

no depression of melting point on admixture with the authentic sample.<sup>3)</sup> *Anal.* Calcd. for  $C_{23}H_{34}O_5$ : C, 70.74; H, 8.78. Found: C, 70.69; H, 8.75.

**6-Methoxy-3 $\beta$ ,5-dihydroxy-5,6-secoandrostan-17-one 3-Acetate 5,6-Peroxide (IIc) and 6 $\beta$ -Formyl-3 $\beta$ ,5-dihydroxy-B-nor-5 $\beta$ -androstan-17-one 3-Acetate (IVc)**—A solution of 5 g. of 3 $\beta$ -hydroxyandrost-5-en-17-one acetate (Ic) in 400 cc. of  $CH_2Cl_2$  containing 1% of MeOH was treated with an ozonized air as described above. One tenth of the ozonized mixture was separated, the solvent was removed to give a semisolid product, which was recrystallized from hexane-Me<sub>2</sub>CO to yield 6-methoxy-3 $\beta$ ,5-dihydroxy-5,6-seco-6-androstan-17-one 3-acetate 5,6-peroxide (IIc) melting at 147~148° (decomp.). *Anal.* Calcd. for  $C_{22}H_{34}O_7$ : C, 64.37; H, 8.35; OCH<sub>3</sub>; 7.55. Found: C, 63.92; H, 8.21; OCH<sub>3</sub>, 7.20. IR  $\nu_{\max}^{Nujol}$   $cm^{-1}$ : 3280 (OH), 1730, 1240 (OAc).

The residual mixture ozonized was reduced with Zn dust and AcOH and cyclized with alumina as described above to yield 3.16 g. (64%) of 6 $\beta$ -formyl-3 $\beta$ ,5-dihydroxy-B-nor-5 $\beta$ -androstan-17-one 3-acetate (IVc) of m.p. 132~134°. *Anal.* Calcd. for  $C_{21}H_{30}O_5$ : C, 69.58; H, 8.34. Found: C, 69.45; H, 8.21.

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### Summary

Cholesterol acetate (Ia), 3 $\beta$ -hydroxypregn-5-en-20-one acetate (Ib) and 3 $\beta$ -hydroxyandrost-5-en-17-one acetate (Ic) were ozonized in dichloromethane containing a small amount of methanol to give the corresponding 3 $\beta$ -acetoxy-5-hydroxy-6-methoxy-5,6-peroxy-5,6-seco steroid compounds (IIa, b, c), which on reduction with zinc dust and acetic acid afforded 3 $\beta$ -acetoxy-5-oxo-5,6-seco steroid-6-als (IIIa, b, c). Cyclization reaction of (IIIa, b, c) was conducted by stirring with alumina in benzene solution to yield 6 $\beta$ -formyl-B-nor-5 $\beta$ -cholestane-3 $\beta$ ,5-diol 3-acetate (IVa), 6 $\beta$ -formyl-3 $\beta$ ,5-dihydroxy-B-nor-5 $\beta$ -pregnan-20-one 3-acetate (IVb) and 6 $\beta$ -formyl-3 $\beta$ ,5-dihydroxy-B-nor-5 $\beta$ -androstan-17-one 3-acetate (IVc), respectively.

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### Toshio Kakimoto, Kyoze Hayashi, and Tomoji Suzuki: Synthesis of Quinoline Derivatives of Amino Acid.

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One of the main requirements among satisfactory chemotherapeutic agents is desired to penetrate into or to be absorbed readily by micro organisms against which it is directed. It is already known that bacterial growth is inhibited to some extent by 3-(4-quinolyl)alanine and other heterocyclic amino acids.<sup>1)</sup> Our principal project has been a little far from investigating competitive growth inhibition by amino acid analogs and rather an effect of compounds in which the side chain of the characteristic 2-amino-propionic acid and 2-aminobutyric acid is attached at its  $\omega$ -carbon to quinoline and its nucleus substituent has been studied.

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1) D. F. Elliott, A. T. Fuller, C. R. Harington: *J. Chem. Soc.*, 1948, 85.

As a preliminary exploration of this idea, the synthesis of 3-(8-quinolyl)alanine (I), 3-(3-bromo-8-quinolyl)alanine (II), 3-(5-nitro-8-quinolyl)alanine (III), 3-(2-quinolyl)alanine (IV) and  $\alpha$ -amino-2-quinolinebutyric acid (V) have been studied.

For the synthesis of I~IV, 8-bromomethylquinoline and its derivatives were condensed with ethyl acetamidocyanoacetate and the product was hydrolyzed to the desired amino acid by conc. hydrochloric acid (Chart 1).

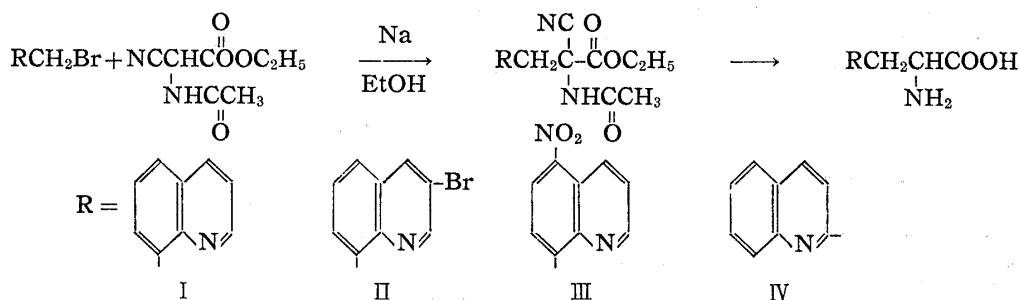


Chart 1.

$\alpha$ -Amino-2-quinolinebutyric acid was prepared by the following method; the Mannich base from quinoline hydrochloride, formaldehyde and diethylamine was condensed in the usual manner with ethyl acetamidocyanoacetate and acidic hydrolysis of the condensation product gave the desired amino acid (Chart 2).

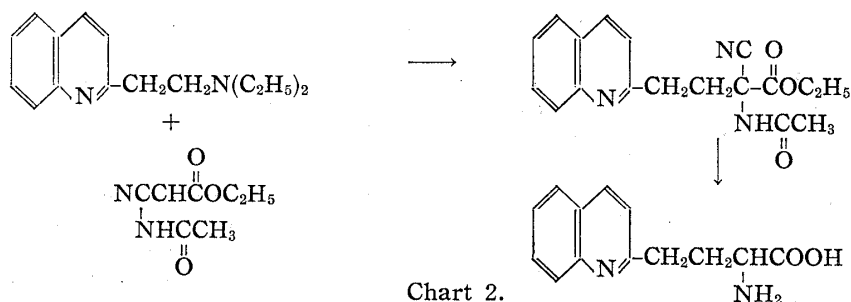


Chart 2.

The bacteriostatic activity of these compounds will be reported later.

### Experimental\*2

**3-(8-Quinolyl)alanine (I)**—i) Ethyl  $\alpha$ -acetamido- $\alpha$ -cyano-8-quinolinepropionate: Ethyl acetamidocyanoacetate (3.56 g.) was added to a cooled solution of 0.46 g. of Na in 30 ml. of abs. EtOH and 4.86 of 8-bromomethylquinoline<sup>2)</sup> was then added and the mixture was refluxed for 4~5 hr. after standing for 1 hr. at room temperature. The solvent was removed and the residue was dissolved in a small volume of H<sub>2</sub>O and extracted three times with Et<sub>2</sub>O and dried. An evaporation of the Et<sub>2</sub>O extract gave 5.15 g. of white needles after recrystallized from hyd. EtOH. m.p. 162~163°. *Anal.* Calcd. for C<sub>17</sub>H<sub>17</sub>O<sub>3</sub>N<sub>3</sub>: C, 65.58; H, 5.50; N, 13.50. Found: C, 64.93; H, 5.45; N, 13.37.

ii) 3-(8-Quinolyl)alanine (I): Ethyl  $\alpha$ -acetamido- $\alpha$ -cyano-8-quinolinepropionate (3.0 g.) was dissolved in 30 ml. of 25% HCl and the mixture was heated under reflux for 5 hr. An excess of HCl and water were removed *in vacuo* and the residue was dissolved in 100 ml. of H<sub>2</sub>O. The solution was passed through a column of Amberlite IR-120 which was washed with distilled H<sub>2</sub>O until no Cl<sup>-</sup> was detected in the effluent. The absorbed amino acid was eluted with 0.5N NH<sub>4</sub>OH and the eluate was concentrated *in vacuo*, followed by precipitation with EtOH, and recrystallized from hyd. EtOH-Me<sub>2</sub>CO to give 1.4 g. of I, white needles. m.p. 228~239°(decomp.). *Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.58; H, 5.76; N, 12.81. Rf value: 0.45 (BuOH:AcOH:H<sub>2</sub>O=4:1:1).

**3-(8-Quinolyl)alanine Dihydrochloride**—It was obtained by the usual manner and recrystallized from hyd. EtOH to white needles, m.p. 235~236°(decomp.). *Anal.* Calcd. for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>2</sub>: C, 49.84; H, 4.88; N, 9.69. Found: C, 49.95; H, 5.09; N, 9.66.

\*2 All melting points are uncorrected.

2) J. Howitz, P. Nöther: Ber., 39, 2705 (1906).

**3-(3-Bromo-8-quinolyl)alanine (II)**—i) Ethyl  $\alpha$ -acetamido- $\alpha$ -cyano-3-bromo-8-quinoline propionate: Under the same condition as ethyl  $\alpha$ -acetamido- $\alpha$ -cyano-8-quinoline propionate, it was obtained by the condensation of 0.6 g. of ethyl acetamidocyanoacetate, 1.1 g. of 3-bromo-8-bromoethylquinoline<sup>3)</sup> and 0.08 g. of Na in abs. EtOH. The product was recrystallized from hyd. EtOH to pale brown needles. m.p. 165~167°. Yielding, 0.82 g. *Anal.* Calcd. for C<sub>17</sub>H<sub>17</sub>O<sub>3</sub>N<sub>3</sub>Br: C, 52.32; H, 4.13; N, 10.71. Found: C, 52.22; H, 4.12; N, 10.79.

ii) 3-(3-Bromo-8-quinolyl)alanine (II): It was obtained by the hydrolysis of 0.8 g. of ethyl  $\alpha$ -acetamido- $\alpha$ -cyano-3-bromo-8-quinoline propionate with 20 ml. of 25% HCl in the same way as described above. Recrystallization from EtOH gave white powders. m.p. 178°(decomp.). Yielding, 0.43 g. *Anal.* Calcd. for C<sub>12</sub>H<sub>11</sub>O<sub>2</sub>N<sub>2</sub>Br·2HCl: C, 37.33; H, 3.91; N, 7.26. Found: C, 37.10; H, 4.01; N, 7.53. Rf value: 0.58 (BuOH:AcOH:H<sub>2</sub>O=4:1:1).

**3-(5-Nitro-8-quinolyl)alanine (III)**—It was obtained by the same procedure as 3-(8-quinolyl)alanine. Ethyl  $\alpha$ -acetamido- $\alpha$ -cyano-5-nitro-8-quinoline propionate was prepared by the condensation of 0.89 g. of ethyl acetamidocyanoacetate, 1.5 g. of 5-nitro-8-bromomethylquinoline and 0.12 g. of Na in 25 ml. of abs. EtOH. In this case an intermediate was not isolated in a crystalline form but the condensation product was hydrolyzed directly by 25% HCl. Recrystallization from EtOH gave white powders. m.p. 235°(decomp.). Yielding, 0.40 g. *Anal.* Calcd. for C<sub>12</sub>H<sub>11</sub>O<sub>4</sub>N<sub>3</sub>·2HCl: C, 43.10; H, 3.92; N, 12.57. Found: C, 43.03; H, 4.08; N, 12.42. Rf value: 0.50 (BuOH:AcOH:H<sub>2</sub>O=4:1:1).

**3-(2-Quinolyl)alanine (IV)**—It was obtained by the same way as 3-(8-quinolyl)alanine from 0.6 g. of ethyl acetamidocyanoacetate, 0.81 g. of 2-bromomethylquinoline<sup>4)</sup> and 0.08 g. of Na in 30 ml. of abs. EtOH. Hydrolysis of the condensation product with 25% HCl gave IV after a treatment with Amberlite IR-120 as I. Recrystallization from hyd. EtOH gave white powders. m.p. 184~186°. Yielding, 0.37 g. *Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>·H<sub>2</sub>O: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.37; H, 5.71; N, 12.19. Rf value: 0.52 (BuOH:AcOH:H<sub>2</sub>O=4:1:1).

**3-(2-Quinolyl)alanine Dihydrochloride**—It was obtained by the usual manner. White crystals. m.p. 213~215°. *Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>·2HCl: C, 49.62; H, 4.88; N, 9.69. Found: C, 49.84; H, 5.05; N, 9.50.

**$\alpha$ -Amino-2-quinolinebutyric Acid (V)**—To a solution of 2.5 g. of 2-(2-diethylaminoethyl)quinoline<sup>5)</sup> in 50 ml. of abs. EtOH was added 1.78 g. of ethyl acetamidocyanoacetate and 0.40 g. of powdered NaOH. The mixtures were refluxed with stirring under a stream of N<sub>2</sub> gas bubbled through it until the escaping gas no longer contained diethylamine (ca. 6 hr.). Then, a hot solution was filtered, the filtrate was concentrated *in vacuo* and the residue was dissolved in 30 ml. of 25% HCl. The solution was heated under reflux for 5 hr. and the following procedure was in the same way as I. Recrystallization from hyd. EtOH gave white plates. m.p. 265~268° (decomp.). Yielding, 0.34 g. *Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.56; H, 6.11; N, 12.42. Rf value: 0.46 (BuOH:AcOH:H<sub>2</sub>O 4:1:1).

**$\alpha$ -Amino-2-quinolinebutyric Acid Dihydrochloride**—It was obtained by the usual procedure. White crystals. m.p. 238°(decomp.). *Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>·2HCl: C, 51.49; H, 5.32; N, 9.24. Found: C, 51.27; H, 5.59; N, 9.05.

### Summary

To investigate competition growth inhibition of heterocyclic amino acids, five compounds of 3-(8-quinolyl)alanine, 3-(3-bromo-8-quinolyl)alanine, 3-(5-nitro-8-quinolyl)alanine, 3-(2-quinolyl)alanine and  $\alpha$ -amino-2-quinolinebutyric acid were synthesized by the method of amino acid synthesis with ethyl acetamidocyanoacetate.

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3) J. Howitz, W. Schenk: *Ber.*, **38**, 1284 (1905).

4) B. R. Brown, D. L. Hammick: *J. Chem. Soc.*, **1951**, 1147.

5) W. O. Kermack, W. Muir: *Ibid.*, **1931**, 3093.