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(25) The formation of hexafluorophosphate salts would probably be a preferable route, but it was not done in this study.

Tetrazolo[1,5-*b*]-1,2,4-triazines. Syntheses and Structure Determination

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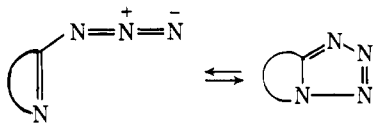
Several 3-azido-1,2,4-triazines were prepared by treating the corresponding 3-hydrazino derivatives with nitrous acid. The azidotriazines spontaneously cyclized into a tetrazolo isomer. These transformations were studied using nuclear magnetic resonance and infrared spectroscopic methods. The tetrazolo isomers were proven to be tetrazolo[1,5-*b*]-1,2,4-triazines by an x-ray crystallographic study on the 5-*p*-chlorophenyl derivative.

Azido-substituted π-deficient nitrogen heterocyclic systems have been extensively investigated.[1] These studies have established that the equilibrium



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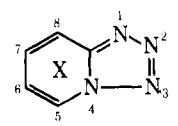
is strongly controlled by (a) the π deficiency of the nitrogen heterocycle; (b) the polarity of the solvents; and (c) to some extent, temperature. The following interpretive statement has been made:[1]

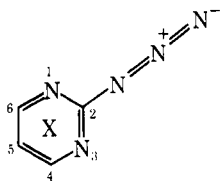
"In azolazines, the azine part of the molecule is responsible for the magnitude of the charge on the N-atom common to both rings. If the negative charge can be further delocalized on other N-atoms in the *m*-position of the azine ring, this enhances the stability of the azido form."

By way of recapitulating the data, the following compounds exist, in dimethyl sulfoxide, as the tetrazolo derivatives:[2-6]



3, X = nil
4, X = N, at position 5
5, X = N, at position 6
6, X = N, at position 7

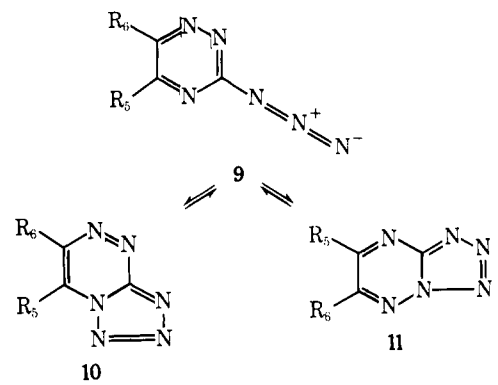
When a nitrogen is substituted at position 8 in the above structure, the azido heterocycles are formed in dimethyl sulfoxide.[7] For example:



7, X = nil (10% in this form)
8, X = N, at position 5 (100% in this form)

The formation of these azido compounds is greatly enhanced by nonpolar solvents (compound **7** in chloroform solution is reported to exist totally in the azido form).[8]

In view of our extensive interest in 1,2,4-triazines and the potential dual possibility of cyclization (**10**, **11**), we decided to study the behavior of some 3-azido-1,2,4-triazines (**9**).



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10 11

Table I. Infrared Absorption Spectra (cm^{-1})

Registry no.	Compd	Phase	Azido bands	Tetrazolo bands
32484-95-0	**11a**	CH_2Cl_2	2150 (s)	
		Nujol		1285 (m), 1085 (m), 980 (m)
59318-29-5	**11b**	CH_2Cl_2	2140 (s)	
		Nujol		1275 (m), 1070 (s), 980 (m)
59318-30-8	**11c**	$CHCl_3$	2120 (s), 2140 (s)	
		Nujol		1285 (s), 1090 (s), 980 (m)
59318-31-9	**11d**	$CHCl_3$	2120 (s)	
		KBr		1295 (s), 1100 (s), 995 (m)
59318-32-0	**11e**	Nujol		1285 (2), 1085 (m), 980 (m)
59318-33-1	**11f**	Nujol		1290 (s), 1090 (s), 985 (m)
59318-34-2	**11g**	Nujol		1300 (s), 1080 (m), 975 (m)
59318-35-3	**11h**	Nujol		1285 (m), 1080 (m), 985 (m)

Table II. Least-Squares Plane Calculations for 5-*p*-Chlorophenyltetrazolo[1,5-*b*]-1,2,4-triazine[a]

Plane	Equation of Plane
A	$0.2881X - 0.8435Y - 0.4533Z + 5.9192 = 0$
B	$0.3081X - 0.8237Y - 0.4760Z + 6.2565 = 0$
C	$0.2911X - 0.8793Y - 0.3770Z + 5.1171 = 0$
D	$0.2949X - 0.8636Y - 0.4089Z + 5.3641 = 0$

Deviation of Atoms from Planes (Å)

Atom	Plane A	Atom	Plane B	Atom	Plane C	Atom	Plane D
C1	−0.004	C1	0.003	C4	−0.005	Cl	0.075
C2	−0.009	N1	−0.004	C5	0.003	C1	−0.057
C3	0.015	N2	0.003	C6	0.003	C2	−0.035
N4	0.011	N3	−0.000	C7	−0.007	C3	−0.079
N5	−0.004	N4	−0.002	C8	0.005	C4	−0.052
N6	−0.009			C9	0.001	C5	−0.002
						C6	0.043
						C7	0.036
						C8	0.009
						C9	−0.040
						N1	−0.024
						N2	0.089
						N3	0.113
						N4	0.019
						N5	0.021
						N6	−0.116

[a] The maximum deviation of any atom from the least-squares plane of the entire molecule was 0.12 Å.

Table III. Bond Angles (deg) for Compound 11f

C1–N1–N2	105.6 (2)	N1–N2–N3	112.3 (2)
N2–N3–N4	104.6 (2)	N3–N4–C1	109.7 (2)
N4–C1–N1	107.8 (2)	N1–C1–N6	130.4 (2)
N3–N4–N5	124.1 (2)	C1–N4–N5	126.2 (2)
N4–N4–C2	111.9 (2)	N5–C2–C3	124.2 (2)
C2–C3–N6	120.9 (2)	C3–N6–C1	115.0 (2)
N4–C1–N6	121.8 (2)	C4–C3–N6	118.4 (2)
C2–C3–C4	120.7 (2)	C3–C4–C9	121.5 (2)
C3–C4–C5	119.6 (2)	C4–C5–C6	120.7 (2)
C5–C4–C9	118.8 (2)	C6–C7–C8	121.8 (2)
C5–C6–C7	119.1 (2)	C8–C9–C4	120.7 (2)
C7–C8–C9	118.9 (2)	C1–C7–C8	118.8 (1)
Cl–C7–C6	119.6 (1)		

The desired compounds (cf. Scheme I) were prepared by treatment of the appropriate 3-hydrazino-1,2,4-triazines with nitrous acid. The Nujol infrared spectra of all of the compounds were devoid of any azido peaks. Consequently, in the solid state at least, we are dealing with the tetrazolo form **10** or **11**. Since all of the compounds show the same tetrazolo frequencies (see Table I) we conclude that they all have cyclized in identical fashion. In order to ascertain whether we are dealing with the tetrazolo[1,5-*b*]-1,2,4-triazines (**11**) or their isomers **10** it became necessary to establish the structure by x-ray crystallography. The most appropriate derivative for this study was the *p*-chlorophenyl derivative **12f**.

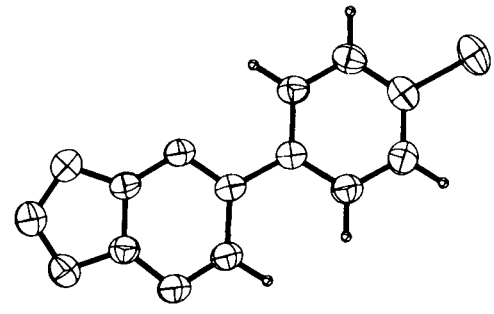
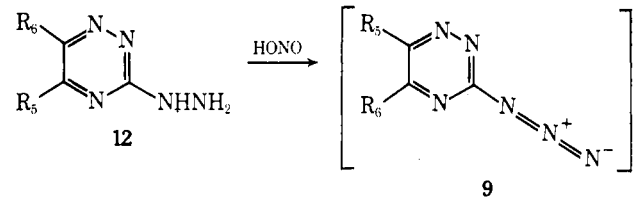


Figure 1. Molecular structure of compound **11f** with the atoms displayed as 40% probability ellipsoids for thermal motion. The standard deviations in the bond lengths are less than 0.003 Å.

Scheme I



12 **9**

	R_5	R_6		R_5	R_6
a	H	H	**e**	C_6H_5	H
b	H	CH_3	**f**	*p*-ClC_6H_4	H
c	CH_3	H	**g**	*p*-$CH_3OC_6H_4$	H
d	CH_3	CH_3	**h**	*p*-$NO_2C_6H_4$	H

Structure of the Tetrazolo Derivative of 3-Azido-5-*p*-chlorophenyl-1,2,4-triazine. The crystal data, final fractional coordinates, and anisotropic thermal parameters of the compound are available as microfilm supplement. The bond angles are listed in Table III, while the bond distances are shown in Figure 1. These data clearly prove that we are dealing with the tetrazolo[1,5-*b*]-1,2,4-triazine (**11**), rather than the N-4 cyclized isomer **10**. The cyclization into N-2 is not unexpected in view of the fact that, as we have previously shown,[9] given a choice, the 1,2,4-triazines will form structures which do not have a formal N=N. However, it is somewhat surprising that the five-nitrogen chain (structure **11**) is more stable, in this instance, than a four-nitrogen one (structure **10**).

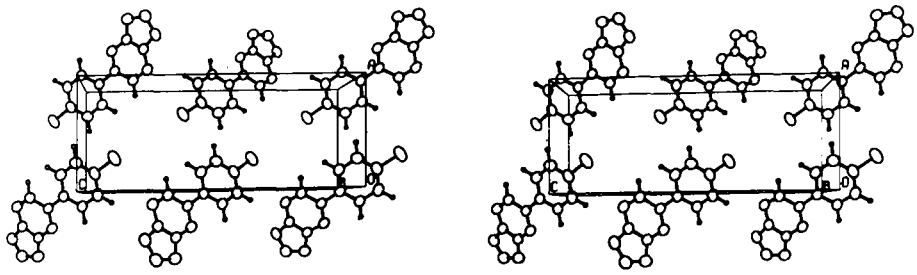


Figure 2. Stereoscopic view of the unit cell packing in **11f**.

Table IV. ^{1}H NMR Spectra of Some Tetrazolo[1,5-*b*]-1,2,4-triazines (Chemical Shifts in τ)

Compd	Solvent[a]	R_6	R_5	J_{AB}, Hz
11a	Me_2SO-d_6	0.96	0.88	1.0
11b	Me_2SO-d_6	7.20	0.83	
	$CDCl_3$	7.12	1.13	
11c	Me_2SO-d_6	0.95	7.18	
	$CDCl_3$	1.31	7.06	
11d	Me_2SO-d_6	7.26	7.23	
	$CDCl_3$	7.22	7.19	
11e	Me_2SO-d_6	0.20	1.52–1.62 (m), 2.27–2.35 (m)	
11f	Me_2SO-d_6	0.24	2.22 (d), 1.52 (d)	
11g	Me_2SO-d_6	0.21	1.52 (d), 2.75 (d), 6.02 (s)	5.5
11h	Me_2SO-d_6	0.10	1.34 (d), 1.54 (d)	4.5

[a] Dilute solutions in indicated solvents; see Scheme I for structure identifications. A Varian HA-100 spectrometer was used to obtain these spectra.

Some other points of interest are (1) the great similarity of all of the nitrogen to nitrogen bond lengths (1.304–1.352 Å); (2) the considerable bond delocalizations in the molecule; (3) the essentially total planarity of the ring system (see Table II).

Thus, by all "classical" definitions, the compound is aromatic.

Infrared Spectral Data. The infrared spectrum of the chloroform extract of the oxidation product of 3-hydrazino-5,6-dimethyl-1,2,4-triazine, taken immediately after completion of the oxidation reaction, shows the presence of an azido group (2120 cm^{-1}). This peak disappears within 50 min and is replaced by the typical tetrazolo peaks (see Table I). Thus, in this compound at least, the tetrazolo structure is the preferred one in chloroform. Chloroform solutions of the oxidation products of the 3-hydrazino-1,2,4-triazine, the 5-methyl and 6-methyl derivatives, again show the presence of an azido group in the infrared spectrum. However, within a very short time, the solution becomes turbid and ultimately no material remains in solution. The precipitated compound in each case is the tetrazolo derivative as established by an examination of the Nujol infrared spectrum. As a result of the insolubility of the tetrazole in chloroform we cannot establish whether there exists an equilibrium between the azido form and the tetrazolo structure of these compounds.

Nevertheless, in view of the behavior of the dimethyl derivative, it seems reasonable to state that, in chloroform at least, the azido structures are unstable and are converted to the tetrazolo forms exclusively.

It is impossible to "trap" the azido forms by evaporation of the freshly prepared chloroform extracts of the oxidation reactions, since the Nujol mull infrared spectra of the solid residues are devoid of azido absorption bands. In fact, the Nujol mull spectra of all of the compounds examined (see Table I) show only typical tetrazolo absorptions.

Table V. ^{1}H NMR Spectra of Some 3-Azido-1,2,4-triazines

Registry no.	Compd[a]	R_5	R_6
59318-36-4	**9b**	7.29	1.61
59318-37-5	**9c**	1.06	7.42
59318-38-6	**9d**	7.36	7.46

[a] Dilute solution in deuteriochloroform. As mentioned in the text, these compounds rapidly cyclize to the tetrazolo structures.

^{1}H NMR Spectral Data. The ^{1}H NMR spectrum of the deuteriochloroform extract of the oxidation product of 3-hydrazino-5,6-dimethyl-1,2,4-triazine taken immediately after oxidation is completed shows four methyl peaks. The intensities of the major two peaks (τ 7.36, 7.46) decrease rapidly and those of the minor 2 peaks (τ 7.19, 7.22) increase correspondingly. Thus, based upon the infrared data, the former peaks belong to the azido form, and the latter to the tetrazolo structure. Again, the methyl peaks due to the azido form disappear totally within 50 min. Since it takes some time to adjust the NMR instrument, the first ^{1}H NMR spectrum cannot be obtained as rapidly as is the case for the infrared spectra. Consequently, the first spectrum (obtained 10 min after completion of the oxidation reaction) shows the azido compound to be present at 35% vs. 65% for the tetrazolo derivative. After 50 min, no azido compound is left. Even though the tetrazolo derivatives of the 5-methyl- and 6-methyl-1,2,4-triazines are rather insoluble in deuteriochloroform, one can nevertheless obtain the ^{1}H NMR spectral data for the azido as well as tetrazole compounds prior to their precipitation from solution. These data are given in Tables IV and V.

The ^{1}H NMR spectra in perdeuteriodimethyl sulfoxide of all of the compounds examined show the presence of only *one* "isomer". Fortunately, the methyl group absorptions in $CDCl_3$ and in Me_2SO-d_6 are nearly the same. Thus, it is clear that in the latter solvent, we are dealing with the tetrazolo compound exclusively (τ 7.23, 7.26). Given this information, we can now compare the chemical shifts of the monomethyl derivatives with those of the dimethyl tetrazolo derivative. The methyl group of the 5-methyl derivative absorbs at τ 7.18 and that of the 6-methyl derivative at τ 7.20. The ring protons, H-6 and H-5, absorb at τ 0.95 and 0.83, respectively. The ^{1}H NMR spectrum of the "parent" tetrazole in perdeuteriodimethyl sulfoxide shows only two protons (τ 0.96 and 0.88, respectively) as an AB system (J_{AB} = 1.0 Hz). Thus, we are again dealing with the tetrazolo derivative.

The question of a rapid equilibrium between the azido and tetrazolo compounds can easily be disposed of by the observation that, in Me_2SO-d_6 at least, these ^{1}H NMR spectra are temperature insensitive (35–150 °C).

Conclusion

This study has established the following facts.

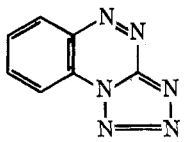
(1) 3-Azido-1,2,4-triazines are unstable and cyclize to the tetrazolo isomers.

(2) The cyclization affords the tetrazolo[1,5-*b*]-1,2,4-triazines exclusively.

(3) The structure assigned to the 5,6-diphenyl derivative without any proof is probably correct.[10]

(4) The tetrazolo[1,5-*b*]-1,2,4-triazine ring system is planar and aromatic by the classical as well as ^{1}H NMR criteria.

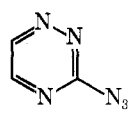
(5) The structure assignment of the tetrazolo[5,1-*c*]-benzo-1,2,4-triazines (**14**), resulting from cyclization of an



14

azido group into N-4 rather than N-2, may well be in error and should be reexamined.[11]

(6) The "addition" of the electron-withdrawing nitrogen to a 2-azidopyrimidine (**16** vs. **15**) is expected to decrease the



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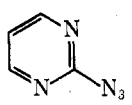
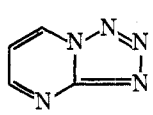


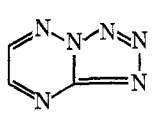
16

electron-donating capacity of the π-deficient heterocyclic ring and consequently should stabilize the azido form.[12] Yet 3-azido-1,2,4-triazines are *not* stable and exist only as these tetrazolo isomers.

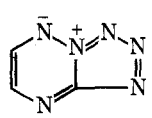
In view of the fact that we are dealing with facile interconversions, we must not only consider the stabilities of the azido structures, but also those of the tetrazolo isomers. If we keep this in mind, it is clear that the tetrazolopyrimidine **17** is going to be less stable than the tetrazolotriazine **18** because of the



17

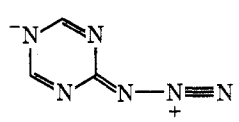


18a



18b

involvement of the extra nitrogen atom in the ground-state stabilization of the bicyclic ring system (**18a,b**). On the other hand, the extra nitrogen in the 3-azido-1,3,5-triazine, reported[8] to be the stable isomer in this ring system, will lend greater stabilization (**19**) to the azido form rather than to the bicyclic structure **20**, where the extra nitrogen would con-



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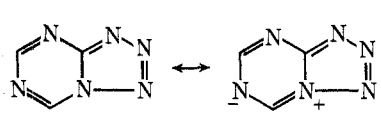

20a **20b**

tribute considerably less to the stabilization (**20a,b**) of the bicyclic system than to the azido form (**19**).

Experimental Section

Tetrazolo[1,5-*b*]1,2,4-triazines. General Procedure. The appropriate hydrazino compound (**12a–h**) (2 mmol) was dissolved in 6 ml of 5 N HCl, the solution was cooled to 0–5 °C, and aqueous $NaNO_2$ (140 mg in 1 ml of H_2O) was added dropwise. The solution was stirred for an additional 15 min while maintaining the temperature at 0–5 °C. The crude tetrazole was separated either by filtration (compounds **11e–h**) or by extraction with $CHCl_3$ (**11a–d**). The compounds thus obtained were recrystallized from absolute methanol (see Table VI).

Table VI. Tetrazolo[1,5-*b*]-1,2,4-triazines[a]

Molecular formula (compd)	Mp, °C	% yield
$C_3H_2N_6$ (**11a**)	174–175	33
$C_4H_4N_6$ (**11b**)	130–131	50
$C_4H_4N_6$ (**11c**)	140–142	82
$C_5H_6N_6$ (**11d**)	138–139	70
$C_9H_6N_6$ (**11e**)	192–193	58
$C_9H_5N_6Cl$ (**11f**)	217–219	90
$C_{10}H_8N_6O$ (**11g**)	194–196	60
$C_9H_5N_7O_2$ (**11h**)	184–186	62

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds in table. Ed.

The ^{1}H NMR spectra for the azido compounds were obtained by extracting the above reaction mixtures with $CDCl_3$ in place of $CHCl_3$.

X-Ray Data Collection. Single crystals of the compound were sealed in thin-walled glass capillaries. The final lattice parameters in Table II were determined from a least-squares refinement of the angular settings of 15 accurately centered reflections ($\theta > 20°$).

Data were taken on an Enraf-Nonius CAD-4 diffractometer with graphite crystal monochromated molybdenum radiation. The diffracted intensities were collected by the ω–2θ scan technique with a takeoff angle of 3.0°. The scan rate was variable and was determined by a fast (20° min^{-1}) prescan. Calculated speeds based on the net intensity gathered in the prescan ranged from 7 to 0.3° min^{-1}. Moving-crystal moving-counter backgrounds were collected for 25% of the total scan width at each end of the scan range. For each intensity the scan width was determined by the equation

$$\text{scan range} = A + B \tan\theta$$

where $A = 0.70°$ and $B = 0.20°$. Aperture settings were determined in a like manner with $A = 4$ mm and $B = 0.87$ mm. Other diffractometer parameters and the method of estimation of the standard deviations have been described previously.[12] As a check on the stability of the instrument and the crystal, two reflections, the (200) and (020), were measured after every 30 reflections; no significant variation was noted.

One independent quadrant of data was measured out to $2\theta = 50°$; a slow scan was performed on a total of 1242 unique reflections. Since these data were scanned at a speed which would yield a net count of 4000, the calculated standard deviations were all very nearly equal. No reflection was subjected to a slow scan unless a net count of 20 was obtained in the prescan. Based on these considerations, the data set of 1242 reflections (used in the subsequent structure determination and refinement) was considered observed, and consisted in the main of those for which $I > 3\sigma(I)$. The intensities were corrected for Lorentz and polarization effects.

Fourier calculations were made with the FOURIER program.[13] The full-matrix, least-squares refinement was carried out using the Busing and Levy program ORFLS.[14] The function $w(|F_o| - |F_c|)^2$ was minimized. No corrections were made for extinction. Atomic scattering factors for Cl, N, and C were taken from Cromer and Waber.[15] Scattering factors for hydrogen were from "International Tables for X-Ray Crystallography".[16] Final bond distances, angles, and errors were computed with the aid of the Busing, Martin, and Levy ORFFE program.[17] Crystal structure illustrations were obtained with the program ORTEP.[18]

Structure Solution and Refinement. The location of the chlorine atom was revealed by the inspection of a Patterson map. The coordinates of all nonhydrogen atoms were deduced from a Fourier map phased on the chlorine atom. Subsequent isotropic least-squares refinement led to an R value of 0.10. Anisotropic refinement gave values of $R_1 = 0.052$ and $R_2 = 0.067$ where

$$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$$

$$R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$$

Unit weights had been used up to this point. Application of a weighting scheme which reduced to contribution of the ten most in-

tense reflections to 1/25, together with the removal of the ($\bar{1}$22) and (102) because of extinction afforded $R_1 = 0.042$ and $R_2 = 0.045$. The addition of the five hydrogen atoms in calculated positions (the C–H bond length was assumed to be 1.00 Å) and further anisotropic refinement gave final values of $R_1 = 0.032$ and $R_2 = 0.034$. Unobserved reflections were not included. The largest parameter shifts in the final cycle of refinement were less than 0.01 of their estimated standard deviations. The value of the standard deviation of an observation of unit weight was 0.91. A final difference Fourier map showed no peak larger than 0.2 e/Å^3. The final values of the positional and thermal parameters are given in the microfilm supplement.[19]

Registry No.—**12a,** 28735-23-1; **12b,** 59318-39-7; **12c,** 28735-26-4; **12d,** 19542-09-7; **12e,** 28735-29-7; **12f,** 59318-40-0; **12g,** 59318-41-1; **12h,** 59318-42-2.

Supplementary Material Available. A listing of the crystal data, final fractional coordinates, and anisotropic structure factors (3 pages). Ordering information is given on any current masthead page.

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Synthesis of 2-Azaestratrienes

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From readily available 3β,5α-dihydroxy-6β,19-oxidoandrostan-17-one 3,5-diacetate (**1**) a facile synthesis of 1,17-dihydroxy-6β,19-oxido-2-oxaandrost-4-en-3-one (**6**) was developed. The key step in this sequence was the regioselective ozonolysis of the bridged, unsaturated α-diketone **5** to the bridged lactol **6** in good yield. This cyclic acid aldehyde **6** was utilized for the preparation of 3-methoxy- and 1,3-dimethoxy-2-azaestratrienes. The 17α-ethynyl-17β-hydroxy derivatives of the 3-methoxy- as well as the 3-cyclopentoxy-2-azaestratrienes were prepared via an alternate pathway from 2-oxaestra-5(10)-ene-3,17-dione (**17**). While these series were devoid of hormonal activity they manifested hypolipemic as well as antiviral properties.

In an earlier communication[1] we had reported the syntheses of several series of 2-aza steroids. This study was an extension of work aimed at determining the effect on biological activity of a heteroatom at the 2 position of the steroid nucleus.[2] In this paper we wish to report in greater detail our investigations into the synthesis of 2-azaestratrienes, the thrust of which has been provided by the interesting biological profile of the 3-methyl ether series (vide infra). Thus, the structural modifications made at the 1 and 3 positions of the aromatic nucleus were attempts to enhance the observed biological properties of this series.

Our initial approach to the 2-aza analogue of estradiol-3-methyl ether utilized the readily available 3β,5α-dihydroxy-6β,19-oxidoandrostan-17-one 3,5-diacetate (**1**)[3] which was converted to the 17-benzoate derivative **2** by treatment with sodium borohydride in methanol[4] and subsequent benzoylation with benzoyl chloride in pyridine, in 85% yield from **1** (Scheme I). Selective hydrolysis of the 3-acetate was accomplished with anhydrous hydrogen chloride in methanol at room temperature providing **3** in 95% yield. Subsequent oxidation of the bridged alcohol **3** with Jones reagent[5] afforded the keto diester **4** in 93% yield.

Following the procedure of Hanna and Ourisson,[6] this material was oxygenated subsequent to the in situ elimination of the 5-acetoxy group by *tert*-butoxide. The conjugated system thus formed enabled oxygenation to occur exclusively at the 2 position generating the bridged α-diketone **5** in yields

Scheme I