Quinazolines. XIII. Synthesis of Polycyclic 2,4-Diaminopyrimidines from Aromatic Amine Hydrochlorides and Sodium Dicyanamide[1,2]

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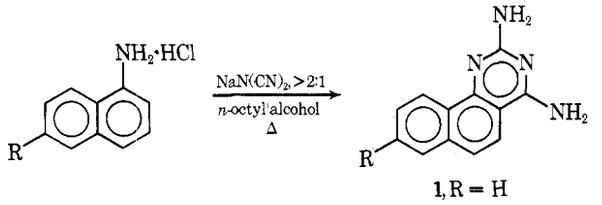
Received May 14, 1974

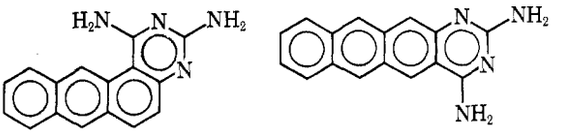
In an earlier communication, N^1,N^5-bis(2-naphthyl)biguanide hydrochlorides were reported to undergo a novel ring closure reaction upon being heated briefly in a high-boiling inert solvent such as diphenyl ether.[3] Cyclization proceeded in an angular manner, *via* electrophilic attack at the more reactive α position of the naphthalene ring, giving 1,3-diaminobenzo[*f*]quinazolines. Subsequently, a modified procedure was reported, whereby a variety of substituted 1,3-diaminobenzo[*f*]quinazolines could be generated in a single step merely on treatment of the appropriate 2-naphthylamine hydrochlorides with excess sodium dicyanamide in refluxing *n*-octyl alcohol, without isolation of the intermediate biguanide salts.[4] Inasmuch as this reaction offered an extremely attractive route to otherwise difficultly accessible condensed 2,4-diaminopyrimidine derivatives, it became of interest to investigate a representative number of aromatic amines with respect to the ease and direction of cyclization. In the present note, we should like to describe the successful use of 1-naphthylamine, 6-chloro-1-naphthylamine, 2-aminoanthracene, 2-aminophenanthrene, and 3-aminophenanthrene in this connection.

As indicated in Table I, 1-naphthylamine and 6-chloro-1-naphthylamine afforded 2,4-diaminobenzo[*h*]quinazoline (**1**) and 2,4-diamino-8-chlorobenzo[*h*]quinazoline (**2**) in yields closely approximating the value obtained with 2-naphthylamine under similar conditions.



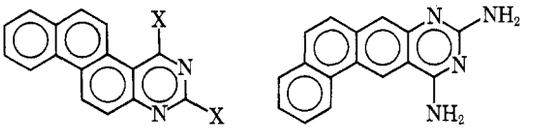
1, R = H
2, R = Cl

The reaction of 2-aminoanthracene gave a product which was formulated as 1,3-diaminonaphtho[2,3-*f*]quinazoline (**3**) rather than the alternative isomer 2,4-diaminonaphtho[2,3-*g*]quinazoline (**4**) on the basis of the well-documented preference of this polycyclic aromatic amine for angular cyclization.[5] Moreover, the lack of ultraviolet absorption above 390 nm in ethanol (Table II) militated against structure **4** because a linear tetracyclic nitrogen heterocyclic derivative of this type would be expected to display bands at much longer wavelength.[6]



3 **4**

The reaction of 2-aminophenanthrene with sodium dicyanamide occurred in 32% yield, giving a nearly colorless product which was formulated as 1,3-diaminonaphtho[2,1-*f*]quinazoline (**5**). The alternative isomer, 2,4-diaminonaphtho[1,2-*g*]quinazoline (**6**) was rejected from consideration because the longest wavelength peak in the ultraviolet spectrum of the product appeared at only 370 nm, which is inconsistent with a structure containing three linear aromatic rings.[6] Furthermore, 2-aminophenanthrene is known to undergo preferential angular ring closure in a number of instances, including the Skraup, modified Doebner, and Conrad–Limpach reactions.[7,8]



5, X = NH_2
9, X = OH

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The reaction of 3-aminophenanthrene was carried out with great interest because the product of angular cyclization, 1,3-diaminonaphtho[1,2-*f*]quinazoline (**7**), would represent an unusual, highly hindered type of condensed 2,4-diaminopyrimidine. Unlike the 2-isomer, 3-aminophenanthrene has been reported to be capable of undergoing cyclization angularly *or* linearly, depending on the particular reaction studied. Thus, while Skraup and Conrad–Limpach reactions give rise to "normal" angular products in accor-

Table I
Condensed 2,4-Diaminopyrimidines Prepared from Arylamine Hydrochlorides and Sodium Dicyanamide[a]

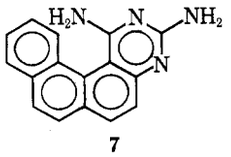
Arylamine·HCl	Reflux time, hr	Product	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1-Naphthylamine·HCl (552-46-5)	40	**1** (33987-13-2)	32	282–284[b]	68.55	4.79	26.65	68.35	4.68	26.76
6-Chloro-1-naphthylamine·HCl (52306-16-8)	18	**2**[c] (52374-28-4)	38	254–255	58.90	3.71	22.90	58.69	3.68	22.87
2-Aminoanthracene·HCl (32666-78-7)	24	**3** (52306-18-0)	40	261–263	73.82	4.64	21.52	73.92	4.64	21.41
2-Aminophenanthrene·HCl (52306-17-9)	20[d]	**5** (52306-19-1)	32	248–251	73.82	4.64	21.52	73.90	4.43	21.52
2-Aminophenanthrene·HCl	18[e]	**9** (52306-20-4)	32	>360	73.27	3.84	10.68	73.29	4.15	10.72
3-Aminophenanthrene·HCl (5345-92-6)	20	**8** (52306-21-5)	8	235–237	73.82	4.64	21.52	73.72	4.75	21.35

[a] Registry no. are in parentheses beneath compound. [b] This compound has also been synthesized from 1-tetralone by condensation with cyanoguanidine, followed by palladium–charcoal dehydrogenation [S. K. Sengupta, S. K. Sengupta, S. Chatterjee, H. K. Protopapa, and E. J. Modest, *J. Org. Chem.*, **37**, 1323 (1972)]. [c] Cl: calcd, 14.49%; found, 14.76%. [d] Standard reaction conditions (see Experimental Section). [e] Stoichiometric proportions (1:2 molar ratio of sodium dicyanamide to 2-aminophenanthrene hydrochloride).

Table II
Ultraviolet Absorption Spectra of Condensed 2,4-Diaminopyrimidines

Compd	EtOH λ_{max}, nm	EtOH $\epsilon \times 10^{-3}$	EtOH (pH 1) λ_{max}, nm	EtOH (pH 1) $\epsilon \times 10^{-3}$
3	223	34.5	228	39.2
	243	24.1	265	49.9
	273	37.6	295	24.8
	282	34.0	305 sh	18.3
	293	47.6	340	5.7
	304	41.9	357	5.4
	318 sh	9.1	388	4.2
	337	8.5		
	352	4.7		
	388	2.9		
5	261	53.8	274	32.9
	277	40.1	282 sh	29.7
	284 infl	34.1	313	12.0
	304 infl	11.9	364	2.1
	329	10.5	380	2.4
	353 infl	5.1		
	370	3.8		
8	255	27.2	221	44.6
	261	28.0	232	33.5
	278	26.3	240	29.4
	298	30.3	284	27.5
	322	11.1	290	26.7
	335	6.4	310	10.9
	378	2.9	330	4.6
	394	3.2	365	3.0
			384	2.7

dance with Marckwald's rule, the Ullmann–Fetvadjian reaction (with 2-naphthol and formaldehyde) leads predominantly to a linear product *via* cyclization on the β position.[9] Apparently, when the energy of the transition state for α cyclization is sufficiently high (for steric reasons, for example), the "normal" process is interdicted and linear products are formed. In the present instance, the reaction of 3-aminophenanthrene gave an 8% yield of a single isomer which was intensely yellow in color (*cf.* the lack of color in **5**). The longest wavelength ultraviolet absorption band occurred at 394 nm, a value consistent with the presence of three linear aromatic rings.[6] On the basis of the low yield and ultraviolet spectral data, we believe the product to be 2,4-diaminonaphtho[2,1-*g*]quinazoline (**8**) rather than **7**. This is the first observed instance of a bisarylbiguanide cyclization proceeding *via* attack at the β position of a naphthalene ring in preference to the α position.



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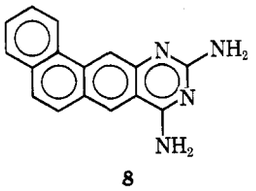

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The use of a *ca.* 2:1 molar ratio of sodium dicyanamide to arylamine hydrochloride in the reactions described above merits comment, inasmuch as this represents a fourfold excess over the stoichiometric amount required for the formation of a bisarylbiguanide salt.[3] In actual fact, the use of stoichiometric proportions (*i.e.*, a 1:2 molar ratio of sodium dicyanamide to arylamine hydrochloride) in this modified version of the bisarylbiguanide cyclization does *not* permit isolation of the desired products. Thus, as indicated in Table I, the reaction of 2-aminophenanthrene performed in the absence of excess sodium dicyanamide gave exclusively 2,4-dihydroxynaphtho[2,1-*g*]quinazoline (**9**), no diamino derivative being recovered on work-up. It appears that sufficient acid is present in the medium to effect hydrolysis of the initially formed diamine on prolonged reflux in *n*-octyl alcohol. This was verified by the observation that heating of the diamine in boiling *n*-octyl alcohol in the presence of a small amount of acid afforded the dihydroxy derivative rapidly and in high yield. When the molar ratio of sodium dicyanamide to arylamine hydrochloride was 1:1, the product turned out to be an approximately 1:1 mixture of the diamine **5** and the dihydroxy compound **9**. An effort was also made to carry out the reaction with a stoichiometric amount of sodium dicyanamide but in the presence of sodium acetate. Under these conditions no cyclized product was recovered at all, probably because neutralization of the arylamine salt had occurred before bisarylbiguanide formation could take place. A systematic evaluation of the effect of other bases was not made, but we believe that the success of the reaction when excess sodium dicyanamide is present probably stems from the ability of this weak base to function as a selective acid scavenger without interfering with biguanide formation or ring closure.

It is also of interest to note that condensed 2,4-diaminopyrimidines were not obtained on reaction of aniline, 1-methyl-2-naphthylamine, or 1-aminopyrene hydrochloride with excess sodium dicyanamide. With 1-methyl-2-naphthylamine, cyclization would have had to occur by attack at the unfavored β position. With aniline hydrochloride, it appears that decomposition of the intermediate N^1,N^5-bisarylbiguanide salt takes place in preference to ring closure. With 1-aminopyrene, we believe that the low basicity of the amino group[10] and the unreactive character of the 2 position[11] conspire to block the reaction.

Experimental Section[12]

Preparation of Arylamines. 1-Naphthylamine and 2-aminophenanthrene are commercially available (Aldrich Chemical Co., Inc.). 6-Chloro-1-naphthylamine[13–15] was obtained from 5-nitro-2-naphthyamine[16] *via* the known two-step sequence involving sucessively a Sandmeyer reaction and reduction with stannous chloride.[15] 2-Aminophenanthrene was prepared from 2-acetylphenanthrene[17] by treatment with sodium azide in trichloroacetic acid as described by Campbell and Temple.[18] 3-Aminophenanthrene was prepared similarly from 3-acetylphenanthrene,[17] with the exception that with this isomer a violent exothermic effect was observed unless care was taken to conduct the Curtius reaction at a temperature not exceeding 50–52°. 1-Methyl-2-naphthylamine was synthesized from 1-methyl-2-naphthol *via* a Bücherer reaction as reported previously.[19] 1-Aminopyrene was obtained from 1-nitropyrene (Koch-Light Laboratories, Ltd.) on reduction with stannous chloride.[20] All the foregoing arylamines were isolated in the form of hydrochloride salts by dissolving the free base in Et_2O, saturating the solution with dry gaseous HCl at 0°, and washing the filtered precipitate thoroughly with CH_2Cl_2. The hydrochloride salts were not purified further prior to reaction with sodium dicyanamide.

Reaction of Arylamine Hydrochlorides with Sodium Dicyanamide. Standard Procedure. A well-stirred suspension of the amine hydrochloride (0.1 mol) and sodium dicyanamide[21] (0.20–0.26 mol) in *n*-octyl alcohol (100–300 ml) was heated under reflux for 18–40 hr (Table I). The mixture was filtered while hot (or after cooling), the filter cake was extracted with CH_2Cl_2, and the combined *n*-octyl alcohol and CH_2Cl_2 solutions were saturated with dry HCl gas and stored in the cold. After several hours, the precipitated hydrochloride salt was collected, washed with CH_2Cl_2, and redissolved in boiling H_2O or dilute HCl. Treatment with decolorizing carbon and basification with NH_4OH or NaOH regenerated the free base, which was purified further by recrystallization from aqueous or anhydrous EtOH. In the preparation of **3**, the original filter cake, which proved to contain most of the product, was digested thoroughly with boiling H_2O, washed with CH_2Cl_2, and recrystallized from *n*-butylamine (decolorizing carbon); hydrochlo-

ride salt formation was omitted in this instance. The yields and physical constants of the products are given in Table I.

Registry No.—Sodium dicyanamide, 1934-75-4.

References and Notes

(1) This investigation was supported in part by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.
(2) Paper XII: A. Rosowsky, P. C. Huang, N. Papathanasopoulos, and E. J. Modest, *J. Med. Chem.*, manuscript in press.
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(12) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in KCl disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Analytical samples were dried in an Abderhalden apparatus over P_2O_5, generally at 70–100° (0.05 mm). Melting points were measured in Pyrex capillary tubes in a modified Wagner–Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938)] or in a Mel-Temp heating block (Laboratory Devices, Inc., Cambridge, Mass.), and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Werby Laboratories, Boston, Mass.
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(18) See ref 7.
(19) W. S. Johnson and F. J. Matthews, *J. Amer. Chem. Soc.*, **66**, 210 (1944).
(20) O. Neunhoeffer and W. Weigel, *Justus Liebigs Ann. Chem.*, **647**, 108 (1961).
(21) This material was obtained through the courtesy of Dr. L. C. Lane, American Cyanamid Co., Stamford, Conn., and was purified as described in the literature [W. Madelung and E. Kern, *Justus Liebigs Ann. Chem.*, **421**, 1 (1922)]. The importance of using purified material is critical, as we have found that sodium dicyanamide contaminated with sodium bromide fails to take part in this reaction.

On the Reaction of α-Diazo Ketones with *m*-Chloroperoxybenzoic Acid

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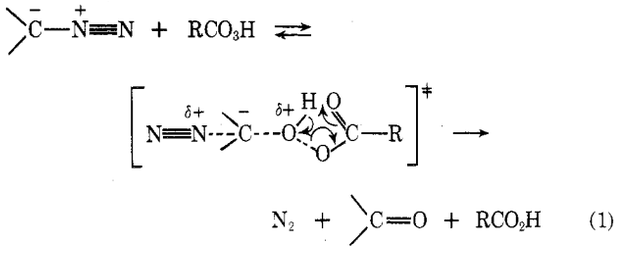
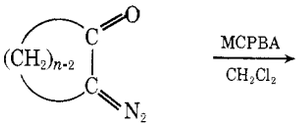
Received April 29, 1974

In a previous paper[2] we have shown that diazodiphenylmethane $Ph_2C{=}N_2$ and substituted diazodiphenylmethanes react with peroxy acids to afford the corresponding diaryl ketones in high yield.

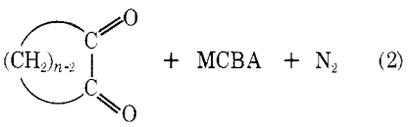
On the basis of kinetic evidence, a reaction mechanism was proposed which involves attack by the nucleophilic carbon atom of the diazo group on the peroxide O–O bond.[2]



Therefore, at variance with what was found for carboxylic acids,[3] it appears that peroxy acids transfer "electropositive" oxygen and not H^+ to the diazo group. We now report that α-diketones are produced in the reaction of some cyclic α-diazo ketones **1a–e** and of acyclic 3-diazo-2-butanone $CH_3CN_2COCH_3$ (**2**) with *m*-chloroperoxybenzoic acid (MCPBA) in the mole ratio of 1:1, in CH_2Cl_2 at 25° (eq 2).



1a, $n = 6$; **1b**, $n = 8$; **1c**, $n = 9$; **1d**, $n = 10$; **1e**, $n = 12$



Yields and kinetic data are shown in Table I. Under the conditions given, the yields of the corresponding α-diketones were essentially quantitative from **1a**, **1d**, **1e**, and **2**. The yields were considerably less with **1b** and **1c** as starting materials, but substantial amounts of suberic and azelaic anhydride, respectively, appeared in the reaction mixtures. These anhydrides undoubtedly arise from the initially formed α-diketones in a subsequent competitive reaction with MCPBA. It is known, in fact, that α-diketones react with peroxy acids in organic solvents[4] and with HO_2^- in aqueous media[5] to yield the corresponding anhydrides, presumably *via* a Baeyer–Villiger type mechanism.[6]

Table I
Yields and Rates of Reaction of Some α-Diazo Ketones with *m*-Chloroperoxybenzoic Acid in Methylene Chloride at 25°

Compd	% yield of[a] α-diketone	$10^2 k_2$,[b] M^{-1} sec^{-1}
1a	99 (glc)	16.8
1b	40 (isol.)[c]	20.5
1c	35 (glc)[c]	30.0
1c	30 (isol.)[c]	30.0
1d	95 (isol.)	12.0
1e	92 (isol.)	4.27
2	96 (glc)	5.52

[a] As determined (±5%) by glc analysis or by isolating (ref 2) and weighing the α-diketone, after reacting the diazo compound with MCPBA in equimolar amounts. [b] Evaluated (±3%) as $k_1/[\text{MCPBA}]_0$, from pseudo-first-order kinetic experiments. [c] Ir analysis of reaction mixtures and comparison with authentic samples showed that the α-diketone produced was accompanied by 25–30% of the parent anhydride, while 20–25% of the α-diazo ketone starting material had remained unreacted.

Indeed, in independent experiments we have verified that 1,2-cyclononanedione, 1,2-cyclooctanedione, and also 2,3-butanedione (biacetyl) all give the corresponding anhydrides in nearly quantitative yields (glc, ir) when allowed to react with MCPBA in CH_2Cl_2.