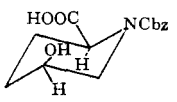
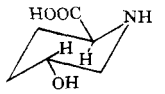
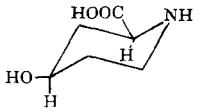
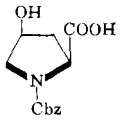
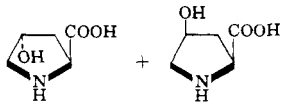
TABLE I

INFLUENCE OF THE BASIC NITROGEN ON THE STEREOCHEMISTRY OF REDUCTION OF KETOAMINO ACIDS TO HYDROXYAMINO ACIDS

Keto-amino acid	Product of reduction with sodium borohydride	Stereospecificity	Reference
N-Carbobenzyloxy-5-keto-L-pipecolic acid		100% *cis*-N-carbobenzyloxy-5-hydroxy-L-pipecolic acid	B. Witkop and C. M. Foltz, *J. Am. Chem. Soc.*, **79**, 192 (1957)
5-Keto-DL-pipecolic acid		Almost exclusively *trans*-5-hydroxy-DL-pipecolic acid	H. C. Beyerman and P. Boekee, *Rec. trav. chim.*, **78**, 648 (1959)
4-Keto-L-pipecolic acid		80% *cis*-4-hydroxy-L-pipecolic acid	J. W. Clark-Lewis and P. L. Mortimer, *J. Chem. Soc.*, 189 (1961)
N-Carbobenzyloxy-4-keto-L-proline		100% *cis* (or allo) 4-hydroxy-L-proline	A. A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, **79**, 185 (1957)
4-Keto-L-proline		25% *trans*- and 75% *cis*-4-hydroxy-L-proline	A. V. Robertson, E. Katz, and B. Witkop, this paper

genate.[11] The loss of tritium in such a case would be an accurate measure of reversion to 4-keto-L-proline.

Experimental

4-Keto-L-proline hydrobromide (35 mg.)[6,12] in 0.5 ml. of water was added drop by drop to a solution of 5 mg. of sodium borohydride-H^3 (100 mC).[13] When the addition was complete the solution was slightly acid, and sufficient cold sodium borohydride (*ca.* 1 mg.) was added to obtain an alkaline solution and hence complete reduction. After 30 min. the reaction mixture was transferred to the top of a column of Amberlite CG-120, type 2 ion exchange resin (70 ml. of 200–400 mesh) prepared in 0.2 *M* ammonium acetate solution in water–ethanol (60:40, v/v). The column was eluted with the same buffer solution and 4-ml. fractions were collected. Aliquots (10 λ) from each tube were spotted on paper and sprayed with isatin reagent. Tubes 13–16 contained 4-hydroxyproline (identified in a cold run by paper electrophoresis). These fractions were combined and the solvent was removed *in vacuo*. The ammonium acetate was then sublimed during 3 hr. at 60°/1 mm. The residue was dissolved in 0.1 ml. of water and 3 ml. of hot ethanol was added. The solution was boiled and acetone was added dropwise until crystallization commenced. After 2 hr. at 0°, 4-H^3-hydroxy-L-proline (5.2 mg.) was collected as colorless needles. Its specific activity was $2.86 \cdot 10^7$ c.p.m./μmole.

Tubes 20–24 contained 4-H^3-4-allohydroxy-L-proline which was worked up in a similar way to give 10.8 mg. of colorless recrystallized product of specific activity $3.24 \cdot 10^7$ c.p.m./μmole. The total recovery of the initial activity present in the sodium borotritide (100 mC) amounts to 1.4%.

(11) C. Mitoma, T. E. Smith, F. M. DaCosta, S. Udenfriend, A. A. Patchett and B. Witkop, *Science*, **129**, 95 (1959).

(12) We are greatly indebted to Dr. Sydney Archer, The Sterling-Winthrop Research Institute, for the preparation of this compound.

(13) Obtained from New England Nuclear Corp., Boston, Mass.

Anomalous Hydrolytic Behavior of Some Basically-Substituted Phthalimides. A Novel Rearrangement of a 4-Aminoquinoline Side Chain[1]

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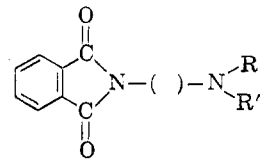
During the preparation of *N*-(2′-methylaminoethyl)phthalimide (No. 1 in Table I) for use as an intermediate, it was found that its hydrochloride on careful neutralization with alkali in cold water did not yield the free base, but the phthalamic acid; further, the phthalimide obtained by heating the phthalamic acid and distilling gave only a transient alkalinity with water, hydrolyzing to regenerate the phthalamic acid. Investigation showed that this unexpected ease of hydrolysis persisted with homologs containing two-, three-, and four-carbon chains between the two nitrogens, although to a lessening degree. In one other case (No. 4 in Table I) the phthalamic acid also crystallized; three other cases showed a reversal of hydrolysis, in which the base was regenerated on steam cone evaporation of the solution.

All of these phthalimides have been previously reported, either as such or, more generally, as the

(1) Supported in part by research grant CY-2975 from the National Cancer Institute, U. S. Public Health Service.

TABLE I
EASE OF HYDROLYSIS OF AMINOALKYL PHTHALIMIDES

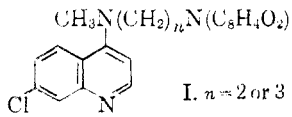


	Alkyl chain	R	R′	Phthalamic acid, m.p.	Hydrolysis[a]
1.	—$(CH_2)_2$—	CH_3	H	187.5–189° dec.[b]	Instantaneous
2.	—$(CH_2)_2$—	C_2H_5	C_2H_5	Unstable	Instantaneous
3.	—$(CH_2)_3$—	CH_3	H	Unstable	Instantaneous
4.	—$(CH_2)_3$—	CH_3	CH_3	107–108.5° dec.[b]	Intermediate
5.	—$CH(CH_3)(CH_2)_3$—	C_2H_5	C_2H_5	Unstable	Slow

[a] Qualitative; based on zero titration of a solution of the first three compounds in aqueous ethanol; No. 4 required about 50% of the theoretical acid after a solution time of two minutes; No. 5's basicity decreased 50% only after several hours. [b] With loss of water to form the phthalimide.

hydrochloride, but search of the many references[2-7] available revealed no mention of this property, other than Shriner's recommendation of neutralization of the hydrochloride below 25° to isolate the base of the diethylaminopropyl homolog and Kanevskaya's mention of relatively easy acid cleavage of some analogs with nuclear substituents. This would refer to a different phenomenon, since the hydrochlorides are stable to water in contrast to the free bases.

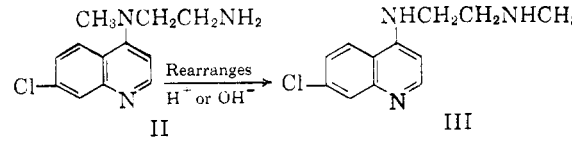
The free bases No. 1 and 3 were obtainable only by the dehydration of the phthalamic acid and vacuum distillation; they both formed glasses in contrast to the mobility of the distilled tertiary bases. They were both successfully condensed with 4,7-dichloroquinoline to give products (I) which still possessed the ease of hydrolysis of the



I. $n = 2$ or 3

parent compound, *i.e.*, they dissolved over a period of several hours at room temperature in a dilute alcoholic solution containing one excess equivalent of sodium hydroxide.

In unsuccessful attempts to synthesize *N*-(7 - chloro - 4 - quinolyl) - *N* - methylethylenediamine: (a) The corresponding phthalimide (I, $n = 2$) was hydrolyzed with ethanolic hydrazine. (b) Its derivative phthalamic acid was hydrolyzed with hydrochloric acid. In each case, the product obtained was 7-chloro-4-(2-methylaminoethyl)aminoquinoline (III). This was confirmed by melting point and mixed melting point



II III

with a sample of the previously unreported III, and by the nonidentity of the phthalamic acid derivatives produced (1) by the action of phthalic anhydride on III and (2) by the partial hydrolysis of compound I ($n = 2$).

(2) S. I. Kanevskaya and V. B. Brasyunas, *Zhur. Obschei. Khim.*, **29**, 1930 (1959).
(3) W. Voigtländer, *Chem. Tech.*, **11**, 323 (1959).
(4) P. C. Jocelyn, *J. Chem. Soc.*, 3305 (1957).
(5) L. A. Rice, *et al.*, *J. Am. Chem. Soc.*, **75**, 4911 (1953).
(6) M. B. Moore and R. T. Rapala, *ibid.*, **68**, 1657 (1946).
(7) K. Miura, *J. Pharm. Soc. Japan*, **62**, 224 (1942).

Experimental

The aminoalkylphthalimides were synthesized by addition of phthalic anhydride to a stirred solution of the diamine in water and evaporation of the solution. If the phthalamic acid was stable, it was isolated at this point by acetone dilution and recrystallization. If not, the residue was heated to achieve dehydration and the phthalimide was distilled *in vacuo*. Physical constants of the base and/or hydrochloride checked literature values in every case.

***N*-Methylaminoethylphthalamic Acid.**—This compound was isolated from the concentrated reaction mixture by acetone dilution in 41% yield. It was recrystallized by dissolving in a small amount of water and precipitating with ethanol, m.p. 187.5–189° dec. Crystallization of this compound was extremely slow.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 58.86, 58.73; H, 6.39, 6.43; N, 12.91.

***N*-Dimethylaminopropylphthalamic Acid.**—This compound was obtained by concentration of the initial reaction mixture; the analytical sample was prepared by evaporating a water solution of the distilled imide and recrystallization from ethanol, m.p. 107–108.5°.

Anal. Calcd. for $C_{15}H_{18}N_2O_3 \cdot 1^1/_2H_2O$: C, 56.4; H, 7.62; N, 10.1. Found: C, 56.18, 56.21; H, 7.71, 7.54; N, 10.01, 10.02.

***N*-[*N*′-(7-Chloro-4-quinolyl)-*N*′-methylaminoethyl]-phthalimide Hydrochloride.**—A mixture of 42 g. of methylaminoethylphthalimide (distilled from crude phthalamic acid), 50 g. of 4,7-dichloroquinoline, and 35 g. of diethanolamine was condensed at 120° for 15 hr., taken up with excess dilute acetic acid, 50 ml. of saturated sodium chloride added, cooled, and filtered. The crude sparingly soluble monohydrochloride weighed 65.7 g. (79%). Recrystallization first from water and then from alcohol gave an analytical sample, m.p. 282–285°.

Anal. Calcd. for $C_{20}H_{16}ClN_3O_2 \cdot HCl \cdot 1^1/_2H_2O$: C, 56.00; H, 4.70; N, 9.79; Cl^-, 8.28. Found: C, 55.49, 55.28; H, 4.79, 4.91; N, 9.72, 9.79; Cl^-, 8.47, 8.42.

The free base melted at 153–154.5°. *Anal.* Calcd.: C, 65.65; H, 4.41; N, 11.49. Found: C, 64.89; H, 4.42; N, 11.39.

N-[N'-(7-Chloro-4-quinolyl)-N'-methylaminopropyl] phthalimide Hydrochloride.—This homolog was synthesized in the same way and isolated as the sparingly soluble hydrochloride. After recrystallization from hot water, it amounted to 82% of the theoretical yield and melted at 139–141°. Recrystallization from ethanol gave 65% recovery of pure material, m.p. 246–248°, s. 150°.

Anal. Calcd. for $C_{21}H_{18}ClN_3O_2 \cdot HCl \cdot 1\text{–}3/4H_2O$: C, 56.35; H, 5.06; N, 9.21; Cl^-, 7.76. Found: C, 56.36, 56.27; H, 5.58, 5.49; N, 9.29, 9.03; Cl^-, 7.79, 7.90.

The free base melted at 118.5–120.5°.

Anal. Calcd.: C, 66.35; H, 4.78; N, 11.06. Found: C, 66.65, 66.41; H, 4.73, 4.78; N, 11.03, 10.94.

7-Chloro-4-(2-methylaminoethyl)aminoquinoline (III).—This compound was produced by the condensation (2 hr. at 115°) of 4,7-dichloroquinoline and 2-methylaminoethylamine.[8] It was purified by distillation (115°/20 μ), crystallization from benzene, and vacuum sublimation. The yield was approximately 50%, m.p. 110–111.5°.

Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.18; H, 5.98; N, 17.83. Found: C, 61.13, 61.25; H, 6.41, 6.45; N, 17.72, 17.98.

N-[2-[Methyl-(7-chloro-4-quinolyl)]aminoethyl]phthalamic Acid.—A mixture of 60 ml. of water, 72 ml. of *N* sodium hydroxide, 30 ml. of ethanol, and 15 g. (36 mmoles) of *N*-[*N'*-(7-chloro-4-quinolyl)-*N'*-methylaminoethyl]phthalimide hydrochloride (I, $n = 2$) was stirred for 1 hr. while it became homogeneous. Acidification with acetic acid precipitated the product. It weighed 14.5 g. and melted at 174–177° dec. An analytical sample obtained by reprecipitating from an alkaline ethanolic solution with acetic acid melted at 172–174° dec.

Anal. Calcd. for $C_{20}H_{18}ClN_3O_3 \cdot H_2O$: C, 59.75; H, 5.01; N, 10.46. Found: C, 59.25, 59.01; H, 5.17, 5.14; N, 10.52, 10.42.

Acid Hydrolysis of Phthalamic Acid.—A 16.8-g. sample of *N*-[2-[methyl-(7-chloro-4-quinolyl)]aminoethyl]-phthalamic acid was hydrolyzed with 100 ml. of 6 *N* hydrochloric acid by heating on the steam cone overnight, concentrated *in vacuo*, diluted to 100 ml., and 5.5 g. of phthalic acid was removed by filtration. The filtrate was concentrated and diluted with ethanol and ether to precipitate 11.3 g. of base hydrochloride. The crystalline base was isolated in 97% yield and recrystallized several times from hydrocarbon solvents. Both recrystallization and vacuum sublimation gave a melting point of 110–112° not depressed by a sample of 7-chloro-4-(2-methylaminoethyl)aminoquinoline (III).

N-[2-(7-Chloro-4-quinolylamino)ethyl]-N-methylphthalamic Acid.—A 5.9-g. sample of the above material was allowed to react with an equimolar quantity of phthalic anhydride in ethanolic solution. The precipitated product was filtered and reprecipitated from alkaline solution with acetic acid. It weighed 8.3 g. and melted at 250–255°.

Anal. Calcd. for $C_{20}H_{18}ClN_3O_3 \cdot 2H_2O$: C, 57.20; H, 5.27; N, 10.01. Found: C, 57.98; H, 5.88; N, 9.32.

Hydrazine Hydrolysis.—A sample of the phthalimide free base (I, $n = 2$) was refluxed for 2 hr. with an equivalent amount of molar ethanolic hydrazine and gave a product which on recrystallization and sublimation proved to be identical with that from the acid hydrolysis.

(8) The usual method of attachment of an amine to a 4-chloroquinoline; *cf.*, R. M. Peck, R. K. Preston, and H. J. Creech, *J. Am. Chem. Soc.*, **81**, 3988 (1959).

A New Method of Preparation of 2,2'-Biquinoxalines[1]

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The synthesis of some 2,2'-biquinolines and 2,2'-bipyridines by catalytic dehydrogenation of the corresponding quinolines and pyridines has been described by prolonged heating of a mixture of the heterocyclic base and 10% by weight of 5% palladium-on-carbon catalyst, usually at a reflux temperature of the base.[2] Modest yields (2–21%) of coupled product were formed by such treatment.

2,2-Biquinoxalines have not been studied extensively, and no generally applicable unambiguous syntheses of compounds of this class have been reported. We have encountered a new method of preparation of 2,2'-biquinoxalines as an outgrowth of an attempt to prepare 2-vinylquinoxaline by heating 2-methylquinoxaline with paraformaldehyde at 160–165° in an autoclave. Under these conditions, a high-melting red-brown crystalline compound was obtained in about 5% yield. This compound was shown to have the molecular formula, $C_{18}H_{14}N_4$, by elemental analysis and molecular weight determination. The structure, 3,3'-dimethyl-2,2'-biquinoxaline, was assigned on the basis of the following observations: (1) Quinoxaline was found to react under the same conditions to give an almost quantitative yield of 2,2'-biquinoxaline (identical with authentic sample). (2) 2,3-Dimethylquinoxaline failed to form a coupled product even upon prolonged heating at 200°. (3) The same products are formed in the absence of paraformaldehyde under otherwise similar conditions. (4) The infrared absorption spectrum of the product from 2-methylquinoxaline exhibits absorption bands in the region characteristic of four adjacent aromatic hydrogens. (5) The ultraviolet absorption spectrum of this compound exhibits absorption maxima at much longer wave length than does the ultraviolet absorption spectrum of 2-methylquinoxaline indicating conjugation between aromatic rings.

Yields of the coupled product from 2-methylquinoxaline were enhanced by heating at higher temperatures. For example a 39% yield of coupled product was obtained by heating at 200° for six hours, whereas only a 5% yield was realized by heating at 160–165° for four hours. Slight catalytic activity was exhibited by 5% palladium-on-carbon

(1) Financial support of this work by a grant (CY-3751) from the National Cancer Institute, U.S. Public Health Service, is gratefully acknowledged.

(2) H. Rapoport, R. Iwamoto, and J. R. Tretter, *J. Org. Chem.*, **25**, 373 (1960).