected amidine salt, **5c**, whose assigned structure was verified by its ir spectrum and its elemental analysis.

Anal. Calcd for $C_{17}H_{19}O_2N_3$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.5; H, 6.6; N, 14.2.

The salt began to melt at 160 °C, but it was converted at this temperature to the corresponding quinazolone, **4c**, which solidified from the melt. A sample of the amidine salt (1 g), contained in a test tube, was fused in an oil bath kept at 180 °C. The salt melted rapidly with evolution of water vapor which was condensed on the cool upper portion of the test tube. The melt resolidified within a few minutes. The product was recrystallized from ethanol–water solution to give *N*-(*p*-dimethylaminophenyl)-2-methylquinazol-4-one (**4c**), in the form of white crystals (0.8 g, mp 227–228 °C). The compound was identified by its ir spectrum and elemental analysis.

Anal. Calcd for $C_{17}H_{17}ON_3$: C, 73.09; H, 6.14; N, 15.04; mol wt, 279.4. Found: C, 73.1; H, 6.3; N, 14.9; mol wt, 278.

Another sample of **5c** (2.0 g) was dissolved in dilute aqueous NaOH. Precipitation of the quinazolone, **4c**, began within 5 min and was complete within 1 h. The product (1.8 g) was identified as **4c** by its ir spectrum and its melting point, 227–228 °C, which showed no depression when mixed with the product obtained by fusion.

Reaction of Benzoylanthranil (1b) with Aniline to Give *o*-Benzamidobenzanilide (3b). Benzoylanthranyl (3 g, mp 122 °C), which was prepared according to the procedure of Anschutz,[10] was allowed to react overnight at reflux temperature with aniline (3 g) in benzene (50 ml). The product separated in the form of a white powder (3.8 g, mp 286–287 °C). It was identified as *o*-benzamidobenzanilide (**3b**) by its melting point and ir spectrum, which were identical with those of an authentic sample.

Acknowledgment. The author is indebted to Dr. J. J. McBrady for interpretation of the ir and NMR spectra.

Registry No.—**1a**, 525-76-8; **1b**, 1022-46-4; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 99-98-9; **4a** HCl, 52692-90-7; **4b**, 22316-59-2; **4c**, 58426-38-3; **5a**, 34264-61-4; **5b**, 58426-41-8; **5c**, 58426-42-9; **7**, 621-09-0; anthranilic acid, 118-92-3.

References and Notes

(1) Presented before the 9th Great Lakes Regional Meeting of the American Chemical Society, St. Paul, Minn., June 1975, Abstract No. 521.
(2) (a) J. C. Sheehan and G. D. Daves, *J. Org. Chem.*, **29**, 3599 (1964); (b) H. Herlinger, *Angew. Chem.*, **76**, 437 (1964); (c) G. Doleshall and K. Lambert, *Tetrahedron Lett.*, 1195 (1963); (d) A. F. Hegarty and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 6568 (1970).
(3) (a) I. Serlin and A. H. Markhart, *J. Polym. Sci.*, **60**, S-19 (1962); (b) B. Sillion and G. deGaudemaris, French Patent 1 423 631 (1965).
(4) L. A. Errede, U.S. Patent 3 367 977 (1967); 3 408 326 (1968); 3 440 228 (1969).
(5) (a) G. Heller and G. Fiesselman, *Justus Liebigs Ann. Chem.*, **324**, 134 (1902); (b) R. Anschutz and O. Schmidt, *Ber.*, **35**, 3470 (1902); (c) M. T. Bogert and V. J. Chambers, *J. Am. Chem. Soc.*, **27**, 653 (1905); (d) M. T. Bogert and H. A. Seil, *ibid.*, **27**, 1305 (1905); (e) *ibid.*, **29**, 517 (1907); (f) M. T. Bogert and A. Bender, *ibid.*, **36**, 576 (1914).
(6) (a) J. K. Lundquist in "Chemistry of Carbon Compounds", Vol. IVB, E. H. Rodd, Ed., Elsevier, Amsterdam, 1958, pp 1299–1318; (b) R. C. Elderfield, Ed., "Heterocyclic Compounds", Vol. 6, Wiley, New York, N.Y., 1957, p 353.
(7) R. A. Scherrer and H. R. Beatty, *J. Org. Chem.*, **37**, 1681 (1972).
(8) N. Walker, *J. Am. Chem. Soc.*, **77**, 6698 (1955).
(9) A. W. Hoffman, *Z. Chem.*, 161 (1866); Beilstein, **12**, 248.
(10) R. Anschutz, O. Schmidt, and A. Greiffenberg, *Ber.*, **35**, 3481 (1902).

Acylanthranils. 2. The Problem of Selectivity in the Reaction of Acetylanthranil with Anilines

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Anilines attack acetylanthranils preferentially at the carboimino center rather than at the carbonyl center despite the greater reactivity of the latter group toward nucleophilic agents. Anthranilic acid is a notable exception that gives predominantly *o*-(*o*-acetamidobenzamido)benzoic acid, the product produced via reaction at the carbonyl site.

Reinvestigation[1] of the reaction of benzoxazinones (i.e., acylanthranils), **1**, with anilines, **2**, showed that the diamide, **3**, and quinazolone, **4**, products are formed via alternate pathways a and b as shown in Chart II of ref 1, and not sequentially **4** from **3** as was suggested by earlier investigators.[2]

Acylanthranils undergo many of the reactions of acid anhydrides, but at a much slower rate. They can be considered in effect as cyclic mixed anhydrides that react with amines via two alternative electrophilic sites, namely at the carbonyl group to give via pathway b a neutral diamide **3**, or at the carboimino group to give via pathway a an amidine salt **5**. Presumably the reaction via both pathways is kinetically first

Table I. Reaction Products of 1 with Anilines, H_2NPhR

Aniline	R substituents	Rxn conditions: Solvent	Rxn conditions: Temp, °C	Mp, °C (yield)[f] of products: 5	4	3	a/b = 5 and/or 4/3
a	None	*a*	RT	115–116 (80)	147–148 (15)		>50/1
b	*p*-CH_3	*a*	RT	119–120 (85)	151–152 (13)		>50/1
c	*p*-$(CH_3)_2N$	*a*	RT	158–160 (60)	227–228 (36)		>50/1
d	*p*-H_2N	*a*	RT	96–98 (90)	226–227 (8)		>50/1
e	*p*-CH_3O	*a*	RT	123–124 (65)	267–268 (33)		>50/1
f	*p*-CO_2H	*b*	60		280–281 (30)[g]		>50/1
g	*m*-CF_3	*c*	100		139–140 (85)[g]		>50.1
h	*m*-OH	*d*	RT	130–135 (81)	122–126 (17)		>50/1
i	*o*-CH_3	*a*	RT		113–114 (85)[g]		>50/1
j	*o*-Et	*d*	RT		249–250 (55)[g]		>50/1
k	*o*-CH_3O	*a*	RT		131–132 (70)[g]		>50/1
l	2,4,6-$(CH_3)_3$	*d*	RT	122–123° (70)	99–100 (15)[g]		>50/1
m	2,6-$(Et)_2$	*d*	RT		108–109 (69)[g]		>50/1
n	*o*-CO_2H	*e*	Reflux		255–257 (5)	215–216 (92)	1/18

[a] Benzene. [b] Pyridine. [c] Neat. [d] Et_2O. [e] Toluene. [f] % acetylanthranil units isolated as product indicated given in brackets. [g] Most of the remainder of the acetylanthranil units were isolated as *o*-acetamidobenzoic acid indicating incomplete reaction and/or reaction with H_2O liberated via cyclodehydration of **5** to give **4**.

order with respect to **1** and to **2**, so that the observed product ratio should be a measure of the ratio of the rates of reaction for the corresponding pathways, i.e.

$$\frac{\text{4 and/or 5}}{\text{3}} = \frac{\text{reaction via pathway a}}{\text{reaction via pathway b}} = \frac{k_a}{k_b}$$

The results obtained by the earlier investigators,[2] who caused numerous acylanthranils to react with numerous amines, suggest that b is the preferred reaction pathway (i.e., $b/a \gg 1$), which is consistent with the known relative reactivity of anhydride >C=O vs. >C=N– groups. Our own result[1] with benzoylanthranil (i.e., 2-phenyl-4*H*-benzoxazin-4-one, **1a**), was also consistent with this generality. On the other hand, the corresponding acetamidine salts were obtained exclusively when acetylanthranil (i.e., 2-methyl-4*H*-benzoxazin-4-one, **1b**) was made to react with aniline, *p*-toluidine, and *p*-dimethylaminoaniline (i.e., $a/b \gg 1$), which is inconsistent with the above generality. It was of interest, therefore, to investigate this reaction further to determine which set of results was the exception and why.

To this end, it was necessary to establish a convenient separation and identification procedure, which would permit a rapid completion of the materials balance for each sample. The chemical properties of the products are sufficiently different to permit separation by conventional chemical procedures as described previously. These procedures were simplified by utilizing an equivalent amount of amine instead of an excess in a neutral solvent to ensure conversion to a product mixture of no more than three major components. The separation sequence was standardized as described in the Experimental Section. The materials balance data indicated that usually more than 95% of the reactants were recovered as one or more of three products plus *o*-acetamidobenzoic acid which is formed via hydrolysis of unreacted acetylanthranil. In most cases, the structural assignment of the product isolated could be verified on the basis of its ir spectrum, since the characteristic absorption patterns for each product as a class were established with model components as summarized in the Experimental Section. Experience gained in the separation of known mixtures of these components showed that small amounts of **3** might sometimes be missed, if it were present as a minor component of a mixture that was 99% **4** or its conversion product **5**. Conversely, small amounts of **5** (or **4**) might sometimes be missed, if it were present as a minor component of a mixture that was 98% **3**. It was decided, therefore, to interpret conservatively in this and subsequent studies the isolation of **4**, or its precursor **5**, exclusive of **3** as $a/b > 50/1$, and the isolation of **3** exclusive of **4** (or **5**) as $a/b < 1/25$. It was also decided to round all values of a/b within this range to the nearest whole number to ensure emphasis on the qualitative conclusions rather than the quantitative. The data obained in this investigation, using aromatic amines **a–n**, are summarized in Table I.

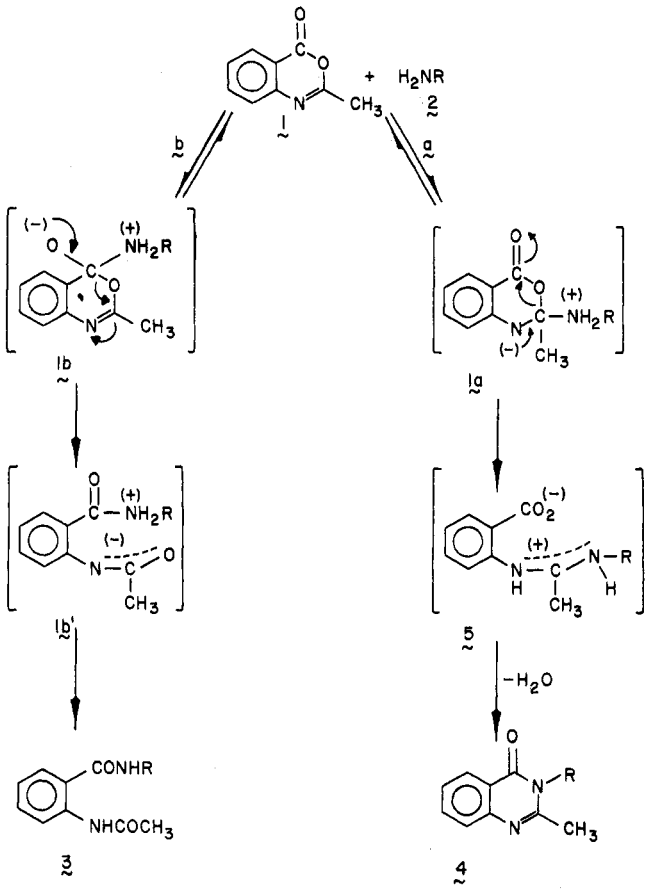
These results show clearly that anilines, with the notable exception of anthranilic acid (**2n**), attack acetylanthranil at the carboimino center rather than the carbonyl center. This generalization is contrary to that expected on the basis of the relative reactivity of the anhydride >C=O and >C=N– groups at the 4 and 2 positions of **1**, respectively. It was suggested by Katritzky[3] that the explanation may lie in the relative stability of the ionic intermediates for the alternative pathways, rather than in the competitive rates for initial attack by the nucleophile on the alternative electrophilic centers as shown for example in Chart I.

Addition of the amine to acetylanthranil gives reversibly either zwitterion intermediate **1a** or **1b**. These cyclic intermediates can open to give respectively **5**, which is relatively stable, and **1b′**, which forms **3** immediately via a proton shift. It was pointed out by one of the referees that the principal net effects in these competitive ring openings is the transfer of a negative charge from N to O, when going from **1a** to **5**, and from O to N, when going from **1b** to **1b′**. Since O is more electronegative than N, the former transfer should be favored over the latter, and consequently pathway a occurs preferentially despite the fact that the first step along pathway b may be faster than the corresponding step along pathway a.

This result is similar to that observed when a mixed anhydride such as $CH_3CO_2COCF_3$ is made to react with a nucleophile. It is the fluorocarboxy anion $CF_3CO_2^-$ that is the more stable leaving group, despite the fact that the carbonyl attached to the fluorocarbon group in the more electrophilic center.[4] Similarly, $CF_3SO_2OCOCH_3$ is an outstanding acetylating agent that produces $CF_3SO_3^-$ as the more stable anion.[5]

Although anilines react with acetylanthranil preferentially via pathway a, the primary product **5** is not always isolated as a stable intermediate, even at room temperature. The derivatives of para-substituted anilines and aniline itself precipitate at room temperature as fast as they are formed in a neutral solvent, which serves to prevent cyclodehydration in solution. These amidine salts are usually quite stable as crystalline solids at room temperature. These intermediates, however,

Chart I



are soluble in basic solvents, such as pyridine, so that they are converted rather rapidly, when prepared in these media, to the corresponding quinazolones, especially at somewhat higher temperature. The acetamidine salt derivatives of ortho-substituted anilines, however, are usually not isolated, even when prepared in neutral solvent at room temperature. These derivatives are more soluble and tend to undergo cyclodehydration rapidly in the presence of unreacted amine to give the corresponding quinazolone. The water, liberated in this cyclization, reacts in turn with residual acetylanthranil to give acetylanthranilic acid,[1] which lowers proportionately the yield of products formed with the amine as indicated by somewhat lower yields (ca. 80% instead of ca. 95%) realized with the anilines **f, g, i, j, k,** and **m.** The acetamidine salt derivative of 2,4,6-trimethylaniline was the only ortho-substituted aniline that afforded an isolable intermediate owing to its insolubility. This salt, however, was unstable even in the solid state, since it underwent cyclodehydration within a few months at room temperature.

In view of the ease with which acetamidine derivatives of ortho-substituted anilines undergo cyclodehydration to the stable quinazolone, the observation that anthranilic acid (**2n**) reacts with **1** via pathway b instead of a is all the more noteworthy, since it indicates that this inversion in selectivity is attributable to site differentiation at the moment of attack by the amine rather than manifestations of equilibrium conditions that ensue this event. One suspects immediately that this inversion with anthranilic acid is due to intramolecular hydrogen bonding with the ortho-carboxylic acid group, which decreases the nucleophilicity of the amino group electronically and sterically. It was concluded, however, that this result is not due primarily to simple decreased basicity caused by the electron-withdrawing effect of the electronegative substituent, since the selectivity ratio a/b was not affected either by a meta CF_3 group (aniline, **3g**) or by a para CO_2H group (aniline, **3f**)

Table II. Relevant Ir Absorption Patterns for Product Characterizations

Acetylanthranil (1)	Sharp band at 5.7 μ for semianhydride >C=O Sharp band at 6.1 μ for >C=N–
N-Acetylanthranilic acid (6)	Broad absorption from 3.3 to 4.5 μ for acid OH v sh band at 5.9 μ for acid C=O v sh band at 6.1 μ for amide C=O sh band at 6.6 μ for NH
Acetamidines 5	Broad absorption from 3.3 to 4.2 μ for internal salt Band at ca. 6.3 μ for salt carbonyl
Quinazolones 4	sh band at ca. 5.9 μ for –CONR– carbonyl sh band at ca. 6.1 μ for >C=N–
o-Acetamidobenzamides 3	sh band at ca. 3.0 μ for NH sh band at ca. 6.0 μ for amide C=O Band at ca. 6.5 μ for NH band

despite the fact that higher temperatures were required in both cases to compensate for the decreased reactivity of the nucleophile. In other words, these electronegative substituents on the aromatic amine served only to decrease markedly the overall reaction rate, $k_a + k_b$, but did not affect significantly the relative ratio k_a/k_b, which determines selectivity.

More experimentation is planned to elucidate whether this change in selectivity is indeed due to some form of steric hindrance, as suspected, or to a change in mechanism, both owing to intramolecular hydrogen bonding of the nucleophilic center with the ortho carboxylic acid.

Experimental Section

General Procedure for Reaction of Acetylanthranil with Amines. Acetylanthranil (**1**, 0.03 mol) and an equivalent weight of the amine **2** were dissolved in a neutral solvent (ca. 50 ml, usually benzene or Et_2O), and reaction was allowed to occur at room temperature overnight. If the corresponding acetamidine salt, **5**, separated from solution, it was removed by filtration and washed with fresh solvent. Otherwise the solution was taken directly to dryness at ca. 60 °C by evaporation under vacuum. The residue was leached with dilute aqueous base to remove **5** and/or residual **1**. The alkaline extract was allowed to remain at room temperature overnight to ensure conversion of solvated **5** to insoluble quinazolone, **4**, which was removed conveniently by filtration. Any residual **1** was recovered as *N*-acetylanthranilic acid by acidification of the mother liquor. The residue, from which the acid components were removed by extraction with base, was then extracted with dilute acid to dissolve **4** and/or residual unreacted **2**. Neutralization of this extract with dilute base caused precipitation of any quinazolone, which was collected by filtration and purified further by recrystallization from a suitable solvent, usually methanol. Any residue that resisted sequential extraction with aqueous base and acid was purified further by recrystallization from a suitable solvent, usually heptane or methanol, to give the *o*-acetamidobenzanilide, **3**, in crystalline form.

After the products were separated chemically as described above, their expected structural assignment was verified spectrophotometrically by their ir spectra. The relevant ir absorption patterns which are characteristic for the starting material and all the possible products are given in Table II.

The known chemistry and limited possibilities usually permitted easy differentiation and assignment of structure on the basis of these ir patterns. In cases of doubt, however, the tentative assignment was substantiated by the corresponding NMR data and/or elemental analysis data, which were consistent with the assigned structures. A sample of the acetamidine salt, **5**, was usually converted to the corresponding quinazolone, **4**, by solution in dilute aqueous base at room temperature and subsequent separation of the precipitate by filtration.

Chemical separation of the product mixture and isolation into its acid, base, salt, and neutral components as described above usually accounted for about 95% of the acetylanthranil allowed to react with the amine in question. The melting points and the percent anthranil units isolated as the respective products of reaction with amines **2a–n** are given in Table I.

Registry No.—1, 525-76-8; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 99-98-9; **2d**, 106-50-3; **2e**, 104-94-9; **2f**, 150-13-0; **2g**, 98-16-8; **2h**, 591-27-5; **2i**, 95-53-4; **2j**, 578-54-1; **2k**, 90-04-0; **2l**, 88-05-1; **2m**, 579-66-8; **2n**, 118-92-3; **3n**, 58426-37-2; **4a**, 2385-23-1; **4b**, 22316-59-2; **4c**, 58426-38-3; **4d**, 27440-42-2; **4e**, 30507-16-5; **4f**, 4005-05-4; **4g**, 1788-98-3; **4h**, 40671-68-9; **4i**, 72-44-6; **4j**, 7432-25-9; **4k**, 4260-28-0; **4l**, 58426-39-4; **4m**, 58426-40-7; **4n**, 4005-06-5; **5a**, 34264-61-4; **5b**, 58426-41-8; **5c**, 58426-42-9; **5d**, 58426-43-0; **5e**, 58426-44-1; **5h**, 58426-45-2; **5l**, 58426-46-3; **6**, 89-52-1.

References and Notes

(1) Part 1: L. A. Errede, *J. Org. Chem.*, preceding paper in this issue.
(2) (a) G. Heller and G. Fiesselman, *Justus Liebigs Ann. Chem.*, **324**, 134 (1902); (b) R. Anschutz and O. Schmidt, *Ber.*, **35**, 3470 (1902); (c) M. T. Bogert and V. J. Chambers, *J. Am. Chem. Soc.*, **27**, 653 (1905); (d) M. T. Bogert and A. Bender, *ibid.*, **36**, 576 (1914).
(3) A. Katritsky, private communication.
(4) G. A. Olah, "Friedel-Crafts Chemistry", Wiley, New York, N.Y., 1973, p 134.
(5) A. Germain and A. Commeyrais, *J. Chem. Soc., Chem. Commun.*, 1345 (1972).

The Chemistry of Hindered Systems. 2. The Acyloin Reaction—an Approach to Regiospecifically Hydroxylated Tetramethylazacycloheptane Systems

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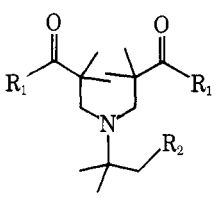
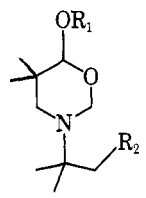
An unusually stable ϵ-lactone, **9**, has been synthesized in high yield by treating mixed animal **7** with 2 equiv of the Grignard reagent generated from ethyl 2-bromoisobutyrate in ether at 0–10 °C. A solvent dependence for this reaction was observed. Reaction of ester lactone **9** under modified acyloin conditions (5 equiv of chlorotrimethylsilane was used as an anion trapping agent) gave acyloin **18** in 68% yield. Infrared studies of the OH stretch region of **18** allowed assignment of several hydrogen bonds and helped to establish possible conformations of **18**. Reduction of **18** with $NaBH_4$ in ethanol at 25 °C was found to occur stereoselectively giving only cis triol **22**. Reduction of **18** with $LiAlH_4$ in refluxing THF gave a 9:1 ratio of cis **22** to trans **24**. The stereochemistry of the triols was established by ^1H NMR techniques employing both achiral and chiral shift reagents and by their ^{13}C NMR spectra. Oxidation of **22** was found to give dialdehyde **5** which was shown to exist in its ϵ-hemiacetal form **25**. In separate experiments, **25** was found to be unstable to prolonged exposure (8 days) to methanol at 25 °C or to heating at 100 °C for 3 h giving, in both cases, aldehyde **26** in high yield. Stereoelectronically controlled reverse Mannich reactions are postulated to explain the latter results. Several molecules, **8** (see ref 6) and **10**, isolated in these studies have been shown to display some anticancer activity.

Our continuing interest in the syntheses[1] and properties[2] of hindered *N-tert*-butyl-3,3′-iminodiesters such as **1** and its aldehyde analogue **2**, which has been shown to undergo a facile rearrangement in alcoholic solvents to give 6-alkoxytetrahydro-1,3-oxazines **3**,[1b,3] a new class of molecules which have been shown to display some anticancer properties,[4] has prompted us to undertake a study of the related hydroxylated systems **4**,[5] **5**, and **6** which we feel might be expected to show



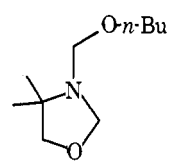
1, R_1 = OEt; R_2 = H
2, R_1 = R_2 = H
4, R_1 = OEt; R_2 = OH
5, R_1 = H; R_2 = OH



3a, R_1 = CH_3; R_2 = H
3b, R_1 = Et; R_2 = H
6, R_1 = CH_3; R_2 = OH

different solubility characteristics. Our efforts directed toward the syntheses of these molecules and studies of their properties will be discussed.

Synthesis of Diester 4 and Lactone 9. Since there are no regiospecific procedures for attaching an OH group to an unactivated alkyl group (e.g., the *tert*-butyl group on diester **1**), a modification of the approach used to synthesize **1**[2] which would allow incorporation of the desired OH group on **4** was devised. Mixed aminal **7** was prepared in 73% yield by treating 2-methyl-2-amino-1-propanol with 2 equiv of formaldehyde and 1 equiv of *n*-butyl alcohol. A minor product, bisoxazolidine **8**, was also isolated from this reaction in ca. 20% yield and was later synthesized by an independent route.[6]



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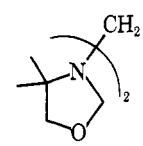

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Treatment of aminal **7** (Scheme I) with 2 equiv of the Grignard reagent generated from ethyl 2-bromoisobutyrate under mild conditions in anhydrous ether gave, after normal acid–base work-up, a crude material which did not have the properties expected for the desired diester **4**, but which was identified after purification as ethyl *N*-2-(1-hydroxy-2-methylpropyl)-3,3′-imino-2,2,2′,2′-tetramethyldipropionate ϵ-lactone (**9**). An oil, which was identified as monoadduct **10**, was also isolated from this reaction along with small amounts of an isobutyrisobutyrate adduct **11**. The yields of **9** (35–62%) and **10** (10–35%) varied depending on the scale of the reaction and stirring efficiency since insoluble magnesium salts were formed during this reaction. When THF was used as the solvent in this reaction isobutyrisobutyrate adduct **11** and monoadduct **10** were isolated in 57 and 26% yields, respectively. No lactone was recovered in this case.

The overall recovery of lactone **9** from these reactions could be increased since: (1) diadduct **11** was found to undergo a reverse Claisen reaction to give **10** in high yield when treated with sodium ethoxide in refluxing ethanol; and (2) monoad-