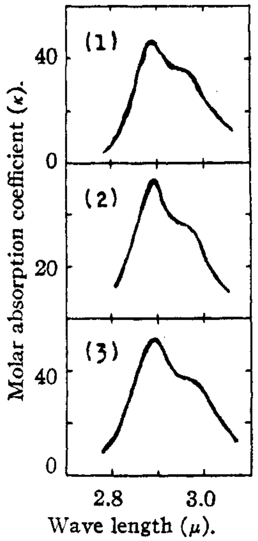

Fig. 1.—Near infrared absorption curves of acetylglycine N-methylamide in dilute carbon tetrachloride solutions at 60°. Concentrations and absorption path-lengths are: (1) 0.0006 mole/l. 5 cm.; (2) 0.0003 mole/l. 10 cm.; (3) 0.00015 mole/l. 20 cm.

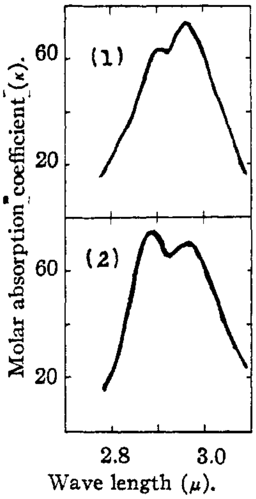

Fig. 3.—Near infrared absorption curves of acetylglycine N-methylamide in dilute carbon tetrachloride solutions at 30°. Concentrations and absorption path-lengths are: (1) 0.0003 mole/l. 5 cm.; (2) 0.00015 mole/l. 10 cm.

the first step of molecular association would be the formation of a dimer, only the monomer–dimer equilibrium is taken into consideration. Figure 2 shows the relation between concentration c and degree of association α calculated for the different values of equilibrium constant K from the law of mass action. (κ of the dimer band is proportional to α, and κ of the monomer band to $1 - \alpha$.) An inspection of this figure reveals that the effect of dilution upon the decrease of α is remarkable. Thus the dilution of a solution from 0.0006 mole/l. to 0.00015 mole/l. results in the decrease of α by one-third for $K = 55$, and by one-half for $K = 1097$.[3] (There is no need of taking the value of K greater than 1097, because κ corresponding to the 2.8 μ band for the 0.0006 mole/l. solution at 60° (Fig. 1) is about one-half of that for the 0.0003 mole/l. solution at 30° (Fig. 3) and, therefore, α cannot be greater than 50% for 0.0006 mole/l. solution at 60°.) For the smaller values of K the decrease in α is more pronounced.

On the other hand the changes in κ for the NH bands of acetylglycine N-methylamide actually observed on dilution from 0.0006 mole/l. to 0.00015 mole/l. at 60° are very small. This fact shows that the 2.98 μ band observed by us in dilute solutions at 60° arises almost solely from the intramolecularly hydrogen-bonded NH group.

We have made similar absorption measurements on dilute solutions of the same compound at 30°, again keeping $c \times l$ constant. On dilution of a solution from 0.0003 mole/l. to 0.00015 mole/l. an appreciable increase of κ for the 2.90 μ band and an appreciable decrease of κ for the 2.98 μ band have been observed (see Fig. 3). This shows that at 30° even in a solution as dilute as 0.0003 mole/l. there is an appreciable molecular association in this compound and that the 2.98 μ band must be considered to arise partly from the NH group involved in the abnormally strong *intermolecular* hydrogen bonding. However, as the actually observed changes in κ are far smaller than those for the case in which the 2.98 μ band would solely arise from the *intermolecularly* hydrogen-bonded NH group, we can surely consider that even at 30° the 2.98 μ band arises for the most part from the NH group involved in the *intramolecular* hydrogen bonding.

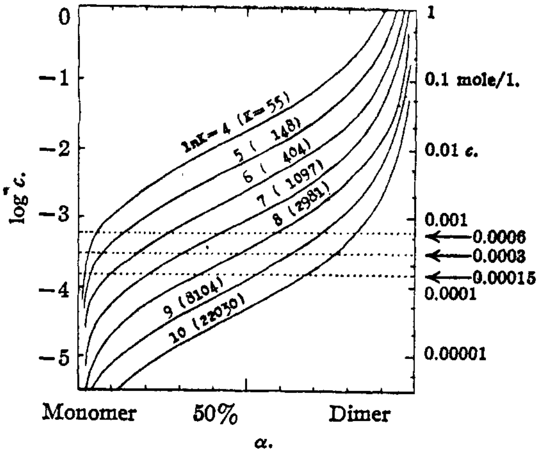

Fig. 2.—Relations between concentration c and degree of association α for different values of equilibrium constant K.

According to what we have stated above we can confirm our previous conclusion that in dilute carbon tetrachloride solutions of acetylglycine N-methylamide the molecules take partly the "B form."

HONGO, TOKYO, JAPAN RECEIVED AUGUST 14, 1951

[3] For δ-valerolactam which forms a dimer with the double *intermolecular* hydrogen bond in its carbon tetrachloride solution K was found to be 45 at 60.7° (Tsuboi, *Bull. Chem. Soc. Japan*, **24**, 75 (1951)).

Camoquin Relatives[1]

BY H. J. NICHOLAS[2] AND J. H. BURCKHALTER[2]

Camoquin (I) and O-methyl Camoquin (II) are known to possess high antimalarial activity in birds, and the former is now marketed for the treatment of human malaria. Many close analogs of these compounds have already been described,[3] but none apparently possesses an advantage over Camoquin. We have been interested in making somewhat wider variations in structure in order to observe the effect upon antimalarial potency. Two such products, V and VIII, have now been prepared, but they also are inferior to Camoquin.

V was prepared by starting with 2-methoxy-5-nitrophenylacetonitrile (III), which was made from the corresponding benzyl chloride. III was reduced catalytically to the desired intermediate

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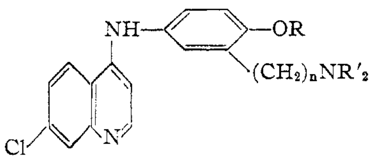
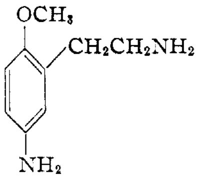
[1] Camoquin is a registered trademark name of Parke, Davis and Co., Detroit.

[2] University of Kansas, Lawrence, Kansas.

[3] (a) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb and A. L. Rawlins, THIS JOURNAL, **70**, 1363 (1948); (b) J. H. Burckhalter, *J. Am. Pharm. Assoc.*, **38**, 658 (1949).



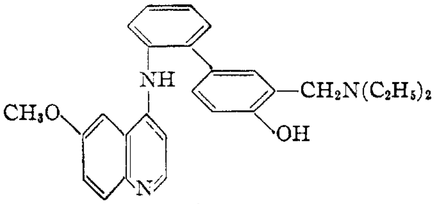
	n	R	R′
I,	1	H	C_2H_5
II,	1	CH_3	C_2H_5
V,	2	CH_3	H



IV

diamine IV, but only in very low yield. Condensation of IV dihydrochloride with 4,7-dichloroquinoline gave V in good yield.

In order to obtain VIII, 2-amino-4′-hydroxybiphenyl was acetylated to its O,N-diacetyl derivative (VI) which was converted to 4-(2-acetamidophenyl)-α-diethylamino-*o*-cresol (VII) by treatment with diethylamine and formaldehyde.[4] VII was then deacetylated with boiling concentrated hydrochloric acid, and after adjustment of the *p*H was condensed with 4-chloro-6-methoxyquinoline to give VIII.



VIII

In may be noted that VIII represents the result of the insertion of an *o*-phenylene group in the side chain of antimalarial SN 10,274,[5] which is eight times as potent as quinine in chicks (*i.e.*, Q8). Compound V is related to both II (Q25) and SN 1,603[6] (Q6) which is the primary amino analog of Camoquin (Q25). Quinine equivalents of 2 for V and 0.8 for VIII against *Plasmodium gallinaceum* in chicks have been assigned by Dr. R. J. Porter, of the University of Michigan, Ann Arbor. These results do not encourage further syntheses in this area.

Experimental

2-Methoxy-5-nitrophenylacetonitrile (III).—A solution of 100 g. of 2-methoxy-5-nitrobenzyl chloride[7] in 300 ml. of absolute alcohol was added slowly to a stirred solution of 32.2 g. of potassium cyanide in 100 ml. of water. Stirring was continued, and the mixture was kept at 75–80° for 2.5 hours while it darkened and potassium chloride separated out. The hot mixture was filtered and cooled whereupon the solid nitrile crystallized. Recrystallization first from benzene and then from alcohol yielded 65 g. (68%) of a yellow product; m.p. 111–113°.

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20. Found: C, 56.63; H, 4.25.

β-(5-Amino-2-methoxyphenyl)-ethylamine (IV) Dihydrochloride.—A mixture of 32 g. of III and 200 ml. of absolute methanol was subjected to three atmospheres of hydrogen in the presence of Adams catalyst. The solid was kept in solution by means of heat. After two hours, no more hydrogen was being taken up, and the amount consumed corresponded to a complete reduction of the nitro group to amino. After removal of the platinum catalyst, 0.6 g. of sodium hydroxide and Raney nickel was added and the clear brown solution reduced further. After 12 hours, the theoretical amount of hydrogen was consumed. The mixture was filtered through fritted glass and the volume of the filtrate reduced by evaporation. The residue was extracted with ether–benzene solution, and the extract was washed with water before it was dried over potassium carbonate. The desired product IV was precipitated as a yellow dihydrochloride from the filtered solution by means of alcoholic hydrogen chloride; m.p. 238–240° dec. Recrystallization from methanol elevated the melting point to 245–247° dec.; yield 7 g. (17%).

Anal. Calcd. for $C_9H_{14}N_2O\cdot 2HCl$: N, 11.72. Found: N, 11.94.

4-(3-β-Aminoethyl-4-methoxyanilino)-7-chloroquinoline (V).—A mixture of 8 g. of IV dihydrochloride, 6.7 g. of 4,7-dichloroquinoline, 50 ml. of water and 25 ml. of dioxane was heated at reflux temperature for 4 hours. A yellow solid separated when the mixture was cooled. After it was collected, washed with water and dried, 11 g. (a theoretical yield) of V was obtained as a light gray colored material; m.p. 185–190°. Recrystallization first from isopropyl alcohol and then from ethanol changed the melting point to 198–200°.

Anal. Calcd. for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53. Found: C, 66.03; H, 5.25.

2-(4-Acetoxyphenyl)-acetanilide (VI).—A mixture of 30 g. of 2-amino-4′-hydroxybiphenyl (92.6% purity),[8] 15 g. of acetic anhydride and 100 ml. of glacial acetic acid was heated to boiling for two hours. The liquid was then removed under reduced pressure and the oily residue dissolved in 100 ml. of hot alcohol. Upon cooling the solution, 30 g. (74% yield) of a crystalline product with a purplish tint was obtained; m.p. 183–185°. Recrystallization from isopropyl alcohol effected no change in melting point.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.62. Found: C, 71.86; H, 5.76.

4-(2-Acetamidophenyl)-α-diethylamino-*o*-cresol (VII) Hydrochloride.—A mixture of 8 g. of VI, 1 g. of paraformaldehyde, 5 g. of diethylamine and 75 ml. of isopropyl alcohol was heated to boiling for two hours and then evaporated to an oily consistency. An excess of alcoholic hydrogen chloride was added. After evaporation of the solvent and repeated triturations with mixtures of alcohol, acetone and ether, an off-white crystalline product was finally obtained; m.p. 235–240° dec. After recrystallization from methanol, 5 g. (36% yield) of the desired cresol was obtained; m.p. 245–250° dec.

Anal. Calcd. for $C_{19}H_{24}N_2O_2\cdot HCl\cdot 2^1/_3H_2O$: C, 57.93; H, 7.68. Found: C, 57.74; H, 7.20.

4-[2-(6-Methoxy-4-quinolylamino)-phenyl]-α-diethylamino-*o*-cresol (VIII).—A mixture of 5 g. of VII hydrochloride and 25 ml. of concentrated hydrochloric acid was heated to boiling for two hours, and then cooled and brought to a *p*H of about 4 by the addition of concentrated ammonium hydroxide. A solution of 2.8 g. of 4-chloro-6-methoxyquinoline in 15 ml. of dioxane was added, and the mixture was heated to boiling for two hours. After cooling the solution, it was treated with an excess of ammonium hydroxide to precipitate an oil which soon solidified. Recrystallized with difficulty first from an ethanol–methanol mixture and then from methanol, the product VIII was obtained in a yield of 3 g. (55%); m.p. 208–210° dec.

Anal. Calcd. for $C_{27}H_{29}N_3O_2$: C, 75.85; H, 6.84. Found: C, 75.84; H, 6.86.

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(4) It will be noted that the basic conditions apparently liberated the phenolic group and allowed the Mannich reaction to occur.

(5) Ref. 3a, Table IX.

(6) Ref. 3a, Table XII.

(7) U. S. Patent 2,278,996.

(8) Kindly supplied by General Aniline and Film Corporation.

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An Interpretation of Bond Lengths in Alkali Halide Gas Molecules

BY R. T. SANDERSON

Alkali halide gas molecules are considered to contain highly polar covalent bonds. The bond