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_6 (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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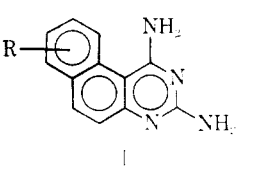
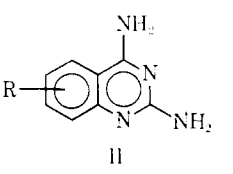
Received March 23, 1970

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,



I



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-

(1) This investigation was supported in part by a research grant (CA6516) and a research career development award (K3-CA-22,151) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

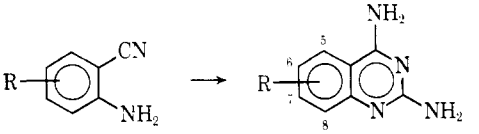
(2) (a) A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **31**, 2607 (1966); (b) A. Rosowsky and E. J. Modest, *J. Heterocycl. Chem.*, **3**, 387 (1966); (c) E. P. Burrows, A. Rosowsky, and E. J. Modest, *J. Org. Chem.*, **32**, 4090 (1967) (paper V of this series).

(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.

ticular, it was hoped that the significantly greater water solubility of 2,4-diaminoquinazolines might facilitate their biological transport and result in more favorable chemotherapeutic properties.

Occasional references can be found in the literature concerning the antifolic and antibacterial properties of 2,4-diaminoquinazolines;[4] however, only a limited amount of chemical work is published.[5] In this paper, we should like to report on the synthesis of 2,4-diaminoquinazolines by a relatively seldom-used approach, starting from anthranilonitriles. Our interest in the use of anthranilonitriles was prompted by an earlier finding in this laboratory that 1-cyano-2-naphthylamine condensed readily with cyanamide in the presence of pyridine·HCl at elevated temperature,[2a] whereas no reaction could be effected upon prolonged treatment with guanidine in refluxing 2-methoxyethanol. This observation made it desirable to seek additional information concerning the possible influence of structure upon the reactivity of the *o*-aminonitrile system.[6] To this end, we prepared a series of anthranilonitriles bearing Me, Cl, and MeO substituents at various positions, and carried out condensation reactions with three potential 2,4-diaminopyrimidine ring-forming reagents, namely, cyanamide, cyanoguanidine, and guanidine.

The anthranilonitriles used in this work were synthesized *via* standard routes. For example, 4-methyl-2-nitroaniline was converted into 4-methyl-2-nitrobenzonitrile through a Sandmeyer reaction, and the latter compound was reduced to 4-methylanthranilonitrile (IIIa) with $SnCl_2$.[7] Similarly prepared from the appropriately substituted *o*-nitroanilines were 6-Me-,[8] 4,5-Me_2-, 4-Cl-,[9] 4,5-Cl_2-, 4-MeO-,[10] and 6-methoxyanthranilonitriles[11] (IIIc–IIIe, IIIg–IIIi). 5-Methylanthranilonitrile (IIIb) was obtained by pyrolysis of 5-methylisatin,[12] and 5-chloroanthranilonitrile (IIIf) was synthesized from *p*-chloroaniline by iodination and subsequent reaction with CuCN in pyridine.[13] Of the aforementioned anthranilonitriles, IIId and IIIg have not been reported previously.



IIIa-i IIa-i

Representative examples of the reaction of anthranilonitriles with cyanamide, cyanoguanidine, and guanidine are given in the Experimental Section. The reaction with cyanamide and pyridine·HCl was performed essentially as reported earlier for 1-cyano-2-naphthylamine.[2a] For the condensation with cyanoguanidine, the anthranilonitriles were converted into HCl salts, which were fused with cyanoguanidine by heating at *ca.* 160° for 10–15 min. For the reaction with guanidine, equivalent amounts of the anthranilonitrile and guanidine·HCl were added to a solution of NaOMe in 2-methoxyethanol, a slight excess of base being used. The mixture was refluxed for several days, the progress of the reaction being monitored by uv spectroscopy and tlc.

Attempted condensations with guanidine in lower-boiling alcohols were unsuccessful. All the anthranilonitriles were condensed with cyanamide, but only a few selected examples were condensed with cyanoguanidine and guanidine. Yields for all the reactions and physical constants for the 2,4-diaminoquinazoline products are shown in Table I.

Examination of the yields listed in Table I allows certain tentative conclusions to be drawn concerning (1) the influence of substituents upon the reactivity of anthranilonitriles and (2) the efficacy of the three pyrimidine ring-forming reagents. Where a direct comparison can be made, there appears to be little or no difference between cyanamide and cyanoguanidine, as might be expected. Reactions in which cyanoguanidine was used all gave yields of approximately 30%, regardless of substituent variation. Among the reactions carried out with cyanamide, the possibility of some substituent dependence was indicated by the low yields obtained with anthranilonitriles containing Cl *para* to CN. A fairly low yield was also obtained with 6-methoxyanthranilonitrile. In the case of guanidine reactions, there appears to be a slight preference for Cl-substituted anthranilonitriles. After 8-days reflux, the reaction of Me- and MeO-substituted anthranilonitriles proceeded only in trace amount, as evidenced by tlc and uv spectroscopy. In contrast, the chlorinated analogs gave yields of approximately 10% after 3-days reflux. Previously reported successful condensations of guanidine with such heterocyclic *o*-aminonitriles as 4-amino-5-cyanopyrimidines[14] and 3-aminopyrazinecarbonitriles[15] apparently cannot be extended to the carbocyclic series; in the latter instance,

(4) (a) E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. M. Rollo, and P. B. Russell, *Brit. J. Pharmacol.*, **6**, 185 (1951); (b) G. H. Hitchings, G. B. Elion, and S. Singer, *Chem. Biol. Pteridines, Ciba Found. Symp.*, **1954**, 290 (1954); (c) O. D. Bird, V. Oakes, K. Undheim, and H. N. Rydon, *Pteridine Chem., Proc. Int. Symp., 3rd*, **1962**, 417 (1964); (d) J. J. Burchall and G. H. Hitchings, *Mol. Pharmacol.*, **1**, 126 (1965).

(5) The following is a representative listing of the approaches reported in the literature to date: (a) 2,4-diamino-6-methylquinazoline (IIb) *via* chlorination and amination of 2,4-dihydroxy-6-methylquinazoline [V. Oakes, H. N. Rydon, and K. Undheim, *J. Chem. Soc.*, 4678 (1962)]; (b) 2,4-diaminoquinazoline from anthranilonitrile and cyanamide or cyanoguanidine in aq acid [W. Zerweck and W. Kunze, German Patent 737,931 (July 1, 1943); *Chem. Zentralbl.*, **144** [2], 2015 (1943)]; (c) IIb and other alkyl-substituted analogs from anthranilonitriles and cyanoguanidine under fusion conditions, and also from 2,4-dihydroxyquinazolines *via* chlorination and amination [G. H. Hitchings, E. A. Falco, and K. W. Ledig, U. S. Patent 2,945,859 (July 19, 1960); *Chem. Abstr.*, **54**, 24820 (1960)]; (d) 2,4-diaminoquinazoline from quinazoline and $NaNH_2$ in $PhNMe_2$ [S. Skraup, German Patent 958,197 (Feb 14, 1957); *Chem. Abstr.*, **53**, 8177 (1959)]; (e) 2,4-diaminoquinazoline from 2-tetralone *via* cyanoguanidine fusion and Pd-C dehydrogenation [E. J. Modest, S. Chatterjee, and H. Kangur Protopapa, *J. Org. Chem.*, **30**, 1837 (1965)]; (f) 2,4-diamino-6-nitroquinazolines from 2-chloro-5-nitrobenzonitriles and guanidine [John Davoll, British Patent 1,078,887 (Aug 9, 1967); *Chem. Abstr.*, **68**, 6668 (1968)].

(6) For a discussion of substituent effects upon the reaction of anthranilonitriles with CS_2 and also an extensive bibliography on the chemistry of *o*-aminonitriles, see E. C. Taylor, A. McKillop, and R. N. Warrener, *Tetrahedron*, **23**, 891 (1967).

(7) (a) M. T. Bogert and A. Hoffman, *J. Amer. Chem. Soc.*, **27**, 1293 (1905); (b) G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, 2551 (1929).

(8) (a) S. Gabriel and A. Thieme, *Chem. Ber.*, **52**, 1079 (1919); (b) J. Kenner and E. Witham, *J. Chem. Soc.*, **119**, 1452 (1921).

(9) R. L. McKee, M. K. McKee, and R. W. Bost, *J. Amer. Chem. Soc.*, **69**, 940 (1947).

(10) A. H. Cook, I. M. Heilbron, K. J. Reed, and M. N. Strachen, *J. Chem. Soc.*, 861 (1945).

(11) P. Friedländer, S. Bruckner, and G. Deutsch, *Justus Liebigs Ann. Chem.*, **388**, 23 (1912).

(12) G. R. Bedford and M. W. Partridge, *J. Chem. Soc.*, 1633 (1959).

(13) K. W. Breukink, L. H. Krol, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **76**, 401 (1957).

(14) (a) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Amer. Chem. Soc.*, **82**, 5711 (1960); (b) H. Graboyes, G. E. Jaffe, I. J. Pachter, J. P. Rosenbloom, A. J. Villani, J. W. Wilson, and J. Weinstock, *J. Med. Chem.*, **11**, 568 (1968).

(15) J. H. Jones and E. J. Cragoe, Jr., *ibid.*, **11**, 322 (1968).

Table I
Synthesis and Physical Constants of 2,4-Diaminoquinazolines

Compd II	R	Method[a]	% yield[b]	Mp, °C (of anal. sample)	Empirical formula	Analyses[c]
a	5-Me	A	33	210–211[d]	$C_9H_{10}N_4$	C, H, N
		C	[e]			
b	6-Me	A	31	255.5–256.5[f,g]	$C_9H_{10}N_4 \cdot 0.5H_2O$	C, H, N
c	7-Me	A	36	226–227	$C_9H_{10}N_4$	C, H, N
		B	24			
		C	[e]			
d	6,7-Me_2	A	45	253–254[f]	$C_{10}H_{12}N_4 \cdot 0.25H_2O$	H, N; C[f]
e	6-Cl	A	37	269–271.5[i]	$C_8H_7N_4Cl$	C, H, Cl, N
		B	33			
		C	*ca.* 10[h]			
f	7-Cl	A	14	229.5–230.5	$C_8H_7N_4Cl$	C, H, Cl, N
		B	33			
		C	*ca.* 10[h]			
g	6,7-Cl_2	A	9	270–270.5[f]	$C_8H_6N_4Cl_2$	C, H, Cl, N
		C	*ca.* 10[h]			
h	5-MeO	A	16	208–209[f]	$C_9H_{10}N_4O$	C, H, N
i	7-MeO	A	32	229–230	$C_9H_{10}N_4O$	C, H, N
		B	31			
		C	[e]			

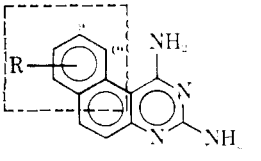
[a] Method A: H_2NCN–$C_5H_5N \cdot HCl$; method B: $H_2NC(=NH)NHCN$ on HCl salt; method C: $H_2NC(=NH)NH_2$. [b] Actual yields are probably higher in some cases; the values reported are after one crystallization. [c] Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ± 0.4% of the theoretical values. [d] Lit.[5c] 212–13°. [e] Slight reaction after 8 days. [f] Analytical sample prepared by vacuum sublimation. [g] Lit.[5a] 256°. [h] Reaction worked up after 2 days. [i] According to a publication which appeared after the completion of this work [J. K. Horner and D. W. Henry, *J. Med. Chem.*, 11, 946 (1968)], IIe has mp 268–273°. [j] C: calcd, 62.31; found, 62.79.

the use of cyanamide or cyanoguanidine in the presence of acid seems clearly preferable.

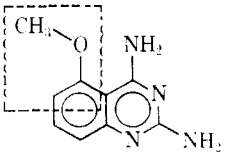
Biological Results.—The 2,4-diaminoquinazolines synthesized in this program were examined in several *in vitro* and *in vivo* bioassay systems at The Children's Cancer Research Foundation. In microbiological systems,[16] significant activity [ID_{50} (50% inhibiting dose) < 10 μg/ml] was observed against *Streptococcus faecalis*, *Lactobacillus arabinosus*, and *Pediococcus cerevisiae* (Table II); little or no activity was shown in the *L. casei* 7469/riboflavin (0.01 μg/ml) or *L. fermenti* 9338/thiamine (0.01 μg/ml) test systems. With the exception of the 7-MeO derivative (IIi), all of the compounds were active against KB cells (human epidermoid carcinoma) in culture,[17] with ID_{50} values in the range 0.7 to 5 μg/ml. Six compounds (IIa, IIc, IId, IIe, IIh, and IIi) were tested *in vivo* against two transplantable mouse lymphatic leukemias in ascitic form: L1210 leukemia in BDF/1 hybrid mice and P1534 leukemia in DBA/2 inbred mice. Compounds were injected intraperitoneally daily for 4 days beginning on the first day after tumor implantation, at 4 logarithmically spaced dose levels. At nontoxic doses none of the compounds tested significantly prolonged survival of L1210 leukemic mice. However, IIc at 7.5 mg/kg per day × 4 and IIh at 10 mg/kg per day × 4 prolonged the life span of P1534 leukemic mice by 24% and 25%, respectively, beyond the survival time of untreated controls.

Two interesting structure–activity correlations can be made on the basis of the inhibition data in bacterial systems presented in Table II (systems 1–4). The first of these is that the growth-inhibitory activity of substituted 2,4-diaminoquinazolines in the bacterial systems tested appears to follow the order of substitution, 7- < 6- < 5-, with the 6,7-disubstituted compounds tending to occupy a position intermediate between the 6- and 7-monosubstituted analogs. The second is that for any given position of substitution, activity does not appear to depend very much upon whether the substituent is Me, Cl, or MeO. This is illustrated by the activity of IIc, IIf, and IIi against *S. faecalis*, for example.

The two most active compounds in bioassay systems 1–4 (Table II) are IIa and IIh, each of which contains a 5 substituent. Although these analogs exhibit a fairly high order of activity in several microbial systems, the high level of activity of IIh against the folate-requiring species *S. faecalis* is particularly interesting, inasmuch as it approaches that of the 1,3-diaminobenzo[*f*]quinazolines studied previously in this laboratory.[2,3] The MeO group in IIh and C-9 and C-10 in I can occupy nearly identical positions in space relative to the 2,4-diaminopyrimidine ring. Furthermore, the fact that the O atom in the MeO of IIh is hydrophilic in character, whereas C-10 in I is hydrophobic, appears to have little or no influence upon the degree of enzyme inhibition in the *S. faecalis* assay. A possible interpretation is that these atoms do not participate in direct binding to the enzyme, and may in fact lie in a cleft or cavity wherein their hydrophilic or hydrophobic character is irrelevant. The bulk of hydrophobic binding, according to this hypothesis, would then have to be provided by groups slightly further removed from the 2,4-diaminopyrimidine ring, such as the Me group in IIh or the C-9 atom in I.



I



IIh

(16) G. E. Foley, R. E. McCarthy, V. M. Binns, E. E. Snell, B. M. Guirard, G. W. Kidder, V. C. Dewey, and P. S. Thayer, *Ann. N. Y. Acad. Sci.*, **76**, 413 (1958).

(17) G. E. Foley and H. Eagle, *Cancer Res.*, **18**, 1012 (1958); H. Eagle and G. E. Foley, *ibid.*, **18**, 1017 (1958).

TABLE II
In Vitro GROWTH-INHIBITORY ACTIVITY OF 2,4-DIAMINOQUINAZOLINES (ID_{50} IN μg/ml)

Compd II	R	Assay system[a] 1	2	3	4	5
a	5-Me	0.25	0.32	0.8	1.5	5
b	6-Me	0.4	3	3.5	0.55	1.8
c	7-Me	5	4	10^+	10	3
d	6,7-Me_2	1.3	2.8	2.9	1.7	3
e	6-Cl	0.7	3	3.4	1.6	2
f	7-Cl	3.1	6	10^+	10^+	1
g	6,7-Cl_2	0.24	2.6	2.6	0.55	0.7
h	5-MeO	0.036	0.25	0.25	0.13	1
i	7-MeO	5	10^+	10^+	10^+	10^+

[a] System 1: *Streptococus faecalis* 8043/folate (0.001 μg/ml); system 2: *Lactobacillus arabinosus* 17-5/pantothenate (0.01 μg/ml); system 3: *L. arabinosus* 17-5/nicotinate (0.01 μg/ml); system 4: *Pediococcus cerevisiae* 8081/citrovorum factor (0.01 μg/ml); system 5: KB cells (human epidermoid carcinoma) in Eagle's medium (see ref 17 for *in vitro* assay methods).

Experimental Section

Uv spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Ir spectra were taken in KCl disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Melting points were measured in Pyrex capillary tubes in a modified Wagner–Meyer apparatus[18] at a heating rate of 2°/min, and are corrected wherever possible. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

Synthesis of Anthranilonitriles. 4-Methylanthranilonitrile (IIIa).—4-Methyl-2-nitrobenzonitrile, mp 91.5–94° (lit.[7a] 99.8°), was prepared in 49% yield from 4-methyl-2-nitroaniline by the diazotization procedure of Morgan and Coulson.[7b] Reduction with $SnCl_2$ in HCl as described by Bogert and Hoffman[7a] gave a 68% yield of IIIa, mp 89–91° (lit. 90°,[7b] 94°[7a]).

5-Methylanthranilonitrile (IIIb).—5-Methylisatin was converted into its oxime in 75% yield; mp 224.5–226.5° (lit.[19] 225–226°). Pyrolysis of the oxime according to Bedford and Partridge[12] afforded a 16% yield of IIIb, mp 58.5–60.5° (lit.[12] 59–60°), after successive crystallizations from EtOH–H_2O and Et_2O–*n*-heptane (Darco).[20]

6-Methylanthranilonitrile (IIIc).—Following the standard procedures used for the synthesis of IIIa, 6-methyl-2-nitroaniline was converted in 65% yield into 6-methyl-2-nitrobenzonitrile, mp 107.5–108° (lit. 109–110°,[8a] 115°[8b]). Reduction of the latter with $SnCl_2$ in HCl gave an 83% yield of IIIc, mp 126.5–128° (lit. 127–128°,[8a] 131°[8b]).

4,5-Dimethyl-2-nitrobenzonitrile.—To a solution of 16.6 g (0.1 mole) of 4,5-dimethyl-2-nitroaniline in 100 ml of hot AcOH was added 50 ml of 6 *N* HCl. The mixture was stirred and cooled at 10° until a dense ppt of finely divided HCl salt was formed, and diazotization was carried out by adding in one portion a solution of 7.5 g (0.11 mole) of $NaNO_2$ in 20 ml of H_2O. The cold diazotized mixture was filtered and added slowly with stirring to a solution of 30 g of KCN and 27 g of $CuSO_4 \cdot 5H_2O$ in 150 ml of H_2O at 40°. When the evolution of N_2 subsided, 90 ml of H_2O was added, the mixture was heated to 55–60° for 20 min, and another 200 ml of H_2O was added. The solid was filtered, washed with H_2O, dried, and extracted with toluene in a Soxhlet apparatus. The extract was treated with Darco and evapd to dryness and the residue was crystallized from 4:1 Et_2O–Me_2CO (Darco); yield 9.45 g (54%), mp 169–170°. Two recrystallizations from *i*-PrOH furnished the analytical sample, mp 174.5–176.5° (lit.[21] 170°). *Anal.* ($C_9H_8N_2O_2$) C, H, N.

4,5-Dimethylanthranilonitrile (IIId).—To a stirred solution of 20.6 g (0.0914 mole) of $SnCl_2 \cdot H_2O$ in a mixture of 17 ml of 12 *N* HCl and 5 ml of hot AcOH at 25–30° was added slowly 4.93 g (0.028 mole) of the preceding nitro compd. After being stirred overnight, the red solution was cooled and basified to pH 8 with 40% NaOH. The solid was filtered, washed to neutrality with H_2O, dried *in vacuo*, and extracted with $CHCl_3$ (2 × 500 ml). The combined extracts were concd to dryness and the residue was crystallized from C_6H_6; yield 2.5 g (61%). Two more crystallizations from C_6H_6 with the aid of Darco afforded the analytical sample, mp 147–148°. *Anal.* ($C_9H_{10}N_2$) C, H, N.

4-Chloroanthranilonitrile (IIIe).—Diazotization of 4-chloro-2-nitroaniline according to the usual method gave 4-chloro-2-nitrobenzonitrile, mp 93–97° (lit.[22] 98°), and reduction of the latter with $SnCl_2$ in HCl as prescribed by McKee and coworkers[9] afforded IIIe, mp 156–158° (lit.[9] 161–162°).

5-Chloroanthranilonitrile (IIIf).—Following the route specified by Breukink and coworkers,[13] *p*-chloroaniline was converted in 53% yield into 4-chloro-2-iodoaniline, mp 41–42° (lit.[13] 40.5–41.5), and the latter was transformed in 72% yield into IIIf, bp 101–102° (0.7–0.8 mm) [lit.[13] 158–159° (10 mm)], mp 95.5–96° (lit. 95–95.5°,[13] 96–98°[12]), by reaction with CuCN in refluxing pyridine.

4,5-Dichloro-2-nitrobenzonitrile.—To a stirred solution of 6.7 g (0.097 mole) of $NaNO_2$ in 60 ml of concd H_2SO_4 at 6° was added rapidly 20 g (0.097 mole) of 4,5-dichloro-2-nitroaniline.[23] The diazotization mixture was heated to 70° in order to effect complete solution, and was then cooled, and added gradually with stirring to an ice-cold solution of 29 g (0.45 mole) of KCN and 27 g (0.11 mole) of $CuSO_2 \cdot 5H_2O$ in 150 ml of H_2O. The temp rose spontaneously to 50°, and vigorous N_2 evolution was observed. After being heated 5–10 min to 60° on the steam bath, the mixture was diluted with 800 ml of H_2O and chilled. The solid was filtered, washed to neutrality with H_2O, dried *in vacuo*, and extracted with PhMe in a Soxhlet apparatus. The PhMe extract was treated with Darco and evapd to dryness, and the residue was crystallized from *i*-PrOH; yield 4.1 g (20%): orange solid, mp 118.5–119°. Repeated crystallizations from *i*-PrOH afforded the analytically pure sample, mp 129.5–130°. *Anal.* ($C_7H_2Cl_2N_2O_2$) C, H, Cl, N.

In another run, in which the diazotization was carried out in the usual mixture of AcOH and HCl instead of in H_2SO_4, there was obtained a 17% yield of nitrile, mp 113–115°. However, a considerable amount of starting material apparently failed to undergo diazotization in this medium, and rendered the purification of the desired product quite difficult. In some instances, diazotization in AcOH–HCl failed completely, only starting material being recovered.

4,5-Dichloroanthranilonitrile (IIIg).—Following the procedure described for the synthesis of IIId, reduction of the preceding nitro compound with $SnCl_2$ in HCl gave a 63% yield of IIIg; mp 162–163° (CCl_4). Two additional crystallizations from CCl_4, followed by vacuum sublimation at 70° (0.005 mm), afforded an analytically pure sample, mp 163–164°. *Anal.* ($C_7H_4Cl_2N_2$) C, H, Cl, N.

4-Methoxyanthranilonitrile (IIIh).—Diazotization of 4-methoxy-2-nitroaniline gave a 67% yield of 4-methoxy-2-nitrobenzonitrile, mp 131–135° (AcOH–H_2O). Further recrystallization from AcOH-heptane afforded analytically pure orange-yellow needles, mp 137.5–139° (lit.[10] 140°). Reduction of this compd with $SnCl_2$ in HCl as reported by Cook and coworkers[10] gave a 50% yield of IIIh as pale yellow leaflets, mp

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(20) Darco G-60 activated carbon, Atlas Chemical Industries, Inc., Wilmington, Del.

(21) A. Brändström and S. A. I. Carlsson, *Acta Chem. Scand.*, **21**, 983 (1967).

(22) A. Claus and H. Kurz, *J. Prakt. Chem.* [2] **37**, 197 (1888).

(23) Normal diazotization conditions are nearly ineffectual with this compound because of the strong deactivating influence of the two Cl substituents. The diazotization conditions reported here were taken from A. F. Holleman and F. E. van Haeften, *Recl. Trav. Chim. Pays-Bas*, **40**, 67 (1921), who used 2,4-dichloro-6-nitroaniline.

94–95° (lit.[a] 96°), after two crystallizations from Et_2O–heptane (Darco).

6-Methoxyanthranilonitrile (IIIi).—*m*-Dinitrobenzene was converted into 2-methoxy-6-nitrobenzonitrile by reaction with KCN in refluxing aq MeOH.[24] Reduction of the nitro compd with $SnCl_2$ in HCl at 40–50° gave a 30% yield of IIIi, mp 141–143° (lit.[a] 141°) after several crystallizations with the aid of Darco, first from Et_2O–heptane, then from AcOH–H_2O, and finally from EtOH.

Synthesis of 2,4-Diaminoquinazolines. Reaction with Cyanamide (Method A). 2,4-Diamino-6-chloroquinazoline (IIe). An open pear-shaped flask containing a mixture of 0.5 g (0.00327 mole) of IIIf, 0.5 g (0.0119 mole) of crystalline cyanamide,[25] and 2.0 g (0.017 mole) of pyridine·HCl was immersed in an oil bath preheated to 180°. With the formation of a clear melt, the internal temp rose rapidly and reached a max of 164° before subsiding gradually. At 150° the flask was removed from the bath and allowed to cool. The partly resolidified melt was triturated with 10 ml of 95% EtOH until all the gummy material dissolved and only a yellow powder remained. The latter was filtered, washed with Et_2O in order to remove any unreacted IIIf, and digested with 30 ml of boiling H_2O. After removal of an insoluble residue, the filtrate was basified with 10% Na_2CO_3, and the gelatinous ppt was collected, washed dropwise with cold H_2O, and crystallized from H_2O (Darco); yield 0.27 g (37%). Two more crystallizations from H_2O (Darco) afforded analytically pure yellow needles, mp 269–271.5°.

Reaction with Cyanoguanidine (Method B). 2,4-Diamino-7-methoxyquinazoline (IIi).—A cold solution of 1.0 g (0.0067 mole) of IIIh in 40 ml of Et_2O was treated with dry HCl, and the ppt was collected, washed with Et_2O, and dried *in vacuo* to give 1.2 g (96%) of IIIh·HCl, mp 176–179°. An open pear-shaped flask containing a mixture of this material and 0.55 g (0.0065 mole) of cyanoguanidine was immersed in an oil bath preheated to 165°. The internal reaction temp was maintained at 158–164° for 10 min. The fused solid was dissolved in 25 ml of boiling H_2O, and the solution was cooled below 10° and basified with concd NaOH. The gummy yellow solid was filtered and washed with Et_2O to remove unreacted IIIh, and the residue was crystallized from 10 ml of H_2O (Darco); yield 0.38 g (31%), mp 230–231°. Repeated crystallization from H_2O furnished the analytical sample, yellow needles, mp 229–230°.

Reaction with Guanidine (Method C). 2,4-Diamino-7-chloroquinazoline (IIf).—To a solution of 0.37 g (0.0069 mole) of NaOMe in 12 ml of 2-methoxyethanol were added successively 0.63 g (0.0066 mole) of guanidine·HCl and 0.5 g (0.0033 mole) of IIIe. The mixture was refluxed with magnetic stirring for 71 hr. NaCl was removed from the hot reaction mixture by filtration and the filtrate was evapd to dryness under reduced pressure. The residue was triturated with 10 ml of Et_2O to remove unreacted starting material, IIIe. Crystallization of the Et_2O-insoluble residue from 35 ml of H_2O (Darco) afforded colorless needles, which were again triturated with 10 ml of Et_2O; yield 0.058 g (9%). An analytical sample, prepared separately *via* method A and crystallized 3 times from H_2O, melted at 229.5–230.5°.

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(25) We are grateful to the American Cyanamid Co., Bound Brook, N. J., for supplying us with a sample of crystalline cyanamide.

Acknowledgment.—The authors wish to express their thanks to Dr. George E. Foley and coworkers for the *in vitro* bioassay studies, to Dr. Victor M. Rosenoer and Miss Barbara Brown for the *in vivo* mouse tumor data, and to Dr. E. C. Taylor, Department of Chemistry, Princeton University, for his helpful comments on the manuscript.

Synthesis and Activity of Some 3-Aryl- and 3-Aralkyl-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamides

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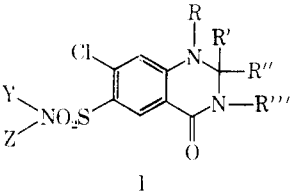
Received January 8, 1970

A series of 3-aryl- and 3-aralkyldi- and -tetrahydro-4-oxo-6-quinazolinesulfonamides have been synthesized and tested for pharmacological activity. Several of the compounds have been found to be potent diuretics.

The high biological activity of some benzothiadiazines[1] and 2-alkylquinazolinones[2] prompted us to investigate a series of 3-aryl and 3-aralkyl di- and tetrahydro-4-oxo-6-quinazolinesulfonamides. The compounds chosen for study are illustrated[3a] by the general formula I where R, R′, R″, Y, Z = H, alkyl, aryl, aralkyl, R‴ = aryl or aralkyl; R and R′ may also be absent (1,2-double bond).



I

The most interesting compounds, from a pharmacological point of view,[3b,c] were those in which the heterocyclic ring was saturated. So far the most promising of the compounds tested is 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide (metolazone) which is a potent, virtually nontoxic diuretic and natriuretic. The compounds were prepared in several ways; initially the unreduced precursors were reduced with $NaBH_4$–$AlCl_3$ mixture,[4] typical examples being illustrated in Scheme I.

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