of sulfonium salts, iodonium salts, and an ortho–meta–para mixture of 2-chloro-6-fluoro benzylated toluenes (Scheme III).

The reaction of the 85/15 mixture of **3d** and **2d** in 96% sulfuric acid in the presence of toluene gave pure **3d** containing less than 10 ppm of **2d** in 98% recovery. Recently, specific hydrogenation of 3-benzyladenine **2a** to adenine and toluene was reported.[16] This method was not applicable in our case, however, due to the presence of the chlorine atom in **2d** which was partially removed during the hydrogenation.

In summary, the specific dealkylation of 3-benzyladenines in concentrated sulfuric acid to form adenine and benzyl carbenium ions was observed. The carbenium ion was trapped via transalkylation with toluene in order to prevent polymer formation. Accordingly, this observation was successfully applied to the purification of crude alkylation mixtures to obtain pure 9-benzyladenines.

Experimental Section

General Methods. ^{1}H NMR spectra was recorded at 60 MHz with a Hitachi Perkin-Elmer R-24A instrument and at 100 MHz with a Varian Associates XL-100 instrument. Me_4Si was used as an internal standard. ^{19}F NMR spectra were obtained with a Varian XL-100 instrument at 94.1 MHz. The product ratio of **2d** and **3d** was determined by high-performance LC[17] using a 5-μm porous silica column (Du Pont, Zorbax-SIL) eluted with $CHCl_3$/MeOH (95/5) and detected at 254 nm. The 3-isomer analysis at the parts per million level (less than 10 ppm) was achieved by high-performance LC using a reverse-phase column.[17]

Alkylation of Sodium Adeninate. The following is a typical preparation. Into a 250-mL three-necked flask fitted with a mechanical stirrer, thermometer, and pressure-equalized dropping funnel, connected to a Firestone valve (Ace Glass Co., Vineland, NJ, Catalog No. 8766-12), were charged sodium adeninate (7.85 g, 50 mmol) and 100 mL of sieve-dried acetone containing 1.25 g of Aliquat 336 (a mixture of tetraalkylammonium salts in which the alkyl groups are primarily caprylyl, manufactured by General Mills).

To this suspension was added dropwise over a 10-min period a solution of α,2-dichloro-6-fluorotoluene (9.8 g, 50 mmol) in 10 mL of acetone at room temperature and the resulting mixture was boiled under reflux for 6 h. The reaction mixture was cooled to room temperature, and the solids were collected by filtration, washed with acetone (2 × 15 mL) and then stirred with 50 mL of 0.1 N sodium hydroxide for 15 min to remove unreacted sodium adeninate and NaCl. The solid was collected by filtration, washed with water (2 × 20 mL), and dried in vacuo to give 13.1 g (yield 95%) of a mixture of **2d** and **3d**. This mixture was recrystallized three times from acetic acid–water, affording **3d** (high-performance LC, wt % of **3d** = 99.6%; **2d** = 0.3%). A sample of **2d** was obtained from the mother liquor (high-performance LC, wt % of **3d** = 0.6%; **2d** = 99.4%). Similarly, the alkylation of 1 with benzyl, *p*-nitrobenzyl, and *p*-methoxybenzyl chloride gave the crude alkylation mixtures **2a**/**3a**, **2b**/**3b**, and **2c**/**3c**, respectively.[12]

Dealkylation of 2d in the Presence of Toluene. To a vigorously stirred suspension of a crude alkylation mixture consisting of an 85/15 ratio of **2d** and **3d** (50 g, 0.2 mole) in 100 mL of toluene was added dropwise 96% sulfuric acid (100 mL) with ice–water cooling as required to maintain a temperature of 50–60 °C. The mixture was heated with stirring at 60 °C for 8 h, cooled to room temperature, and poured into 300 mL of ice–water. The mixture was transferred to a steam-jacketed separatory funnel and heated to 90 °C in order to redissolve the precipitate. The aqueous layer (about 400 mL) was separated at 90 °C and washed with 50 mL of hot toluene to remove the transalkylation product. The aqueous layer was made basic (pH 10) at 50 °C by addition of concentrated ammonium hydroxide. The precipitated, colorless solid was collected and washed with boiling water (3 × 100 mL) and 50% methanol (2 × 100 mL). The yield of **3d** was 47.8 g (99%): mp 247–248 °C; high-performance LC wt % of **3d** = 100.01%; 3-isomer **2d**, none detectable (<10 ppm). Anal. Calcd for $C_{12}H_9N_5ClF$: C, 51.90; H, 3.27; N, 25.22; Cl, 12.77. Found: C, 51.67; H, 3.04; N, 25.29; Cl, 12.81.

The toluene layer was concentrated in vacuo, and the residue was purified by vacuum distillation to give 6.04 g (95.3%) of an *o*-, *m*-, and *p*-(2-chloro-6-fluorobenzyl)toluene mixture: bp 120–123 °C (0.05 mmHg); mass spectrum, *m/e* 234, 236; ^{1}H NMR ($CDCl_3$) δ 2.22 and 2.37 (total 3, CH_3), 4.1 (m, 2, CH_2), 6.9 (m, 7, aromatic protons). The ortho–meta–para ratio was found to be 2:1:3.5, obtained by ^{13}C NMR.[18] Anal. Calcd for $C_{14}H_{12}FCl$: C, 71.64; H, 5.16. Found: C, 71.48; H, 5.09.

Dealkylation of 2d in the Presence of Dimethyl Sulfide. This reaction was carried out the same as above, using dimethyl sulfide in place of toluene. The reaction mixture was sampled by aliquot and examined by ^{1}H NMR after dilution with CD_3COOD. The new doublet ($^4J_{HF}$ = 1.7 Hz) was observed at 1.2 ppm higher field than the methylene peak in **2d** accompanied by a singlet at 1.0 ppm lower field relative to dimethyl sulfide. This ^{1}H NMR observation supports the structure of 2-chloro-6-fluorobenzyldimethylsulfonium salt. After the usual workup a 98% yield of **3d** was obtained. High-performance LC wt % of **3d** = 99.6%. There was less than 10 ppm of **2d** observed by high-performance LC. Dealkylation of **2d** in the presence of iodobenzene was carried out the same as above and **3d** was obtained (86% yield) which showed a satisfactory high-performance LC analysis of the 3-isomer level.

Acknowledgment. We thank Mr. A. M. DeMarco for his technical assistance.

Registry No. 1, 73-24-5; **2a**, 7280-81-1; **2b**, 75347-16-9; **2c**, 75347-17-0; **2d**, 68220-23-5; **3a**, 4261-14-7; **3b**, 5134-49-6; **3c**, 56046-26-5; **3d**, 55779-18-5; α,2-dichloro-6-fluorotoluene, 55117-15-2; benzyl chloride, 100-44-7; *p*-nitrobenzyl chloride, 100-14-1; *p*-methoxybenzyl chloride, 824-94-2; *o*-(2-chloro-6-fluorobenzyl)toluene, 75347-18-1; *m*-(2-chloro-6-fluorobenzyl)toluene, 75347-19-2; *p*-(2-chloro-6-fluorobenzyl)toluene, 75347-20-5.

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(18) We thank Mr. R. A. Reamer for the ^{13}C NMR studies.

(19) Formation of oxocarbenium ions by the solvolytic decomposition of nucleoside analogues has recently been suggested; see: Lönnberg, H.; Käppi, R. *Tetrahedron* **1980**, *36*, 913 and references therein.

Syntheses and Characterization of Some Tetra- and Pentaazaindene *N*-Oxides

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In connection with our work on 1,2,4-triazines and their *N*-oxides,[1,2] it was of interest to examine the effect that a 1-oxide in 1,2,4-triazines has upon the mode of cyclization of an appropriate 3-substituted-1,2,4-triazine 1-oxide. To this end we prepared 3-hydrazino-1,2,4-triazine 1-oxide (**1**) and treated it with the one-carbon cyclizing agent **2**, so

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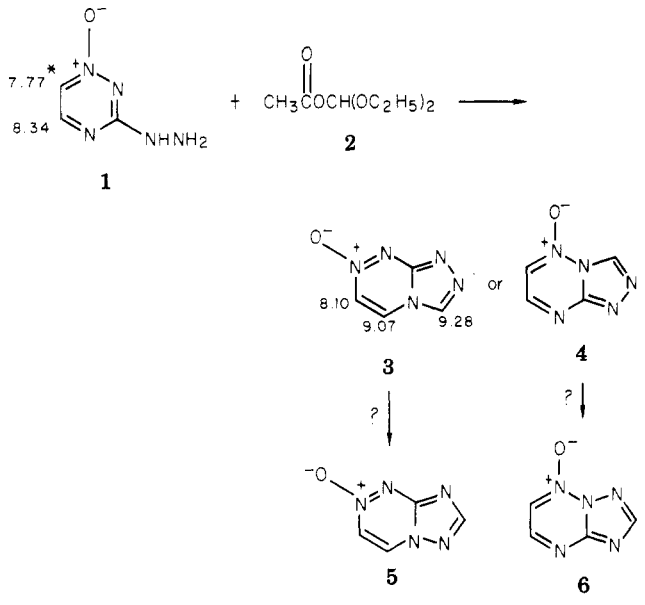
Scheme I[a]



[a] Chemical shifts (δ) in 1% Me_4Si/Me_2SO-d_6 (all values are corrected to Me_2SO).

successfully used by Tisler, Stanovnik, and others.[3]

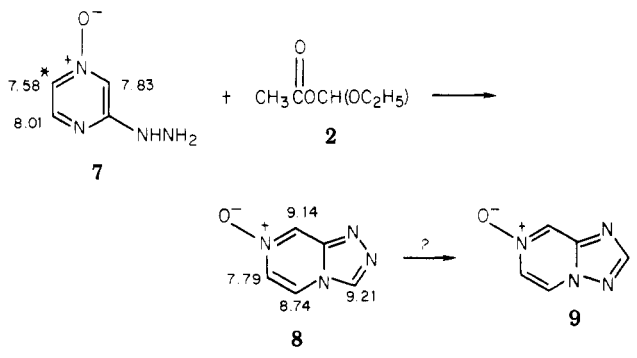
A priori, one might expect to get either the N-4 cyclized compound **3** or the isomeric N-2 cyclized material **4**. The potential also exists for either of these compounds to undergo a Dimroth rearrangement to isomers **5** and **6**, respectively. The only known example of a 3-substituted-1,2,4-triazine cyclizing into the 4-position involves a 2-methyl-3-azido-1,2,4-triazine.[4] In all other reported instances, cyclization occurs on N-2 rather than N-4.[1]

The reaction of the triazine **1** with compound **2** (see Scheme I) affords one product only, in high yield. The compound has the expected molecular formula, $C_4H_3N_5O$, and its mass spectrum shows the M – 16 ion anticipated for an *N*-oxide. The ^1H NMR spectrum of the compound has an AB pattern (δ 9.07 and 8.10) and a singlet (δ 9.28). There are numerous examples in the literature that have established that H-3 in 1,2,4-triazolopolyazaindenes absorb in the range δ 9.15–9.30,[1] while H-2 in the 1,3,5-triazolopolyazaindenes resonates in the range δ 8.50–8.80.[1]

The fact that the singlet in compound $C_4H_3N_5O$ resonates at δ 9.28 clearly establishes that no Dimroth rearrangement has taken place and that we are dealing either with the N-4 cyclized compound **3** or its isomeric N-2 cyclized product **4**. We might also mention that if we are dealing with compound **4**, the peri-situated oxygen should cause H-3 to become more deshielded than would be the case if there were no oxygen at that position. Since H-3 does not resonate at a more deshielded position, the compound must have structure **3** rather than **4**. However, more solid evidence must be amassed before this conclusion can stand.

In order to do this, we prepared 3-hydrazinopyrazine 1-oxide (**7**) and reacted it with the cyclizing agent **2** used in the previously described reaction. In this instance, cyclization is possible in only one direction to afford compound **8** or its Dimroth rearrangement product **9** (Scheme II). The compound obtained from this reaction did indeed have the correct elemental formula, $C_5H_4N_4O$, expected for either compound **8** or **9**. The mass spectrum, as anticipated for a N-oxide, shows a P – 16 ion. The ^1H NMR spectrum shows a singlet at δ 9.21 and an ABX pattern (δ 7.79, 8.74, and 9.14, respectively). The chemical shift of the singlet is clearly in agreement with the presence of an H-3 (structure **8**), rather than an H-2 (structure **9**). Thus, the compound in question is the 1,2,4-triazolo derivative **8**. Since the chemical shift of H-3 in the triazine derivative **3** is the same as that of H-3 in the pyrazine derivative **8**, we can now unequivocally state that 3-hydrazino-1,2,4-triazine 1-oxide (**1**) cyclizes into the 4- rather than the 2-position. Thus, the presence of the 1-oxide in compound **1** has decreased the nucleophilicity of N-2 to such an extent that N-4 becomes more nucleophilic than N-2.

Scheme II[a]



[a] See footnote *a*, Scheme I.

This represents the first example of not only the synthesis of a triazolopyrazine and diazolo-1,2,4-triazine *N*-oxide (**3** and **8**) but also a synthetic approach to the triazolo-1,2,4-triazine ring system starting with a 1,2,4-triazine rather than a 1,2,4-triazole.[1]

Experimental Section

Melting points were taken with a Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid-sample injector; the ionizing voltage was 70 eV. Elemental analyses were determined by the Analytical Services Laboratory of the University of Alabama, Chemistry Department.

3-Hydrazino-1,2,4-triazine 1-Oxide (1).[5] To a solution of 1.0 g (7.8 mmol) of 3-methoxy-1,2,4-triazine 1-oxide in 20 mL of dry tetrahydrofuran (THF) was added 0.5 mL (15 mmol) of 95+% hydrazine. Dry methanol was then added to dissolve any excess hydrazine not in solution. The yellow precipitate which began to form within minutes was collected after 2 h: 0.76 g, 76% yield; mp 191–192 °C. Anal. Calcd for $C_3H_5N_5O$: C, 28.34; H, 3.93; N, 55.12. Found: C, 28.36; H, 3.96; N, 54.88.

3-Hydrazinopyrazine 1-Oxide (7). To 615 mg (4.7 mmol) of 3-chloropyrazine 1-oxide[6] in 10 mL of dry THF was added 0.3 mL (8.9 mmol) of 95+% hydrazine. Enough absolute methanol was then added to dissolve any of the nondissolved hydrazine. After 48 h a white precipitate which had formed was collected. This precipitate was suspended in EtOH (absolute) and triethylamine for 24 h. The resulting yellow solid was recrystallized from absolute EtOH: 328 mg, 55% yield; mp 200–200.5 °C. Anal. Calcd for $C_4H_6N_4O$: C, 38.11; H, 4.76; N, 44.43. Found: C, 37.94; H, 4.53; N, 43.87.

1,2,4-Triazolo[3,4-*c*](1,2,4)triazine 7-Oxide (3). To 200 mg (1.6 mmol) of 3-hydrazino-1,2,4-triazine 1-oxide was added 0.7 mL (4.3 mmol) of diethoxymethyl acetate. The solution was then heated on a steam bath for 10 min during which time a precipitate formed. This brown solid was collected by vacuum filtration. The brown solid was sublimed at 160 °C (0.05 mmHg) to give a white

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compound: 193 mg, 90% yield; mp 190–191 °C dec. Anal. Calcd for $C_4H_3N_5O$: C, 35.03; H, 2.18; N, 51.09. Found: C, 35.02; H, 2.31; N, 50.33.

1,2,4-Triazolo[3,4-*c*]pyrazine 7-Oxide (8). To 100 mg (0.8 mmol) of 3-hydrazinopyrazine 1-oxide was added 0.5 mL (3.0 mmol) of diethoxymethyl acetate. This solution was allowed to stand at room temperature for 24 h. The light brown precipitate which formed was collected and washed with ethanol. Recrystallization from absolute ethanol yielded an off-white compound: 46 mg, 43% yield; mp 204–205 °C dec. Anal. Calcd for $C_5H_4N_4O$: C, 44.14; H, 2.94; N, 41.46. Found: C, 44.26; H, 2.61; N, 41.16.

Registry No. 1, 65481-57-4; 2, 14036-06-7; 3, 75431-21-9; 7, 74803-26-2; 8, 74803-29-5; 3-methoxy-1,2,4-triazine 1-oxide, 27531-67-5; hydrazine, 302-01-2; 3-chloropyrazine 1-oxide, 6863-76-9.

Nicotinic Acid Crown Ethers.[1] Synthesis and Structural Characterization of Polyethereal Macrocyclic Lactones from 6-Chloronicotinic Acid

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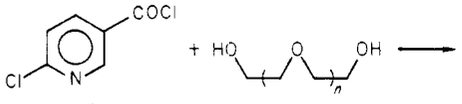
Recently, we described the synthesis of crown ethers possessing a 2-oxanicotinate moiety and demonstrated a distinct template effect on cyclization.[3] In view of the few examples of pyridine macrocyclic lactones[4] and the absence of 1,4-bridged nicotinate macrocycles, we herein describe the inclusion of a 6-oxanicotinate moiety into a novel series of cross-ring macrocycles.

6-Chloronicotinic acid was transformed (100%) in excess refluxing thionyl chloride[5] into 6-chloronicotinoyl chloride (1). Subsequent treatment of 1 with 1 equiv of disodium diethylene glycol in benzene at 78 °C afforded the 2:1 bisester 2 in nearly quantitative yields. Under these mild



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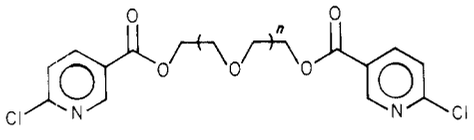
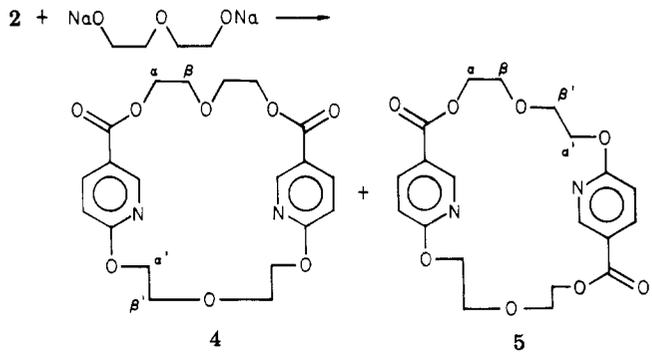


2, n = 1
3, n = 4

reaction conditions, direct heteroaryl substitution reactions are negligible. Bisester 3 was prepared (90%) in a similar manner from 1 upon treatment with pentaethylene glycol.

Cyclization was accomplished upon treatment of 2 with disodiodiethylene glycolate in refluxing xylene (138 °C) to generate isomeric 2:2 macrocycles 4 and 5 in 5.5 and 6.4% yield, respectively. Due to the similarity in physical and selected spectral (NMR and mass spectra) data,



4 5

structural differentiation between these isomers was not possible. Thus, colorless crystals of the 141–142 °C melting isomer were grown by slow evaporation of a chloroform solution. X-ray data were collected on an Enraf-Nonius CAD-4 diffractometer, using graphite-monochromatized Mo Kα radiation (λ = 0.71069 Å) and a crystal of dimensions 0.40 × 0.30 × 0.22 mm. The crystal data are as follows: $C_{20}H_{22}N_2O_8$, mol wt 418.4; triclinic space group $P\bar{1}$; a = 7.651 (2), b = 10.237 (2), c = 12.754 (2) Å; α = 101.51 (1), β = 95.26 (2), γ = 94.23 (2)°; Z = 2; d_c = 1.429 g cm^{-3}; μ (Mo Kα) = 1.04 cm^{-1}. Intensity data were collected by the θ–2θ scan technique, employing variable scan rates, which varied from 0.80 to 10.0 deg min^{-1} in order to measure all data with approximately equal precision. No significant decrease in the intensity of periodically remeasured reflections was noted. All data in one hemisphere having $2° \leq \theta \leq 20°$ were measured and corrected for background and Lorentz and polarization effects; no absorption corrections were necessary.

The structure was solved by a combination of direct (MULTAN 78)[6] and Fourier methods (SHELX).[7] Least-squares refinement was based upon F, and was carried out by using data having $F_{obsd} > 3\sigma(F_{obsd})$. Nonhydrogens were refined with isotropic temperature factors; hydrogen atoms were placed in calculated positions 1.08 Å from atoms to which they are bonded, and their isotropic temperature factors were refined. Convergence was achieved with R = 0.061 for 967 data and 143 variables. Nonhydrogen atom positions and hydrogen atom parameters are given in the supplementary material.

The conformation of 4 is illustrated in Figure 1. The pyridine rings are nearly parallel, deviating by 7.4°, and are separated by 4.33 Å between ring centers. The ethereal linkage to the heteroaromatic ring is cis in both cases, as is generally true with similar imidate moieties in related macrocyclic systems.[8] Torsion angles are 30.4° for N1–C1–O8–C20 and 5.4° for N2–C16–O6–C17; the larger angle is indicative of the release of steric strain caused by the juxtaposition of the pyridine subunits. The two ester linkages are quite different, being anti to N1 and syn to N2, again a favorable mode to circumvent the repulsive heteroaromatic interactions. Those torsion angles are −5.0° and 180.0° for C3–C4–C6–O2 and C14–C12–C11–O5, re-

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