[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Some N^1-(6-Methoxy-8-quinolylaminoalkyl)-N^5-isopropyldiguanides and Related Compounds[1]

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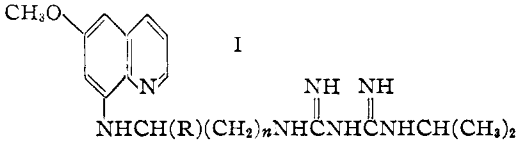
Five N^1-(6-methoxy-8-quinolylaminoalkyl)-N^5-isopropyldiguanides, isolated as their monohydrochlorides, are described. The method by which 1-cyano-3-isopropylguanidine, an intermediate used in the synthesis of the new diguanides, is prepared has been shown to be applicable as well to the preparation of N^1-(6-methoxy-8-quinolylaminoalkyl)-N^3-cyanoguanidines, by the preparation of two new compounds of this class.

The preparation of an analog of Paludrine in which the role of the *p*-chlorophenyl residue was played by a 6-methoxy-8-quinolyl moiety has been reported.[2]

We have prepared a group of somewhat similar compounds whose structures may be described by the general formula, I, in which *n* is 1, 2, 3 or 4, when R is hydrogen and *n* is 3 when R is a methyl group.


I

$\mathrm{NHCH(R)(CH_2)_nNH\overset{\overset{NH}{\|}}{C}NH\overset{\overset{NH}{\|}}{C}NHCH(CH_3)_2}$

Considerable preliminary experimentation led finally to a choice of the reaction of 1-cyano-3-isopropylguanidine with the appropriate 8-(aminoalkylamino)-6-methoxyquinoline monohydrochloride as the most suitable approach to the desired compounds. In a well-stirred melt of the reactants under an inert atmosphere, condensation occurs smoothly in the neighborhood of 150°; reaction is substantially complete when the melt solidifies and prevents further stirring.

Crystallization proved ineffective as a means of purifying the diguanides; traces of impurity could not be removed by this means. However, by allowing a solution of the diguanide in alcohol to pass through a column of aluminum oxide, it proved possible to hold the impurities on the column. Elution of the yellow band of adsorbed product by alcohol was stopped before the dark brown band containing impurities had progressed beyond the midpoint of the column.

Attempts to purify the diguanides by separating them as their chelate complexes with copper did not lead to a satisfactory method of purification; the quinoline reactants also form chelate complexes with copper thus rendering separation of the diguanide from starting material difficult.

Preparation of the several 8-(aminoalkylamino)-6-methoxyquinolines necessary followed procedures previously reported.[3] The bases were isolated conveniently for our purpose as their monohydrochlorides, of which only that of 8-(2-aminoethylamino)-6-methoxyquinoline has been previously reported.[4]

Attempts to isolate the free base from N^1-(2-(6-methoxy-8-quinolylamino)-ethyl)-N^5-isopropyldiguanide monohydrochloride were unsuccessful; the separation by crystallization of a sample of free base which gave satisfactory analytical results was found to be impossible. When the free base was dissolved in concentrated hydrochloric acid a new salt separated whose orange-yellow crystals decomposed at 116–120°. Potentiometric titration of chloride ion indicated that this new salt was a dihydrated tetrahydrochloride, a finding which is in accord with the experience of Gupta, *et al.*,[5] who prepared hydrated trihydrochlorides from N^1-(8-quinolyl)-N^5-aryl diguanides. The additional 8-amino group in the present compounds should allow the separation of a tetrahydrochloride from strongly acidic solutions.

1-Cyano-3-isopropylguanidine was prepared by two methods, that of May[6] who achieved the preparation by ammonolysis of 1-cyano-3-isopropyl-2-methyl-2-thiopseudourea, but did not isolate the crystalline guanidine or characterize it, and that of Curd, *et al.*,[7] who utilized the reaction between sodium dicyanamide and isopropylamine hydrochloride. In our hands the latter method proved the more convenient. We were, however, able to obtain pure crystalline 1-cyano-3-isopropylguanidine by May's method. In one experiment in which we attempted to substitute sodium cyanamide (assaying 65%) for free cyanamide in May's procedure, desulfurization of the expected thiopseudourea took place, probably under the influence of the alkali in the sodium cyanamide solution with the result that a sulfur-free product, undoubtedly 1-cyano-3-isopropyl-2-ethyl-2-pseudourea, was obtained in good yield.

The method of Curd, *et al.*,[7] by which the intermediate, 1-cyano-3-isopropylguanidine, was prepared has been shown to be applicable as well to the preparation of N^1-(6-methoxy-8-quinolylaminoalkyl)-N^3-cyanoguanidines by the preparation of N^1(2-(6-methoxy-8-quinolylamino)-ethyl)-N^3-cyanoguanidine and N^1-(5-(6-methoxy-8-quinolylamino)-amyl)-N^3-cyanoguanidine.

Experimental

8-(5-Aminoamylamino)-6-methoxyquinoline Monohydrochloride.—The preparation of this monohydrochloride was

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(1) From a thesis submitted by Raymond J. Kray in partial fulfillment of the requirements of the Ph.D. degree, June, 1951.

(2) E. L. May and E. Mosettig, *J. Org. Chem.*, **12**, 869 (1947).

(3) A. W. Baldwin, *J. Chem. Soc.*, 2959 (1929); A. A. Beer, *J. Gen. Chem. (U.S.S.R.)*, **9**, 2158 (1939), *C.A.*, **34**, 4148 (1940); L. W. Kissinger, I. Von and M. Carmack, THIS JOURNAL, **68**, 1563 (1946); H. S. Mosher, *ibid.*, **68**, 1565 (1946); D. C. Quinn and R. J. Robinson. *J. Chem. Soc.*, 555 (1943); R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1524 (1946).

(4) N. L. Drake and J. A. Garman, *ibid.*, **71**, 2425 (1949).

(5) P. R. Gupta, B. H. Iyer and P. C. Guha, *Current Science (India)*, **17**, 53 (1948).

(6) E. L. May, *J. Org. Chem.*, **12**, 437, 443 (1947).

(7) F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murray and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).

typical of the method used for the other similar substances. The corresponding dihydrochloride was dissolved in a small amount of water and the orange-colored solution was brought to *p*H 7 by the addition of finely ground sodium acetate trihydrate. The now yellow solution was warmed gently to bring the remaining solid into solution and then cooled. The monohydrochloride which separated was recrystallized twice from absolute alcohol–ether. In this way 28.4 g. of dihydrochloride yielded 20.5 g. of monohydrochloride whose yellow crystals melted at 96–97°. *Anal.* Calcd. for $C_{15}H_{21}ON_3 \cdot HCl$: Cl^-, 11.98. Found: Cl^-, 11.88, 12.01.

The other monohydrochlorides used and not previously described are listed in Table I.

TABLE I

-6-Methoxyquinoline	M.p., °C.	% (Cl^-) Calcd.	% (Cl^-) Found
8-(4-Amino-1-methylbutylamino)	106–107	11.98	11.84, 11.89
8-(4-Aminobutylamino)	68–69	12.58	12.47, 12.52
8-(3-Aminopropylamino)	142–143	13.61	13.52, 13.48

N^1-(2-(6-Methoxy-8-quinolylamino)-ethyl)-N^5-isopropyldiguanide Monohydrochloride (II). Method A.—8-(2-aminoethylamino)-6-methoxyquinoline monohydrochloride (4.54 g.) and 3.05 g. of 1-cyano-3-isopropylguanidine were heated and stirred in 15 ml. of butyl cellosolve for 3 hours at 145–155°. Saturated aqueous cupric sulfate solution (50 ml.) was then added to the reaction mixture, whereupon the solution was further diluted with water to about 250 ml. and cooled in an ice-bath. The copper complex of the diguanide separated as pale purple crystals, and was filtered off and washed twice with water. To liberate the diguanide, the chelate complex was dissolved in 12 ml. of concentrated hydrochloric acid, the resulting solution was diluted with 250 ml. of water, and powdered sodium sulfide was added until the solution became basic to litmus whereupon the *p*H of the mixture was brought to between 6 and 7 by means of a few drops of hydrochloric acid. After removal of the copper sulfide by filtration, the resultant aqueous filtrate was concentrated under reduced pressure to about 200 ml. The product (3.4 g.) was separated by filtration and recrystallized from an aqueous sodium chloride solution. The pale yellow crystals (3.3 g., 48%) melted at 197–198°. *Anal.* Calcd. for $C_{17}H_{25}ON_7 \cdot HCl$: C, 53.45; H, 6.89; N, 25.81; Cl, 9.33. Found: C, 53.50, 53.77; H, 6.96, 7.24; N, 25.99, 25.95; Cl, 9.22, 9.33.

Method B.—The starting materials described directly above, 3.0 g. and 2.0 g., respectively, were heated and stirred without solvent under a nitrogen atmosphere at 168–169° (oil-bath temperature) for approximately one hour, at which time the reaction mixture solidified. The mass was thereupon dissolved in 60 ml. of absolute alcohol and this solution was allowed to flow through a column of alumina. Elution of adsorbed product was accomplished with 15 ml. of absolute alcohol. The eluate was added to the solution and alcohol was distilled from the mixture while benzene was added to keep the volume approximately constant. When the solution became turbid, the distillation was discontinued, and the solution cooled to room temperature. Pale yellow platelets (2.8 g., 62%) separated. The product melted at 197–198°, and its melting point was not depressed by the substance prepared by the previously described method.

N^1-(3-(6-Methoxy-8-quinolylamino)-propyl)-N^5-isopropyldiguanide Monohydrochloride (III).—This substance was prepared by a scheme corresponding to method B for (II) directly above. The yield in a 0.06 mole run was 62% of that calculated; the light yellow crystals melted at 215–216° after previously sintering at 211°. *Anal.* Calcd. for $C_{18}H_{27}ON_7 \cdot HCl$: C, 54.87; H, 7.16; N, 24.89. Found: C, 55.18, 55.00; H, 7.28, 7.32; N, 24.91, 24.87.

N^1-(4-(6-Methoxy-8-quinolylamino)-butyl)-N^5-isopropyldiguanide Monohydrochloride (IV).—This diguanide was also prepared by the fusion method (like III). The yield of pale yellow crystals, whose melting point was 172–173° after previous sintering at 171°, was 71% of the calculated amount. *Anal.* Calcd. for $C_{19}H_{29}ON_7.HCl$: C, 55.93; H, 7.41; N, 24.03. Found: C, 56.03, 56.18; H, 7.66, 7.58; N, 24.24, 24.28.

N^1-(4-(6-Methoxy-8-quinolylamino)-1-methylbutyl)-N^5-isopropyldiguanide Monohydrochloride (V).—The fusion method was used in preparing V (53%). Its yellowish crystals sintered at 176° and melted at 177–178°. *Anal.* Calcd. for $C_{20}H_{31}ON_7 \cdot HCl$: C, 56.92; H, 7.64; N, 23.23. Found: C, 57.15, 56.95; H, 7.85, 7.83; N, 22.98, 23.28.

N^1-(5-(6-Methoxy-8-quinolylamino)-amyl)-N^5-isopropyldiguanide Monohydrochloride (VI).—The yield of VI by the fusion method was 64% of that calculated. Its pale yellow crystals sintered at 181° and melted at 183–183.5°. *Anal.* Calcd. for $C_{20}H_{31}ON_7 \cdot HCl$: C, 56.92; H, 7.64; N, 23.23. Found: C, 57.05, 57.11; H, 7.87, 7.84; N, 23.01, 23.32.

1-Cyano-3-isopropylguanidine.—According to May's procedure,[6] 68 g. of 1-cyano-3-isopropyl-2-methyl-2-thiopseudourea yielded 50 g. of product (68%). Crystallized from dioxane, the substance had a melting point of 108.5–109.5° and separated with half a mole of dioxane. The solvent-free guanidine melted at 101–102°. *Anal.* Calcd. for $C_5H_{10}N_4$: C, 47.60; H, 7.99; N, 44.41. Found: C, 47.93; H, 7.94; N, 44.68.

By Curd's method,[7] 64.3 g. of sodium dicyanamide[8] and 68.7 g. of isopropylamine hydrochloride yielded 105.8 g. (86%) of 1-cyano-3-isopropylguanidine whose melting point (from dioxane) was 109–111°.

1-Cyano-3-isopropyl-2-ethyl-2-pseudourea.—This compound was isolated as a by-product during an attempted preparation of the corresponding 2-methyl-2-thiopseudourea for use in the synthesis of 1-cyano-3-isopropylguanidine. The use of a sodium cyanamide assaying 65% and containing sodium carbonate and sodium hydroxide resulted in loss of sulfur at some stage of the reaction and the formation of a sulfur-free product which melted, after purification by crystallization from aqueous alcohol, at 70–71°. *Anal.* Calcd. for $C_7H_{13}N_3O$: C, 54.17; H, 8.44; N, 27.07. Found: C, 54.12, 54.29; H, 8.54, 8.63; N, 27.05, 26.99.

N^1-(5-(6-Methoxy-8-quinolylamino)-amyl)-N^3-cyanoguanidine.—8-(5-Aminoamylamino)-6-methoxyquinoline monohydrochloride (11.9 g.) and 3.6 g. of sodium dicyanamide were heated under reflux in 40 ml. of anhydrous butanol for 3 hours. The cooled solution was filtered to remove sodium chloride, and the filtrate was concentrated under reduced pressure until the product began to separate. The yellow crystals (9.3 g.) were dissolved in 200 ml. of a mixture (60:40) of alcohol and benzene and the solution was poured through a column of alumina. Elution of any adsorbed product was accomplished by means of 40 ml. of alcohol; the eluate was combined with the main body of the solution, and the whole was concentrated under reduced pressure with addition of alcohol from time to time until the last traces of benzene had been removed and the volume of the solution was about 100 ml. Dilution of this solution to turbidity with water and cooling in an ice-bath cause the separation of 6.9 g. (53%) of pale yellow crystals whose melting point was 131–132°. *Anal.* Calcd. for $C_{17}H_{22}ON_6$: C, 62.55; H, 6.79; N, 25.75. Found: C, 62.88, 62.84; H, 6.82, 6.84; N, 25.42, 25.47.

N^1-(2-(6-Methoxy-8-quinolylamino)-ethyl)-N^3-cyanoguanidine.—The preparation of this substance from 0.033 mole each of the required intermediates followed closely the method described directly above. The pale yellow crystals of the product melted at 162–163° after previous sintering at 161°. The yield was 32%. *Anal.* Calcd. for $C_{14}H_{16}ON_6$: C, 59.13; H, 5.66; N, 29.56. Found: C, 59.38, 59.47; H, 6.00, 6.05; N, 29.56, 29.44.

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[8] Kindly supplied by the American Cyanamid Company. We would like to express our gratitude for this material and for a quantity of sodium cyanamide.