washed extract was concentrated and chilled in an ice bath until crystallization occurred. The low melting solid was dissolved in 50 ml of *i*-PrOH and chilled in a Dry Ice bath with the addition of a small amount of hexane to give 27.0 g of 2-chloro-1-cyclopropylmethoxy-4-nitrobenzene, mp 43–47°.

Procedure X. Claisen Rearrangement of *m*-Allyloxy Acetamide.—The *m*-allyloxy acetamide was rearranged in $PhNMe_2$ according to the procedure described by Arnold, *et al.*[3] There was obtained 34.7 g of mixed isomers, mp 135–140°, from 38.6 g of starting ether. Separation was accomplished as follows.

The phenolic mixture was dissolved in 243 ml of 1 *N* NaOH and fractionally precipitated (7 fractions) by addition of 0.5 *N* H_2SO_4 in increments to complete neutralization. The first 5 fractions of mp 157–163° were combined and recrystallized from H_2O to give 10.5 g of 3-hydroxy-4-allylacetanilide, mp 165–166°. Structural verification was made by nmr determination (DMSO).

The last 2 fractions of mp 135–149° were found to be a mixture of the above material with 2-allyl-3-hydroxyacetanilide. Purification was accomplished by 3 fractional reprecipitations and final recrystallization from aqueous MeOH, mp 146–147°.

Procedure Y. 2-Cyclopropylmethoxy-5-nitrophenyl 2-Methallyl Ether.—A solution of 68.0 g of 2-cyclopropylmethoxy-5-nitrophenyl benzoate in 500 ml of 95% EtOH was mixed with 23 g of 50% NaOH and refluxed for 2 hr. The solution was diluted with 500 ml of H_2O and distilled *in vacuo* to remove EtOH. The residue was diluted with a further 500 ml of H_2O and chilled in an ice bath. Acidification with 60 ml of concentrated HCl produced a yellow crystalline product, which was extracted with 500 ml of CH_2Cl_2. The extract was stirred overnight with 500 ml of 10% $NaHCO_3$. The organic layer was washed with 200 ml of H_2O and then evaporated to dryness under reduced pressure (51.0 g). The residue was dissolved in 100 ml of DMF. To this was added 200 ml of C_6H_6, 0.5 g of NaI, and 8.7 g of NaOH. The solution was refluxed and H_2O was removed as formed. The solution was combined with 20 g of methallyl chloride and refluxed for 3 hr. After dilution with 200 ml of H_2O, C_6H_6 was removed *in vacuo*. The crystalline solid was filtered and washed with H_2O. Recrystallization from *i*-PrOH gave 53.0 g of cyclopropylmethyl-2-methallyl-4-nitrocatechol, mp 87–90°.

6,7-Bis(cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxhydrazide.—A mixture of 3.0 g of ethyl 6,7-bis(cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxylate, 3.5 g of $N_2H_4 \cdot H_2O$ (99%), and 50 ml of anhydrous EtOH was heated for 12 hr at 150° in a sealed tube. The yellow product (1.0 g) was filtered, mp 265–267° dec, and found to be essentially pure.

Acknowledgment.—The authors wish to express their gratitude to Mr. Louis Dorfman and his staff for the elemental analyses and spectral determinations.

Anticoccidial Activity in 1-[2-(Cycloalkyl)- and 2-(Cycloalkylmethyl-4-amino-5-pyrimidyl)methyl]pyridinium Salts

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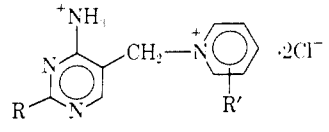
The enhanced anticoccidial activity of 1-[(4-amino-2-cyclopropylmethyl-5-pyrimidyl)methyl]picolinium and lutidinium salts is shown. Comparisons are made with other 2-cycloalkyl- and 2-cycloalkylmethyl derivatives. The structure of the 2 substituent in the types investigated was found to be critical.

In an excellent discussion of thiamine antagonists Rogers[1] outlined the parameters required of this class of antimetabolites as anticoccidial agents. The data show that certain variations are possible in the 2 or 5 positions for retention of activity. Alteration of the 4-amino group, however, leads to a loss of biological activity. Optimum anticoccidial activity was obtained in **1**.



R = Et, Pr, C_2F_5
R′ = 2-Me, 2,4-$(Me)_2$, 4-Me, 2-Me-5-Et

1

The importance of the 2 substituent in determining the degree of anticoccidial activity is demonstrated in the current literature. Thus, the Et derivative is less active than the *n*-Pr derivative, which in turn is more effective than the *n*-Bu or *i*-Bu derivatives. 2-Cycloalkyl moieties, however, have not been investigated, although on the basis of bond length alone cyclopropylmethyl approximates rather closely the length of *n*-Pr (Chart I). Consequently, substances bearing this substituent were prepared as shown in Scheme I.

(1) E. F. Rogers, *Ann. N. Y. Acad. Sci.*, **98**, 412 (1962).

The 2 substituent was further varied to include cyclopropyl, cyclobutylmethyl, and cyclopentyl as a further test of the range of activity possible with these types of substituents.

The synthetic sequence employed conventional reactions, and generally proceeded as expected. In one departure from the procedure outlined in Scheme I, 4-amino-2-cyclobutylmethyl-5-cyanopyrimidine was hydrogenolyzed directly to the 5-carbinol (Scheme II).

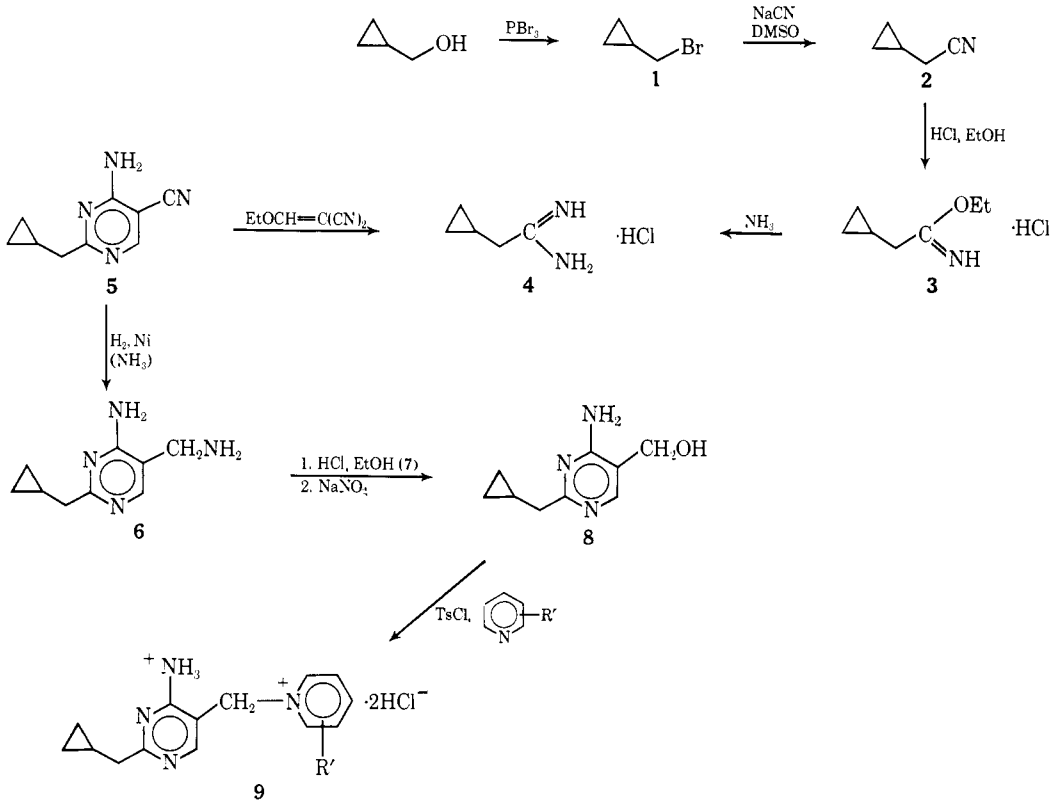
Biological Test Methods. A.—One-day old Leghorn chicks (Shamrock Farms, North Brunswick, N. J. 08902) were kept in electric brooders for **7** days. They were then divided into appropriate experimental and control groups comprising 5–10 birds and placed into cages heated with light bulbs. The 8-day old chicks were inoculated into their crop with approximately 2×10^5 sporulated oocysts of *Eimeria tenella* by incubation. One day prior to infection, the regular starter feed was replaced by medicated diet, consisting of feed with the drug incorporated by mixing in a rotating V-shaped mechanical mixer. Compounds were tested initially at 0.05% does level in the feed. In case of coccidiostatic activity, the dose level was reduced in subsequent experiments to determine the minimal concentration exhibiting anticoccidial efficacy. Death from coccidiosis among unmedicated control birds started approximately 4 days after infection and by the 8th day, 90% or more were dead.

CHART I

For evaluation of coccidiostatic activity, the cumulative mortality on the 8th day after infection was determined in control and treated birds. An 80% protection was considered a marked coccidiostatic effect.

and mixed infections. Thus, maximum anticoccidial activity was attained for the 2,4-lutidinium and 2-picolinium derivatives (**9**, Scheme I; R = 2,4-Me_2, and 2-Me). The corresponding 2-cyclobutylmethyl homologs showed a much lesser anticoccidial effect. The 2-cyclopropyl compounds however, were effective in this infection, though less so than for **9**. Enlarging the ring size to 2-cyclopentyl and 2-cyclohexyl homologs causes a considerable decrease in activity.

SCHEME I



B.—The efficacy tests against mixed coccidial infections were carried out in battery cages. One-day old Peterson Cross (Peterson males X Arbor Acres females) broiler chicks obtained from a commercial hatchery were raised in battery brooders for 2 weeks before the test. Ten birds, 5 males and 5 females, were randomly selected for each group. The treatments were replicated 2, 3, or 4 times.

Feed and H_2O were available to the chicks *ad ilbitum*. The medicated feed was offered starting 2 days before infection and it was the only feed throughout the trial period. The coccidia inoculum was prepared by mixing a calculated number of sporulated oocysts from pure cultures of *E. acervulina*, *E. necatrix*, and *E. tenella*. The inoculum was administered into the crop to each individual chick with an automatic pipetting syringe equipped with a No. 7 venous cannula. The criteria for measurement of anticoccidial activity were weight gain, feed conversion, survival, fecal dropping score, and oocyst output.

Biological Results.—The relative anticoccidial activities of compounds tested in this series is (from Table III): **25** > **24** > **29** > **28** > **26**, **27**, in both *E. tenella*

Experimental Section

Melting points and boiling points are uncorrected.

Cyclopropylacetonitrile.—Prepared by the method of Friedman and Schechter,[2a] with minor changes, as shown below. Von Braun and collaborators[2b] utilize cyclopropylmethylbromide and KCN in aqueous EtOH.

A solution of 103.8 g of NaCN in 800 ml of DMSO was warmed to 55–60° and treated with 253 g of bromomethylcyclopropane[3] (vigorous stirring) over 1.25 hr. Periodic cooling with H_2O was required. The reaction was maintained at 70° for 2.5 hr. It was then cooled, poured into H_2O, and extracted with five portions of Et_2O (1300 ml). The extract was washed once with 100 ml of ice-cold 6 *N* HCl and once with 100 ml of H_2O. The dried extract was stipped of solvent and the product distilled, bp 148–150° (116.5 g). *Anal.* (C_5H_7N) C, H, N.

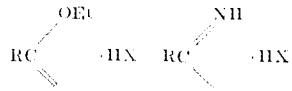
The following procedures are typical of those employed in the synthetic work, and were used throughout with minor modifications.

Ethyl Cyclopropylacetimidate Hydrochloride.—A solution of 358.1 g of cyclopropylacetonitrile in 218 g of anhydrous EtOH at 0° was treated with 167 g of dry HCl. Theroretical uptake took place during 2 hr. The homogeneous solution was diluted with 200 ml of anhydrous Et_2O and refrigerated at −20° for 18

(2) (a) L. Friedman and H. Schechter, *J. Org. Chem.*, **25**, 877 (1960); (b) J. v. Braun, M. Kuhn, and S. Siddiqui, *Ber.*, **59B**, 1081 (1926).

(3) J. S. Meek and J. W. Rowe, *J. Amer. Chem. Soc.*, **77**, 6675 (1955).

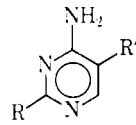
TABLE I



No.	RCN, R=	R= (HX)	R= (HX =)	Mp or bp, °C (mm)	Yield, %	Empirical formula	Analyses
1				148–150 (760)		C_5H_7N	C, H, N
2		 (HCl)		84 dec	32.9	$C_7H_{14}ClNO$	C, H, N
3			 (HCl)	125.5–126	97.0	$C_5H_{11}ClN_2$	C, H, Cl
4				52–56 (15)	100	C_6H_9N	C, H, N
5		(HBr)		79–81	84.0	$C_9H_{16}BrNO$	C, H, Br
6			(HBr)	152–156	86.5	$C_9H_{18}BrN_3$	C, H
7		(HBr)	[a]	82–83	64.2	$C_9H_{16}BrNO$	C, H, Br
8			 (HBr)				[b]
9			 (HBr)				[a]
10			 (HBr)				[b]

[a] Structual verification by nmr. [b] Used without further purification. [c] $n^{25}D$, 1.4376.

TABLE II



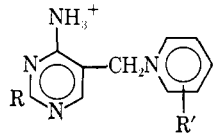
No.	R	R′	Mp, °C	Yield, %	Empirical formula	Analyses
11		CN	182.5–182.8		$C_9H_{10}N_4$	C, H
12		CH_2NH_2	233.5–234		$C_9H_{16}Cl_2N_2$[c]	C, H, N
13		CH_2OH	140–141		$C_9H_{13}N_3O \cdot H_2O$	C, H, N
14		CN	179–181	62.0	$C_{10}H_{12}N_4$	C, H, N
15		CH_2NH_2	259–262	50.8	$C_{10}H_{18}Cl_2N_4$[a]	C, H, N
16		CH_2OH	133–137	75.9	$C_{10}H_{15}N_3O$	C, H, N
17		CN	160–163	31.4	$C_{10}H_{12}N_4$	C, H, N
18		CH_2OH	130–133	65.4	$C_{10}H_{16}ClN_3O$	N
19		CN	185–188	64.8		[c]
20		CH_2NH_2	170–171	73.5		[a, d]
21		CH_2OH	158–162	55.8		[c]
22		$CH_2O(i\text{-}Pr)$	118–120	58.1		C, H, N
23		CH_2Cl	180–181 dec	88.9	[b]	[b]

[a] Dihydrochloride. [b] Monohydrochloride; structural verification by nmr. [c] Structural verification by nmr. [d] Uv max 235, 276 mμ; min at 220, 255 mμ.

hr. Crystallization was induced by scratching and addition of another 700 ml of Et_2O. The crystalline solid was filtered, washed with Et_2O, and vacuum dried (144.3 g, mp 84° dec). A second crop separated on the further addition of Et_2O (132.0 g, mp 84° dec). The combined crops were recrystallized from anhydrous EtOH–Et_2O; no change in melting point occurred. No improvement resulted on further recrystallization. Analysis by nmr indicated a high order of purity, however.

Cyclopropylacetamide·HCl.—A solution of 276 g of ethyl cyclopropylacetamidate·HCl in 220 ml of anhydrous EtOH was chilled to *ca.* −5° in an ice–salt bath, and treated, with stirring, with 165 ml of saturated ethanolic NH_3 (saturated at 0°) added rapidly. The somewhat exothermic reaction was cooled rapidly, and stirred at ice-bath temperature for 3 hr. Slightly basic conditions were maintained by addition of small quantities of ethanolic NH_3. The solution was concentrated *in vacuo* to *ca.* one-third vol. Chilling and scratching gave a mass of white crystals. Et_2O was added carefully with swirling and further chilling. The product was filtered, washed with Et_2O, and vacuum dried (221 g, 97%, mp 125.5–126°). Recrystallization from *i*-PrOH–

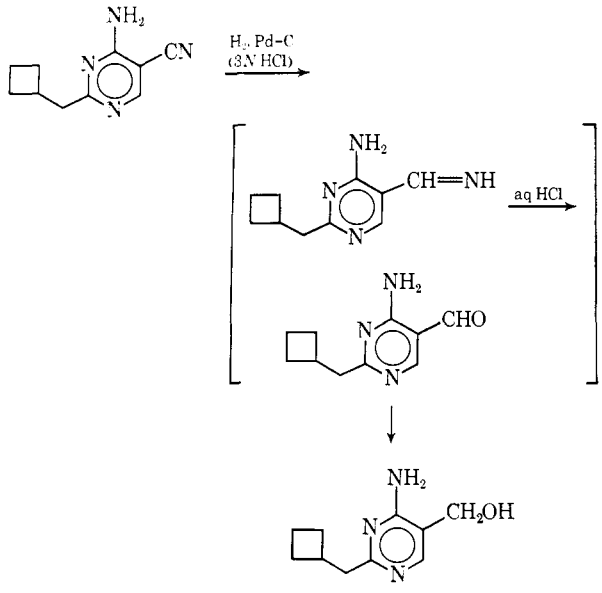
TABLE III



No.	R	R′	Mp, °C	Empirical formula	Analyses
24		2-Me	225.5–226.5	$C_{15}H_{20}Cl_2N_4$	C, H, N
25		2,4-$(Me)_2$	253.2–253.5 dec	$C_{16}H_{22}Cl_2N_4$	C, H, N
26		2,4-$(Me)_2$	249–251 dec	$C_{17}H_{24}Cl_2N_4$	C, H, N
27		2,4-$(Me)_2$	258–260	$C_{17}H_{24}Cl_2N_4$	C, H, N
28		2-Me	227–228 dec	$C_{14}H_{18}Cl_2N_4$	*a*
29		2,4-$(Me)_2$	228–230 dec	$C_{15}H_{20}Cl_2N_4$	*a*
30		2,4-$(Me)_2$	215–220	$C_{18}H_{26}Cl_2N_4$	*a*
31		2-Me	218–220	$C_{17}H_{24}Cl_2N_4$	*a*

[a] Structural verification by nmr.

SCHEME II



Et_2O and drying at 60° (0.1 mm) gave analytically pure material.

4-Amino-2-cyclopropyl-5-pyrimidinecarbonitrile.—A solution of 136.6 g of cyclopropylacetamidine·HCl in 500 ml of anhydrous EtOH was added at 0°, during 0.5 hr to a solution of 23.8 g of Na in 1 l. of anhydrous EtOH under N_2. After 0.25 hr the solution was filtered through a bed of Filter Cel (prewashed with anhydrous EtOH) contained on a sintered glass funnel. The resulting solution was added during 1.25 hr to a solution of 124 g of ethoxymethylenemalononitrile in 1 l. of anhydrous EtOH. The initial reaction temperature of 15° was lowered to 0° after 5–10% of the amidine base had been added. After 6 hr at 0° the product was filtered, washed with cold EtOH, and vacuum dried (140.0 g, mp 182.5–182.8°). The product was analytically pure as isolated.

4-Amino-5-aminomethyl-2-cyclopropylmethylpyrimidine·2HCl.—A solution of 17.4 g of 4-amino-5-cyano-2-cyclopropylmethylpyrimidine, 40 ml of liq NH_3 and 275 ml of MeOH was hydrogenated at 2.8 kg/cm² in the presence of 1 tsp of Davison Sponge Ni catalyst (prewashed with anhydrous EtOH). The combined filtrate and washings, after filtering off the spent catalyst, were evaporated to dryness to give a light yellow solid (22.0 g). This material was dissolved in anhydrous EtOH and acidified to congo red paper with ethanolic HCl. The product which separated on chilling was filtered and washed with *i*-PrOH and Et_2O (11.3 g, mp 233.5–234°).

A second crop was obtained to give 2.7 g of material, mp 232.5–233°, on recrystallization as described above.

4-Amino-2-cyclopropylmethyl-5-pyrimidinemethanol·H_2O.—A solution of 10.2 g of $NaNO_2$ in 450 ml of H_2O was added to a solution of 33.7 g of 4-amino-5-aminomethyl-2-cyclopropylmethylpyrimidine·2HCl during 1 hr at 52°. Heating was continued for 5 hr. The reaction mixture was allowed to stand overnight at room temperature. The solution was treated with Norite and filtered with the aid of Filter Cel. The filtrate was concentrated at the aspirator. The solution was chilled and adjusted to pH 8 with saturated aqueous Na_2CO_3. The solution was extracted with 3 portions of *n*-BuOH. A light yellow solid remained on removal of the solvent from the dried extract (19.6 g, mp 131.5–137°). Purification by recrystallization from *i*-PrOH gave material of mp 140–141° after drying *in vacuo* at 60°; this corresponds to the monohydrate.

Procedure A. 1-[(4-Amino-2-cyclopropylmethyl-5-pyrimidyl)-methyl]-2-picolinium Chloride Hydrochloride.—A solution of 18.5 g of 4-amino-2-cyclopropylmethyl-5-pyrimidylmethanol in 100 ml of 2-picoline was treated with 19.9 g of TsCl, added in small portions with chilling. The resultant homogeneous solution was maintained at −15° for 5 days. A white crystalline mass formed during the first 24 hr. The reaction mixture was diluted with a large volume of Et_2O and stirred. The supernatant was discarded and the residue was triturated repeatedly with Et_2O to elute as much of the excess picoline as possible. Final trituration with *i*-PrOH gave a mass of white crystals which was filtered, washed with *i*-PrOH, and dried (29.8 g, mp 173–179°).

This material was dissolved in 250 ml of H_2O and 5 ml of 0.006 *N* HCl. The solution was passed through Amberlite IRA400 (Cl^-). The column was washed finally with 500 ml of H_2O. Combined eluate and washings were concentrated *in vacuo* to a small volume and finally distilled with *i*-PrOH to remove as much H_2O as possible. The light yellow residue was recrystallized from MeOH–*i*-PrOH (1:1) to give material of mp 225.5–226.5° (dec 251°) (13.9 g).

Procedure B. 1-[(4-Amino-2-cyclopropylmethyl-5-pyrimidyl)-methyl]-2,4-lutidinium Chloride Hydrochloride.—A solution of 73.0 g of 4-amino-2-cyclopropylmethyl-5-pyrimidylmethanol in 385 ml of freshly distilled 2,4-lutidine (bp 155–157°) was treated portionwise with 78.5 g of freshly ground TsCl. The homogeneous reaction was held at −20° for 6 days with occasional swirling. A white solid crystallized from the mixture on addition of EtCOMe and scratching (78.6 g, mp 222–226°, dec 250°) (A). Recrystallization from anhydrous EtOH–EtCOMe gave material, mp 250–250.5° (dec 253°).

The reaction filtrate was concentrated to a small volume to remove excess lutidine. The residue was dissolved in *i*-PrOH and reprecipitated with EtOAc to further remove exess lutidine.

The gummy solid was redissolved in a small amount of *i*-PrOH and treated with a slight excess of HCl–EtOAc to give 3.6 g of material, mp 233–234° (dec 244°). A further crop of 49.4 g of somewhat gummy material was obtained from the filtrate of (A) by addition of EtOAc. This material was dissolved in *i*-PrOH and treated with HCl in EtOAc as described to give an additional 15.2 g of material, mp 235–237° (dec 245°). The combined, partially purified crops were recrystallized twice from anhydrous EtOH–EtOAc to give 76.4 g of compound, mp 253.2–253.5° dec.

Bromomethylcyclobutane.—Prepared by the method of Meek and Rowe.[3] As in the case of bromomethylcyclopropane a pure compound, with no evidence of rearrangement, was obtained by this procedure, which is somewhat more convenient than that of Krug, *et al.*[4]

Cyclobutylacetonitrile.—Prepared by the method given for cyclopropylacetonitrile.

4-Amino-2-cyclopentyl-5-pyrimidylmethanol.—A mixture of 18.8 g (0.1 mole) of 4-amino-5-cyano-2-cyclopentylpyrimidine, 3.5 g of 10% Pd–C, and 250 ml of 2.9 *N* HCl was hydrogenated at 3.3 kg/cm². Theoretical uptake of H_2 occurring during 4.5 hr. The catalyst was filtered and the filtrate concentrated *in vacuo*. Last traces of H_2O were removed by codistillation with *i*-PrOH. Final concentration to a low volume yielded a mass of crystals on chilling and scratching (15.0 g) mp 130–133°.

The base was obtained by solution of the HCl salt in H_2O and addition of 50% NaOH solution. The substance was extracted with *n*-BuOH and the extract was dried ($MgSO_4$). A gummy solid was obtained on removal of the solvent; this became crystalline, mp 101–104° on trituration with EtOAc.

Procedure C. 1-[(4-Amino-2-cyclopropyl-5-pyrimidyl)methyl]-2-picolinium Chloride Hydrochloride.—A suspension of 2.63 g of 4-amino-5-chloromethyl-2-cyclopropylpyrimidine·HCl in 20 ml of 2-picoline was heated on a steam bath for 3 hr with occasional stirring. The suspension was cooled and the hard ball broken up and reheated with 10 ml of fresh 2-picoline for 45 min. The suspension was filtered, washed with Et_2O, and dried (3.46 g mp 226–227°). The substance was heated with 25 ml of *i*-PrOH, chilled, filtered, and dried (3.24 g, mp 227–228° dec). Identity and purity were verified by nmr.

4-Amino-5-chloromethyl-2-cyclopropylpyrimidine·HCl.—A solution of 4.8 g of 4-amino-2-cyclopropyl-5-pyrimidylmethanol in 25 ml of DMF was chilled to 0° and treated with 5.62 g of $SOCl_2$. After 1 hr the reaction mixture was allowed to warm to room temperature and then kept overnight. A gummy product was formed on addition of Et_2O and was triturated several times with Et_2O. A solution of this substance in anhyd EtOH was treated with 10% EtOH·HCl until slightly acidic. The solvent was removed *in vacuo* and distillation repeated with C_6H_6 to give a gummy solid. A crystalline product was isolated on recrystallization from Me_2CO (5.7 g) mp 180–181° dec. Structural verification was by nmr analysis.

4-Amino-2-cyclohexyl-5-isopropoxymethylpyrimidine. A 24.3-g quantity of cyclohexanecarboxamidine·HBr was added to a solution of 2.46 g of Na in 150 ml of *i*-PrOH contained under N_2. To this was added in 1 hr at ice-bath temperature a solution of 18.3 g of α-isopropoxymethyl-β-methoxyacrylonitrile in 50 ml of *i*-PrOH. The reaction mixture was allowed to come to room temperature and was allowed to stir overnight. It was concentrated *in vacuo* as far as possible. The residue was dissolved in 2% HCl and extracted with Et_2O. After basification with Na_2CO_3 solution the product was extracted with CH_2Cl_2. The dried extract was stripped of solvent to give 20.9 g of light yellow needles, mp 109–114°. The product was recrystallized from C_6H_{12} (17.0 g), mp 118–120°. *Anal.* ($C_{14}H_{23}N_3O$) C, H, N; uv max at 234 and 273 mμ, min at 215 and 254; in acid max 249 mμ; min at 220.

Procedure D. 1-[(4-Amino-2-cyclohexyl-5-pyrimidyl)methyl]-2-picolinium Chloride Hydrochloride.—A solution of 6.34 g of 4-amino-2-cyclohexyl-5-isopropoxymethylpyrimidine in 12.7 ml of 2-picoline and 50 ml of xylene was treated with anhydrous HCl which was bubbled in at a moderate rate. The rate was adjusted to maintain the exotherm at about 80°. After about 50 min the temperature dropped. The solution was refluxed with stirring for 2 hr. Addition of a further 6-ml portion of 2-picoline was followed by 1.5 hr additional heating. The supernatant was removed and the residue treated with 25 ml of MeCN. Stirring overnight and filtering gave 8.3 g of solid, mp 218–220°. The structure was verified by nmr determination.

1-[(4-Amino-2-cyclohexyl-5-pyridimidyl)methyl]-2,4-lutidinium chloride hydrochloride was prepared by procedure D.

Acknowledgment.—The authors wish to express their appreciation to Mr. Louis Dorfman and his staff for the elemental analyses and spectral determinations.

(4) R. C. Krug, L. W. Smith, and C. E. Frey, *J. Amer. Chem. Soc.*, **76**, 3222 (1954).

Quinazolines. VI. Synthesis of 2,4-Diaminoquinazolines from Anthranilonitriles[1]

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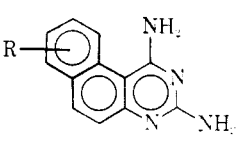
A number of substituted 2,4-diaminoquinazolines have been prepared and studied in microbiological, mammalian cell culture and transplantable mouse tumor systems. Structure–antifolate correlations in microbiological systems are presented, together with an interpretation of the optimal inhibitory activity of the 5-substituted compounds.

As part of a long-standing chemical and biological program involving various types of condensed 2,4-diaminopyrimidine derivatives as candidate chemotherapeutic agents, we have recently reported the synthesis of some 1,3-diaminobenzo[*f*]quinazolines (I),[2] and have presented preliminary data on their antifolic,



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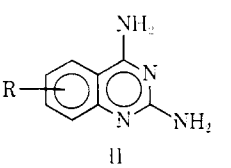

II

antitumor, and antimalarial activity.[3] In connection with this work, it was of interest to prepare a series of simpler 2,4-diaminoquinazoline analogs (II). In par-

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(2) (a) A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **31**, 2607 (1966); (b) A. Rosowsky and E. J. Modest, *J. Heterocycl. Chem.*, **3**, 387 (1966); (c) E. P. Burrows, A. Rosowsky, and E. J. Modest, *J. Org. Chem.*, **32**, 4090 (1967) (paper V of this series).

(3) These results were presented in part before the Division of Medicinal Chemistry at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1967.