of water. The reaction mixture was basified and extracted with chloroform; the extracts were dried over potassium carbonate, filtered, and evaporated *in vacuo*. The resulting light brown oil (20.3 g.) was taken up in 24.4 g. of 48% hydrobromic acid and 50 ml. of *i*-propanol and heated to the boiling point. The solution was then diluted with 300 ml. of *i*-propanol (slow addition to prevent formation of oil); the crystalline precipitate of (quinolyl-8)-(ε-amino-*n*-amyl) ketone dihydrobromide (I) was filtered off, washed with *i*-propanol and ether, and dried *in vacuo*, yield 21.0 g.; the mother liquors gave another 3.0 g., total yield 22.9% (48.4% taking into account recovered quinoline-8-carboxylic acid). A small sample was treated with charcoal and recrystallized from ethanol containing a little aqueous hydrobromic acid, slightly colored rhombs, m. p. 230.0–230.5°.

Anal. Calcd. for $C_{15}H_{18}N_2O \cdot 2HBr$: C, 44.57; H, 4.99; N, 6.93. Found: C, 44.80; H, 4.87; N, 6.92.

A solution of 23.1 g. (0.0592 mole) of I in 25 ml. of 48% hydrobromic acid was heated to 80°, treated with 9.4 g. (0.0588 mole) of bromine in 6 ml. of the same solvent and heated to the boiling point. The solution was then evaporated *in vacuo* until sirupy and, on long standing, a buff-colored solid crystallized which was filtered off and washed with a 3:1 ethanol–*i*-propanol mixture; two crops (16.0 and 5.0 g.) were obtained. A small sample was recrystallized from 48% hydrobromic acid; the analysis (after correction for ash) indicated the presence of a hydrated (quinolyl-8)-(α-bromo-ε-amino-*n*-amyl) ketone dihydrobromide (II).

A portion (4.83 g.) of crude II in 150 ml. of ethanol was treated with 25 ml. of 14% aqueous sodium carbonate solution and shaken for an hour and a half. Adams catalyst (0.15 g.) was then added and the mixture reduced until the rate of hydrogen absorption was negligible; 360 ml. of hydrogen was taken up. The reduction mixture was filtered, the filtrate evaporated and the crude product extracted with chloroform. The extract was freed of solvent on a steam-bath (finally by boiling a 20-ml. portion of *i*-propanol from it), and the residue cooled, treated with 2.3 ml. of 48% hydrobromic acid, and diluted to about 15 ml. with *i*-propanol. The resulting slurry was filtered and the tan crystals rinsed with *i*-propanol, yield 1.8 g. These were dissolved in ethanol and the solution was treated with charcoal, evaporated to a volume of about 5 ml., allowed to crystallize, diluted with *i*-propanol, and filtered; yield 1.4 g. (26% from I) of nearly colorless needles, m. p. 273° dec.

Anal. Calcd. for $C_{15}H_{18}N_2O \cdot 2HBr$: C, 44.57; H, 4.99; N, 6.93. Found: C, 44.74; H, 5.13; N, 6.73.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF STANFORD UNIVERSITY]

The Synthesis of Some α-(2-Piperidyl)-quinolinemethanols[1]

BY R. A. SEIBERT, T. R. NORTON, A. A. BENSON AND F. W. BERGSTROM[2]

In continuation of work initiated[3] at the California Institute of Technology, we have prepared the remaining members in the series, α-(2-piperidyl)-*x*-quinolinemethanol (*x* = 2, 3, 5, 6, 7). The type of synthesis employed was that which had been used for the 4-quinolinemethanol[4] and 8-quinolinemethanol[3] isomers.

It is noteworthy that α-(2-piperidyl)-5-quinolinemethanol (SN 10049)[5] is the only compound in this series other than the 4-analog[4] which exhibits antimalarial activity (in avian tests). For this reason the synthetic work was extended to include 2-phenyl-α-(2-piperidyl)-5-quinolinemethanol[6] and 8-chloro-α-(2-piperidyl)-5-quinolinemethanol.[7] The former was prepared by direct phenylation of the parent compound using an excess of phenyllithium. The latter was prepared from 8-chloro-5-quinolinecarboxylic acid in the usual manner.

Experimental[8]

Ethyl Quinolinecarboxylates.—7-Quinolinecarboxylic acid was prepared by a modification of the method of Skraup and Brunner.[9] To a solution of 105 g. (0.735 mole) of 7-methylquinoline in 1 liter of water and 500 ml. of concentrated sulfuric acid was added three 100-g. (1.0-mole) portions of chromium trioxide with four, fifteen and twenty-four hours of refluxing after additions. The flaky crystalline precipitate of the hydrosulfate which separated upon cooling was removed by filtration, dissolved in 10% sodium hydroxide solution and reprecipitated with acetic acid to give 53 g. (42%) of colorless 7-quinolinecarboxylic acid, m. p. 252–254°. The use of thionyl chloride in the usual manner gave yields of 83–91% of colorless ester, b. p. 145–150° (2 mm.), m. p. 52–53°.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.60; H, 5.51. Found: C, 71.65; H, 5.50.

6-Quinolinecarboxylic acid was prepared in 54% yield according to the method of Schlosser and Skraup[10] with one modification; arsenic acid was used as the oxidizing agent rather than 4-nitrobenzoic acid. Esterification in the usual manner[11] using thionyl chloride gave a 78% yield of ethyl 6-quinolinecarboxylate, b. p. 155° (3 mm.), m. p. 55–57°.

Using arsenic acid as oxidizing agent the method of Cook, Heilbron and Steger[12] gave a 60% yield of 5-quinolinecarboxylic acid, m. p. 338–340°. The ethyl ester, b. p. 153–156° (4 mm.), was prepared using thionyl chloride.

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Stanford University.

(2) Dr. Bergstrom died March 29, 1946; this manuscript was prepared by his collaborators.

(3) Buchman and Sargent, *This Journal*, **68**, 2720 (1946).

(4) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938); see also Senear, Sargent, Mead and Koepfli, THIS JOURNAL, **68**, 2695 (1946).

(5) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(6) *Cf.* Rapport, Senear, Mead and Koepfli, THIS JOURNAL, **68**, 2697 (1946).

(7) *Cf.* Buchman, Sargent, Myers and Seneker, *ibid.*, **68**, 2692 (1946).

(8) All melting points are corrected.

(9) Skraup and Brunner, *Monatsh.*, **7**, 142 (1886).

(10) Schlosser and Skraup, *ibid.*, **2**, 518 (1881).

(11) Einhorn and Feibelmann, *Ber.*, **42**, 4854 (1909).

(12) Cook, Heilbron and Steger, *J. Chem. Soc.*, 413 (1943).

3-Quinolinecarboxylic acid was prepared by the method of Gilman and Spatz.[13] The required 3-bromoquinoline, b. p. 131–135° (6 mm.), was prepared in 40% yield by the method of Edinger[14] which was found superior to the method of Claus and Collischonn.[15] Ethyl 3-quinolinecarboxylate,[16] m. p. 66–69°, was prepared in 86% yield using thionyl chloride in the usual manner.

Ethyl quinaldate, b. p. 145–146° (2 mm.), was prepared by the method of Hammick[17] and Hammick and Dickinson.[18] Unreacted quinaldic acid was recovered by precipitation of the copper salt at *p*H 4.

5-Methylquinoline.[19]—An intimately ground mixture of 413 g. of 5-methyl-8-quinolinecarboxylic acid, 300 g. of calcium oxide, 70 g. of cupric oxide and 70 g. of copper-bronze powder was decomposed by heating over a free flame in 50-g. batches. The combined distillates were dried and redistilled to give 231 g. (73%) of 5-methylquinoline, b. p. 120–130° (7 mm.).

2-Phenyl-5-methylquinoline.—To an ether solution of 0.55 mole of 1.1 *N* phenyllithium at 0° *in vacuo* was added 36 g. of 5-methylquinoline. After standing for thirty minutes the solution was poured onto ice. The ether phase was recovered, dried and distilled to obtain 31.5 g. (57%) of phenylated 5-methylquinoline, b. p. 185–190° (6 mm.). Since the product only partially crystallized on long standing, it may be a mixture of isomers. A portion was converted to the picrate, yellow flakes from alcohol, m. p. 219–220° for analysis.

Anal. Calcd. for $C_{22}H_{16}O_7N_4$: C, 58.93; H, 3.60. Found: C, 58.68; H, 3.55.

2-Phenyl-5-quinolinecarboxylic Acid.[20]—A solution of 7.5 ml. of water, 3.8 ml. of sulfuric acid and 0.8 g. of 2-phenyl-5-methylquinoline was heated at 100° while three 0.80-g. portions of chromic anhydride were added at ten-hour intervals. The solution was finally cooled to precipitate the hydrosulfate of the desired product. The crystalline hydrosulfate was removed by filtration, suspended in water, filtered again and washed with water. The solid was crystallized from glacial acetic acid. After dissolving the product in aqueous sodium hydroxide the solution was treated with norite and filtered. The clear filtrate was acidified with acetic acid at the boiling point. On cooling, colorless crystals of 2-phenyl-5-quinolinecarboxylic acid, m. p. 209–210°, separated.

Anal. Calcd. for $C_{16}H_{11}O_2N$: C, 77.09; H, 4.45. Found: C, 76.99; H, 4.43.

Ethyl 8-Chloro-5-quinolinecarboxylate.—A mixture of 84.0 g. (0.49 mole) of 4-chloro-3-aminobenzoic acid,[21] 59 g. (0.39 mole) of arsenic acid, 88.5 g. (0.96 mole) of glycerol and 111 g. (1.08 moles) of sulfuric acid was heated at 150–160° for five hours. The product was diluted with 300 ml. of water and filtered with Celite while hot. The filtrate was made basic with 6 *N* sodium hydroxide and filtered with Celite while warm to remove tar. The filtrate was acidified with glacial acetic acid and the precipitate was removed by filtration from the cooled solution and washed well with water. The product was dried at 110° to constant weight and 84 g. (83%), m. p. 290–320°, of tan powder was obtained.

A small sample was recrystallized from dioxane and melted at 316–318° (dec.).

Anal. Calcd. for $C_{10}H_6O_2NCl$: equiv. wt., 207.6. Found: equiv. wt., 211.

The crude acid was esterified using thionyl chloride in the usual manner to give a 55% yield of the desired ester, b. p. 170° (2.5 mm.), m. p. 90–92°, after crystallization from petroleum ether.

(13) Gilman and Spatz, THIS JOURNAL, **63**, 1556 (1941).
(14) Edinger, *J. prakt. Chem.*, (2) **54**, 357 (1896).
(15) Claus and Collischonn, *Ber.*, **19**, 2763 (1886).
(16) Kindler, *ibid.*, **69**, 2792 (1936).
(17) Hammick, *J. Chem. Soc.*, **123**, 2882 (1923).
(18) Hammick and Dickinson, *ibid.*, 214 (1929).
(19) Jakubowski, *Ber.*, **43**, 3030 (1910).
(20) Further work on this synthesis was rendered unnecessary by success of the phenylation described below.
(21) Bamberger, *Ber.*, **35**, 3706 (1902).

Anal. Calcd. for $C_{12}H_{10}O_2NCl$: C, 61.15; H, 4.28. Found: C, 60.88; H, 4.33.

Ainley-King Syntheses.—The synthesis of the compounds listed in Table I was based on the procedure described by Buchman and Sargent[3] for the preparation of α-(2-piperidyl)-8-quinolinemethanol. The method of Rubtsov,[22] using sodium ethylate as condensing agent rather than sodium amide (which gave unsatisfactory results), was applied to the condensation of ethyl quinaldate with ethyl ε-benzamidocaproate.

TABLE I

AINLEY-KING SYNTHESES

Product	M. p., °C.	Yield, %	Percentage composition[a] Calcd. C	Calcd. H	Found C	Found H
x-(ε-Aminocaproyl)-quinoline dihydrobromide						
7-	223–224[b]	30[c]	44.57	4.98	44.53	4.98
6-[d]	267–269	26	44.57	4.98	44.74	4.99
5-[e]	235–237	28[f]	44.57	4.98	44.71	5.00
3-[e]	251–253[g]	13[h]	44.57	4.98	44.84	5.12
2-[i]	240–241[j]	45	44.57	4.98	44.23	4.96
8-chloro-5-[k]	272 dec.[l]	11	41.07	4.37	41.29	4.37
x-(ε-Amino-α-bromocaproyl)-quinoline dihydrobromide						
7-	180–181	78	...	..	...	..
6-	128–130	94	37.24	3.97	37.49	4.65
5-	127–132	100	...	..	...	..
3-	...	96	...	..	...	..
2-	180–200	97	...	..	...	..
8-chloro-5-	Hygroscopic	64	...	..	...	..
α-(2-Piperidyl)-*x*-quinoline-methanol dihydrobromide						
7-, SN 10051	308–309	80	44.57	4.98	44.68	5.09
6-, SN 10050	240–242[m]	70	44.57	4.98	44.60	5.10
5-, SN 10049	295 dec.	74	74.36[n]	7.49[n]	74.43[n]	7.48[n]
3-, SN 10048[o]	314–315	25	44.57	4.98	44.91	5.05
2-, SN 10059[p]	234–235 dec.	55	44.57	4.98	44.52	5.10
8-chloro-5-[q]	313 dec.	80	41.09	4.35	41.15	4.41

[a] Microanalyses are by Dr. E. W. D. Huffman, Denver, Colorado. [b] Crystallized from ethanol–isopropanol. [c] Yield is 58% based on the amount of quinoline ester that reacted. [d] A 2:1 molar ratio of sodium amide to esters was used. [e] 1:1 ratio of sodium amide to esters. [f] Yield is 59% based on reacted quinoline ester. [g] Crystallized from ethanol–ether. [h] A major portion of the basic oil isolated was quinoline. [i] Prepared by the method of Rubtsov. The hydrochloric acid hydrolysis required twenty hours. [j] Crystallized from ethanol. [k] A 50% excess of ethyl ε-benzamidocaproate and a two-fold excess of sodium amide over the quinoline ester was used. Attempts to repeat this preparation gave yields of 5% or less. [l] Colorless crystals from ethanol. [m] Crystallized from ethanol–ether. [n] Calculated and found for free base, m. p. 188–189°. [o] Free base, m. p. 189–190° from benzene analysis. [p] Catalytic reduction proceeded only with excess acetic acid present. [q] Free base, m. p. 199–201° from benzene.

2-Phenyl-α-(2-piperidyl)-5-quinolinemethanol (SN 13,804).—To a suspension of 13.3 g. (0.055 mole) of α-(2-piperidyl)-5-quinolinemethanol in 100 ml. of dry ether was added 210 ml. (0.25 mole) of 1.19 molal phenyllithium solution. After shaking *in vacuo* for twenty minutes at 0° and two hours at room temperature, the brown solution appeared homogeneous and was poured onto ice. The product was extracted from the ether phase with 6 *N* hydrochloric acid and treated with Nuchar-C190N to give a colorless solution. The free base was liberated by addition of sodium hydroxide and taken up in chloroform. Evaporation of the dried chloroform solution gave 12.5 g. of white crystalline 2-phenyl-α-(2-piperidyl)-5-quinolinemethanol with a melting point of 214–215° after two crystallizations from benzene. Nine grams of pure free base was converted to the dihydrobromide by addition of excess 48% hydrobromic acid to an ethanol solution fol-

(22) Rubtsov, *J. Gen. Chem. U. S. S. R.*, **13**, 593 (1943) [*C. A.*, **39**, 705 (1945)].

lowed by addition of dry ether. A yield of 12.3 g. (47%) of slightly yellow crystals, m. p. 316–317°, was obtained.

Anal. Calcd. for $C_{21}H_{22}ON_2.2HBr$ (480.23): C, 52.52; H, 5.04; equiv. wt., 240.1. Found: C, 52.47; H, 5.01; equiv. wt., 240.0, 240.8 ($AgNO_3$ titration).

2-Quinolyl-2-piperidylmethane.[23,24]—A solution of 3.0 g. of *o*-aminobenzaldehyde,[25] 3.0 g. of 2-piperidylacetone,[26] 10 ml. of methanol, 40 ml. of water and 2 ml. of 6 *N* sodium hydroxide was warmed on the water-bath for two hours. Excess methanol was allowed to evaporate and the mixture acidified with hydrochloric acid and extracted with chloroform to remove colored impurities. The solution was made alkaline and extracted twice with chloroform and the dried combined extracts were distilled to give the following fractions: 1.0 g. of 2-piperidylacetone, b. p. 60–90° (2 mm.); 2.6 g. yellow oil, b. p. 160–165° (2 mm.). The yellow oil was converted to the hydrochloride and recrystallized twice from a mixture of 10% methanol in absolute ethanol to give colorless needles, m. p. 218–219°.

The same hydrochloride, as shown by lack of depression of the melting point upon mixture of the two products, was prepared similarly by condensation of N-acetyl-2-piperidylacetone, b. p. 200–208° (1.0 mm.), and subsequent hydrolysis by two hours of boiling in 6 *N* hydrochloric acid.

Anal. Calcd. for $C_{15}H_{18}N_2 \cdot HCl$: C, 68.57; H, 7.29; equiv. wt., 262.7. Found: C, 68.59; H, 7.35; equiv. wt., 260.0 ($AgNO_3$ titration).

(23) The structure of this compound was not definitely ascertained. Numerous attempts to oxidize the methylene group were unsuccessful; butyl nitrite, chromic acid and lead tetraacetate were tried and failed to give isolable products.

(24) Condensation of 2-picolyllithium with 2-chloroquinoline failed to give appreciable yields of 2-quinolyl-2′-pyridylmethane in preliminary experiments.

(25) Bamberger and Demuth, *Ber.*, **34**, 1329 (1901). The yield of pure *o*-aminobenzaldehyde, b. p. 80–85° (2 mm.), was 55–67%.

(26) Hess and Eichel, *ibid.*, **50**, 1404 (1917).

Summary

The syntheses have been reported of α-(2-piperidyl)-quinolinemethanols having the 2-piperidylcarbinol group attached to the 2-, 3-, 5-, 6- and 7-positions in the quinoline nucleus; also of 2-phenyl-α-(2-piperidyl)-5-quinolinemethanol and 8-chloro-α-(2-piperidyl)-5-quinolinemethanol. Various quinoline carboxylic ester intermediates and related substances have been described.

STANFORD UNIVERSITY, CALIF. RECEIVED JUNE 22, 1946

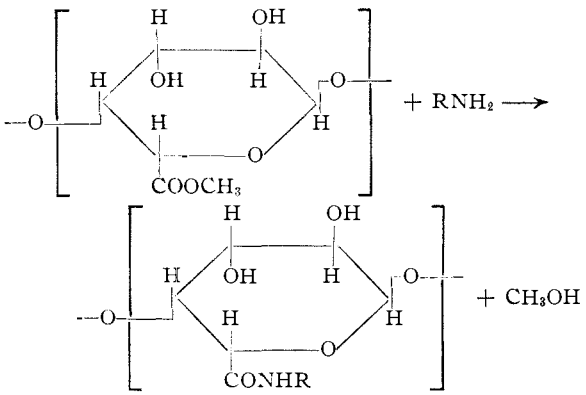
NOTES

Some Polygalacturonide *n*-Alkylamides

BY J. F. CARSON

This paper describes the preparation and properties of several polygalacturonide *n*-alkylamides. Although the neutralization of pectic acids with various amines to yield amine salts has been described,[1] the conversion of the carbomethoxyl groups of pectins to amide groups has not been recorded in the literature.

The amides were prepared by reaction of dry pectins with primary aliphatic amines under anhydrous conditions according to the scheme



Two sets of pectic material were used—one a commercial citrus pectin in which approximately three-fourths of the carboxyl groups were esterified as methyl ester, and the other a polygalacturonide methyl ester with a free acid content of approximately 3%, calculated as anhydrogalacturonic acid. By this reaction, the *n*-propyl- and *n*-butylamides of pectin were prepared, and the ethyl-, *n*-propyl-, *n*-butyl-, *n*-hexyl- and *n*-octylamides were prepared from polygalacturonide methyl ester. Nitrogen and methoxyl analyses indicated that the reaction with ethyl-, *n*-propyl- and *n*-butylamine was substantially complete after seventy-two hours at room temperature; with *n*-hexylamine, reaction was approximately 95% complete, and with *n*-octylamine only 50%. Repeated treatment of the partially reacted octylamide with excess octylamine at 50° increased the extent of the reaction, but did not bring about complete replacement of the ester groups.

The ethyl-, *n*-propyl- and *n*-butylamides were soluble in water to give solutions of low viscosity. They were also soluble in formamide, swelled in the lower alcohols and aliphatic amines, and were generally insoluble in organic solvents. Recovery of the amides from aqueous solution by precipitation into large volumes of ethanol or acetone was difficult, because of the tendency of the products to separate as fine flocs. Aqueous solutions of the ethyl-, propyl- and butylamides prepared from

(1) R. F. Stuewer and A. G. Olsen, *J. Am. Ph. Assn.*, **29**, 303 (1940).