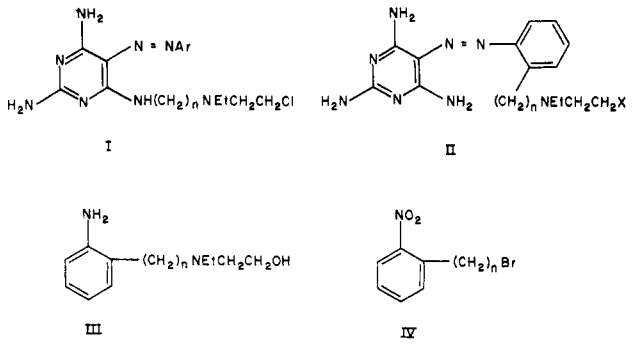

I II

III IV

ethyl-, 3-bromopropyl-, 4-bromobutyl-, and 5-bromopentylbenzene according to lit. procedures.

2-Nitro-(ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkyl)benzenes.—A soln of IV (0.1 mole) and *N*-ethylethanolamine (0.2 mole) in C_6H_6 (150 ml) was refluxed for 24 hr. The PhH layer was washed thoroughly (H_2O) and then extd with 10% HCl. The acid ext was basified and extd with Et_2O, dried, and distd *in vacuo* (Table I).

TABLE I
2-NITRO-(ω-*N*-ETHYL-*N*-2-HYDROXYETHYLAMINOALKYL)BENZENES

n	Bp (mm), °C	Yield, %	Formula[a]
1	145 (0.05)	72	$C_{11}H_{16}N_2O_3$
2	138 (0.10)	68	$C_{12}H_{18}N_2O_3$
3	152 (0.10)	70	$C_{13}H_{20}N_2O_3$
4	116 (0.05)	66	$C_{14}H_{22}N_2O_3$
5	165 (0.10)	52	$C_{15}H_{24}N_2O_3$

[a] All compds were analyzed for C, H, N.

2-Amino-(ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkyl)benzenes (III, *n* = 1–5).—Solns of the nitro compd (0.05 mole) in EtOH (100 ml) were reduced at 50° with 5% Pd/C catalyst (200 mg). The amines were isolated and characterized as the dihydrochlorides (Table II).

TABLE II
2-AMINO-(ω-*N*-ETHYL-*N*-2-HYDROXYETHYLAMINOALKYL)-BENZENE DIHYDROCHLORIDES

n	Mp, °C[a]	Yield, %	Formula[b]
1	151	85	$C_{11}H_{20}Cl_2N_2O_3$
2	132	95	$C_{12}H_{22}Cl_2N_2O_3$
3	169	90	$C_{13}H_{24}Cl_2N_2O_3$
4	142	91	$C_{14}H_{26}Cl_2N_2O_3$
5	172	82	$C_{15}H_{28}Cl_2N_2O_3$

[a] Recrystn from *i*-PrOH–Et_2O. [b] All compds were analyzed for C, H, Cl, N.

2,4,6-Triamino-5-(2-ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkylphenyl)azopyrimidines (II, *n* = 1–5) were prepd by the coupling procedure previously described[1,3,4] and are listed in Table III.

TABLE III
2,4,6-TRIAMINO-5-(2-ω-*N*-ETHYL-*N*-2'-HYDROXYETHYLAMINOPHENYL)AZOPYRIMIDINES (II, *n* = 1–5)

n	Mp, °C[a]	Solvent	Yield, %	Formula[b]
1	185	EtOH	70	$C_{15}H_{22}N_8O$
2	175	EtOH	75	$C_{16}H_{24}N_8O$
3	165	*i*-PrOH	65	$C_{17}H_{26}N_8O$
4	170	*i*-PrOH	80	$C_{18}H_{28}N_8O$
5	*a*		67	

[a] Very hygroscopic: a satisfactory anal. could not be obtd. [b] All compds except **5** were analyzed for C, H, N.

Enzyme Procedure.—Chicken liver dihydrofolate reductase (partially purified) was employed with the protocol previously described.[3,4]

Pyrazoles. 4. Analogs of 3-(3,3-Dimethyl-1-triazeno)pyrazole-4-carboxamide[1]

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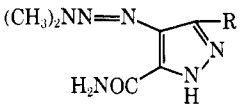
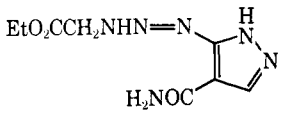
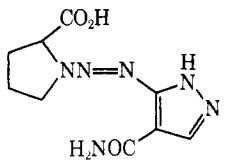
The antileukemic activity exhibited by 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide[2] and its stability toward light and heat[2] prompted a synthesis of closely related compounds for continued study. The isomeric 4-(3,3-dimethyl-1-triazeno)pyrazole-3-carboxamide (Ia) and a homolog of Ia, 4-(3,3-dimethyl-1-triazeno)-5-methylpyrazole-3-carboxamide (Ib), as well as two amino acid derivatives of 3-diazopyrazole-4-carboxamide,[3] II and III, were prepared as described in the Experimental Section.



Ia, R = H
b, R = Me



II



III

Experimental Section[4]

4-Diazopyrazole-3-carboxamide.—To a suspension of 10 g of finely divided 4-aminopyrazole-3-carboxamide[5] in 100 ml of H_2O was added 6 ml of concd HCl. To the resulting soln was added dropwise, at 5°, 5.4 g of $NaNO_2$ in 30 ml of H_2O. A tan-colored ppt formed gradually. The mixt was stirred for 30 min, and the solid was filtered off, washed with cold H_2O and Me_2CO, and dried at 80° to yield 7.5 g (69% yield) of product, which decompd violently with a sharp sound at 220° upon rapid heating, ν 4.5 μ (diazo). *Anal.* ($C_4H_3N_5O$) C, H, N.

4-Diazo-5-methylpyrazole-3-carboxamide was prepd in a similar fashion from 4-amino-5-methylpyrazole-3-carboxamide[6] in 47% yield. In contrast to 4-diazopyrazole-3-carboxamide, this light yellow solid[7] decompd gradually upon heating above 200°. *Anal.* ($C_5H_5N_5O$) C, H, N.

4-(3,3-Dimethyl-1-triazeno)pyrazole-3-carboxamide (Ia).—To 125 ml of EtOAc, satd with anhyd Me_2NH at 20° was added 5 g of finely powdered 4-diazopyrazole-3-carboxamide. The mixt was stirred for 3 hr at room temp. The solid was collected by filtration, washed with EtOAc, and recrystd from MeOH to give 1.6 of Ia, mp 215–216°. *Anal.* ($C_6H_{10}N_6O$) C, H, N.

4-(3,3-Dimethyl-1-triazeno)-5-methylpyrazole-3-carboxamide (Ib), mp 193–194° (MeOH), was prepd in 25% yield from 4-

(1) This investigation was supported by Contract No. PH 43-65-94 with Chemotherapy, National Cancer Institute of the National Institutes of Health, Public Health Services.

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(4) All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

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(7) Although not isolated, the existence of this compd was commented on in ref 6.

diazo-5-methylpyrazole-3-carboxamide and Me_2NH in a similar fashion. *Anal.* ($C_7H_{12}N_6O$) C, H, N.

Ethyl 3-(4-Carbamoylpyrazole-3-yl)-2-triazenoacetate (II).—To a mixt of 40 g of finely powdered glycine·HCl Et ester in 600 ml of EtOAc was added 30 g of Et_3N. The resulting mixt was stirred at room temp for 1 hr. To this was added 20 g of powdered 3-diazopyrazole-4-carboxamide[3] and the mixt was stirred for 24 hr. The solid was collected by filtration and extd repeatedly with hot 50% aq MeOH. The insol solid, which melted at 220–222° dec and possessed $\lambda_{max}^{pH\ 11}$ at 402 nm, has not yet been identified. The filtrate was concd *in vacuo* to yield 9 g of analytically pure II, mp 145°. *Anal.* ($C_8H_{12}N_6O_3 \cdot H_2O$) C, H, N, H_2O.

1-[(4-Carbamoylpyrazol-3-yl)azo]DL-proline (III).—To a mixt of 20 g of finely powdered 3-diazopyrazole-4-carboxamide[3] in 500 ml of MeOH was added 40 g of finely powdered DL-proline. The mixt was stirred at 25° for 18 hr and the solid collected by filtration. It was recrystd from 50% aq MeOH to give 5 g of III, mp 188–189°. *Anal.* ($C_9H_{12}N_6O_3$) C, H, N.

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Steroidal Heterocycles. 14.[1] 1,8a-Epoxy-1,4,4a,5,6,7,8,8a-octahydro-2-hydroxynaphthalene-3-carbonitrile and Related Compounds

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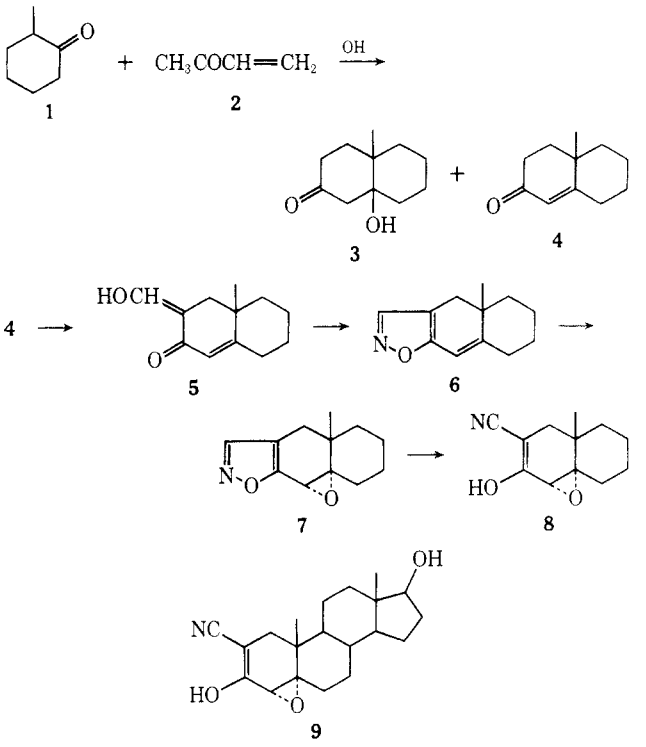
4α,5-Epoxy-3,17β-dihydroxy-5α-androst-2-ene 2-carbonitrile (**9**) and related steroids block the ACTH-induced catabolic and thymolytic responses in castrate male rats.[1] Therefore, it seemed of interest to determine whether related bicyclic compds resembling rings A/B of these steroids would exhibit similar activity. Using known procedures[2-4] indicated in the flow sheet, 2-methylcyclohexanone (**1**) was converted in a series of steps into 1,8a-epoxy-1,4,4a,5,6,7,8,8a-octahydro-4a-methylnaphtho[2,3-*d*]isoxazole (**7**) which was rearranged to **8** with base.

Biological Testing.—Compd **8** showed none of the ACTH-induced catabolic blocking of the corresponding steroid **9** in castrated rats. It did exhibit slight bacteriostatic and fungistatic activities.

Experimental Section

All melting points were taken on a Fisher-Johns melting point apparatus, uncor. Uv spectra were detd in 95% EtOH (Cary 15) and ir in KBr disks (Perkin-Elmer 21). Nmr spectra were measured with (Me_4Si) in $CDCl_3$ (Varian A60). Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theor values.

The author is indebted to Professor W. S. Johnson and Dr. F. W. Stonner for helpful discussion and suggestions, to Dr. Gordon O. Potts and staff for biological evaluation, to Dr. Rudolph K. Kullnig and staff for spectral determinations, and to Mr. K. D. Fleischer and staff for analytical services.



1,8a-Epoxy-1,4,4a,5,6,7,8,8a-octahydro-4a-methylnaphtho[2,3-*d*]isoxazole (7).—The distd hydroxymethylene compd **5**[3] gave an isoxazole **6** with H_2NOH,[3] obtd as an amber resin. Crude resin **6** (no attempt was made to purify **6**) (17.5 g) was dissolved in CH_2Cl_2 (300 ml) and added to H_2O_2 (6 ml; 1.3 g/ml) and maleic anhydride (20 g) in CH_2Cl_2 (100 ml) at 0°.[4] The soln was swirled vigorously, and C_5H_5N (5 drops) was added. The soln became turbid immediately as maleic acid pptd and was kept in a refrigerator overnight. Satd Na_2SO_3 soln was added dropwise with stirring until starch–iodide paper no longer darkened. The soln was washed with $NaHCO_3$ soln, dried ($MgSO_4$), filtered, and concd on a steam bath. Faint yellow, cryst material was obtained (8.89 g; 46.8% yield); the rest was dark amber resin. The product was crystd (EtOAc): mp 85–86°; λ_{max} 237 mμ (6850). *Anal.* ($C_{12}H_{15}NO_2$) C, H, N.

1,8a-Epoxy-1,4,4a,5,6,7,8,8a-octahydro-2-hydroxy-8a-methylnaphthalene-3-carbonitrile (8).—Isoxazole **7** (19.5 g) was dissolved in THF (200 ml), stirred, and cooled in an ice bath. NaOMe (10.8 g) was added and soon a thick ppt of the Na salt of **8** formed. After 2 hr of stirring, Et_2O (100 ml) was added, and the salt was filtered and rinsed with Et_2O. After most of the Et_2O adhering to the salt had dissipated, it was dissolved in H_2O (200 ml), Na_2HPO_4 (10 g) was added, and the soln was acidified with dil HCl. The oily ppt was extd with Et_2O, dried ($MgSO_4$), and concd on a steam bath to afford 18.5 g (85%) of granular crystals, mp 98–100°. They were recrystd (EtOAc): mp 100–102°; λ_{max} 252 mμ (9400), ir 4.54, 5.81 (weak, medium), 6.16 μ. Nmr also indicated a mixt of keto–enol tautomers.[1] *Anal.* ($C_{12}H_{15}NO_2$) C, H, N.

Synthesis of 2-Methylpteridine Derivatives

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We have previously reported on pyrido[2,3-*d*]pyrimidine derivatives, which are potential pteridine antagonists as well as azalogs of nalidixic acid.[1] A continuing

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