NOTES

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3-[8′-Quinolinol-(5′)-yl]alanine and Related Compounds

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An improved method of preparing the two known compounds[1] 5-chloralyl-8-quinolinol (I) and 5-formyl-8-quinolinol (II) and preparation of 3-[8′-quinolinol-(5′)-yl]alanine (V) which, to our knowledge, has not heretofore been reported are presented in this paper. On heating a mixture of 8-quinolinol and chloral at 65°C I was formed in 93% yield. A mixture of I and a solution of sodium in cold acetone after 3 days standing at room temperature yielded the hydrolyzed product II in 67% yield. After the hydrolysis was finished the reaction mixture was filtered [the solid (A) on the filter was worked up to isolate II.]. The chloroform residing in the acetone filtrate (B) was quantitatively estimated as the following by the Cole method[2] with minor modifications. The filtrate (B) was subjected to distillation. To the distillate pyridine and concentrated sodium hydroxide solution were added. On heating, the color of the solution became red, the extinction at wavelength 490 mμ was determined and the concentration of chloroform was quantitatively estimated. In parallel to this, the following control experiment was carried out. A known amount of chloroform was mixed with a solution of sodium in acetone and the resulting solution was treated in the same manner as in the case of hydrolysis of I and the remaining chloroform was estimated by the Cole method. By this control experiment, it was found that about 91% of the chloroform initially added had been destroyed by hydrolytic fission during the treatment under the conditions specified. For interpretation of the mechanism of hydrolysis of I this percentage of chloroform was taken into account. It was indicated that the amount of produced chloroform during the hydrolysis of I was nearly equal to the calculated one from the following scheme

$$Q\text{-}CH(OH)\text{-}CCl_3 \rightarrow Q\text{-}CH(OH)^+ + {}^-CCl_3$$

Q = 8-Quinolinol-(5)-yl

From this, it may be postulated that the hydrolysis of I with sodium acetonate would involve an ionic cleavage affording CCl_3^-, whose mechanism is different from that postulated for the hydrolysis of I in ethanolic potassium hydroxide solution.[1]

On condensation with hippuric acid or hydantoin, followed by treatment with hydroiodic acid and phosphorus, the compound II yielded 3-[8′-quinolinol-(5′)-yl]alanine (V).[3]

Results of Biological Study.[*1] The compound V has been found inactive in antifungal test *in vitro* (50 μg/ml of V indicated inactive against *candida albicans*) and contrary to expectation, it was toxic (tolerated dosis: 500 mg per kg body weight of a mouse either subcutaneously or intra peritoneally).

Experimental

5-Chloralyl-8-quinolinol (I). On adding chloral (22.2 g, 0.15 mol) to 8-quinolinol (14.5 g, 0.1 mol) an orange solid was formed. After standing for 3 days at room temperature until it turned to a light yellow solid, it was heated at 65°C in a water bath for 35 hr. The reaction mixture was treated with 3 N hydrochloric acid (250 ml) at 80°C until the orange reaction mass completely turned to yellow crystalline hydrochloride which was filtered after cooling. It was suspended in hot water (200 ml) and sodium acetate hydrate (40 g) was added to the suspension. The mixture was heated on a water bath (80°C) for 0.5 hr, the resulting orange yellow free base was filtered on cooling, and it was repeatedly washed

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TABLE 1. DERIVATIVES OF 3-[8'-QUINOLINOL-(5')-YL]ALANINE

Compound	Formula	C, % {Calcd {Found	H, % {Calcd {Found	N, % {Calcd {Found	Mp °C[f]	Description	Solvent
Dihydrochloride[a]	$C_{12}H_{12}O_3N_2 \cdot 2HCl$	{47.21 {47.84	{4.59 {3.95	{ 9.18 { 9.23	295	Yellow plates	6N HCl
Monopicrate[b]	$C_{12}H_{12}O_3N_2 \cdot C_6H_3N_3O_7$	{46.85 {46.84	{3.23 {3.17	{15.18 {14.85	240	Needles	EtOH(30%)
Dipicrate[c]	$C_{12}H_{12}O_3N_2 \cdot 2C_6H_3N_3O_7 \cdot 2.5H_2O$	{39.18 {38.78	{3.13 {3.13	{15.24 {14.97	218	Prisms	EtOH(30%)
Diacetyl[d]	$C_{16}H_{16}O_5N_2$	{60.77 {60.52	{5.06 {5.12	{ 8.86 { 8.78	211.5	Colorless needles	Acetone
7-Iodo-[e]	$C_{12}H_{11}O_3N_2I \cdot 1.5H_2O$	{37.40 {37.43	{3.64 {4.11	{ 7.27 { 6.93	200	Tan colored columns	H_2O

a) Dried at 115°C *in vacuo*. b) The quinolinolylalanine (V) (0.116 g, 0.005 mol) was reacted with picric acid (0.23 g, 0.001 mol) in hot water. The crude product when twice recrystallized from dilute ethanol (30%) yielded monopicrate. The mother liquor of the recrystallizations separated dipicrate on concentration. c) Vacuum-dried over potassium hydroxide at room temperature. d) Made by heating a mixture of quinolinolylalanine (V) (0.116 g, 0.0005 mol) acetic anhydride (0.5 g, 0.005 mol) and glacial acetic acid (0.5 m*l*) for 7 min at 100°C. It gave no color reaction with ferric chloride. e) Made in 66%yield by applying the Harington method of iodinating tyrosine to this compound C. R. Harington and R. V. Pitt-Rivers, *Biochem. J.*, **39**, 157 (1945). The compound is soluble in one hundred and sixty times its weight of boiling water. f) All substances melted with decomposition.

with hot water and dried on a water bath, yield 29.7 g (93%). It was pure enough for use in the next step of synthesis. For comparison a portion was recrystallized from acetone. Its identity with that obtained by the known method[1] was ascertained by IR spectra and thin layer chromatography.

5-Formyl-8-quinolinol (II). Chipped sodium (3.6 g, 0.157 mol) was added to the cooled (0°C) acetone (dried with calcium chloride and distilled, 180 m*l*). The mixture was frequently shaken until a homogeneous suspension resulted, whereupon 5-chloralyl-8-quinolinol (9.6 g, 0.03 mol) was added and the resulting mixture was stirred for a few minutes until a homogeneous paste resulted. After standing for 3 days at room temperature the resulting precipitates (A) were filtered, repeatedly washed with acetone [the combined filtrate and washings (B) were stored for the estimation of chloroform] and were dissolved in water (100 m*l*) (charcoal). On acidifying with acetic acid (50%) the filtered aqueous solution afforded a straw yellow solid (4.6 g), mp 160—173°C. A mixture of this solid product, sodium bisulfite (15 g) and water (30 m*l*) was well triturated at about 60°C. After cooling, the mixture was filtered (charcoal) and washed with water. Concentrated hydrochloric acid was added to the combined filtrate and washings (50 m*l*) and the solution was concentrated on a water bath until the odor of sulfur dioxide became faintly discernible. After standing overnight the separated solid was filtered, dissolved in hot water (100 m*l*) and the solution (charcoal) was filtered. On addition of sodium acetate (6 g) to the filtrate the free base separated, which was filtered and washed with water, yield, 3.5 g (67%); mp 176—178°C. It was recrystallized from benzene to form almost colorless prisms, mp 177—178°C. It was identified with the authentic sample of 5-formyl-8-quinolinol[1] by IR spectra and thin layer chromatography.

Estimation of Chloroform in Acetone Solution

(a) Preparation of the Standard Curve. The procedure which has been standardized for measuring the amount of chloroform is essentially similar to that of Cole[2] and the extinction at the wavelength of 490 mμ was determined by spectrophotometer.

From this, the standard curve

$E = 0.281\ C$

E: Extinction

C: g/100 m*l*

Width of the solution = 1 cm

was obtained.

(b) Estimation of Chloroform. The filtrate (B), which was originated from 0.03 mol of chloralylquinolinol (I) was acidified with dilute sulfuric acid, and distilled on a water bath. When no more distillate came out a small amount of acetone was added to the residue and the distillation was continued. The chloroform content in the total distillate was measured by Cole method using the standard curve. Found: $CHCl_3$, 0.28 g (7.8% of the theoretical). Calcd (from the reaction formula) $CHCl_3$, $119 \times 0.03 = 3.58$ g.

(c) Control Test. Chloroform (3.582 g, 0.03 mol) was added to the cooled solution of sodium (3.6 g, 0.157 mol) in acetone (180 m*l*). After 3 days standing at room temperature, the mixture was treated in the same manner as that in the hydrolysis of I. Found: $CHCl_3$, 0.31 g (8.7% of the theoretical).

2-Phenyl-4-[8'-acetoxyquinol-(5')-ylmethylene]-5-oxazolone (III). A mixture of 5-formyl-8-quinolinol

(1.73 g, 0.01 mol), hippuric acid (1.88 g, 0.0105 mol), acetic anhydride (4.6 g, 0.045 mol) and fused sodium acetate (0.8 g, 0.01 mol) was heated at 100°C for 2 hr. After cooling the reaction mixture was treated with ice water (200 m*l*). The separated yellow solid (3.6 g, mp 138—173°C) after being dried at room temperature over potassium hydroxide *in vacuo* was recrystallized from benzene (50 m*l*) to give azlactone (III). Yield, 2.9 g (80%), mp 160—188°C. It gave no color reaction with ferric chloride and can be used without further purification for the next step of synthesis. For analytical purpose, it was recrystallized from benzene. Garnet colored prisms or yellow needles melting at 192°C. Found: C, 70.26; H, 4.41; N, 7.76%. Calcd for $C_{21}H_{14}O_4N_2$: C, 70.39; H, 3.91; N, 7.81%.

2-Phenyl-4-[8'-quinolinol-(5')-ylmethylene]-5-oxazolone. A solution of the acetoxyazlactone (III) (100 mg) in dilute ethanol (33%, 20 m*l*) was heated in a boiling water bath for one half hour. After cooling, the separated solid was filtered and crystallized from benzene to give brownish orange rods, mp 240—248°C (decomp). The solution in ethanol gives a violet brown color with ferric chloride. Found: C, 72.08; H, 3.85; N, 8.83%. Calcd for $C_{19}H_{12}O_3N_2$: C, 72.15; H, 3.80; N, 8.96%.

β-[8-Quinolinol-(5)-yl]-α-benzoylaminoacrylic Acid. A mixture of the azlactone (III) (120 mg) and 3 N hydrochloric acid (3 m*l*) was gently boiled over a free flame for 6 min until complete dissolution of the material into an orange red solution was effected. After cooling the reaction mixture was made alkaline with sodium carbonate solution, the resulting solution was acidified with acetic acid and the separated solid was recrystallized from hot ethanol to give prismatic needles of intense yellow color, mp 208—209°C (decomp). It exhibited a deep brown color with ferric chloride. Found: C, 67.45; H, 4.27; N, 8.18%. Calcd for $C_{19}H_{14}O_4N_2$: C, 68.26; H, 4.19; N, 8.38%.

5-[8'-Quinolinol-(5'-)ylmethylene]hydantoin (IV). A mixture of 5-formyl-8-quinolinol (1.73 g, 0.01 mol), hydantoin (1 g, 0.01 mol), acetic anhydride (5 g, 0.05 mol) and fused sodium acetate (0.85 g, 0.01 mol) was heated at 100°C for 5 hr. After evaporation under reduced pressure and cooling, the residue was treated with ice water. The separated solid (A) was converted to the hydrochloride by treating with hot dilute hydrochloric acid. The hydrochloride was dissolved in dilute sodium hydroxide solution and the solution was acidified with acetic acid to give the deacetylated product (1.5 g, 59%); mp 285—295°C (decomp). Without any further purification, it was used for the next step of synthesis. When crystallized from hot dioxane, it formed yellow prismatic needles, mp 198°C (decomp). It gave a violet brown color reaction with ferric chloride. Found: C, 61.54; H, 3.69; N, 16.14%. Calcd for $C_{18}H_9O_3N_3$: C, 61.18; H, 3.53; N, 16.47%.

The Hydrochloride of IV formed yellow needles and was hydrolysed in water, mp 296—300°C (decomp). Found: C, 50.41; H, 4.18; N, 13.22%. Calcd for $C_{13}H_9O_3N_3 \cdot HCl \cdot H_2O$: C, 50.40; H, 3.88; N, 13.57%.

5-[8'-Acetoxyquinol-(5')-ylmethylene]hydantoin. The solid (A) in the preceding experiment after being dried at room temperature was treated with warm benzene. Recrystallization of the benzene insoluble solid from acetone afforded yellowish leaflets, mp 261—263°C, giving no color reaction with ferric chloride. Found: C, 60.58; H, 3.37; N, 13.95%. Calcd for $C_{15}H_{11}O_4N_3$: C, 60.61; H, 3.70; N, 14.14%.

3-[8'-Quinolinol-(5')-yl]alanine (V).[3] A mixture of hydroiodic acid (52%, 9.8 g, 0.044 mol), red phosphorus (1 g), acetic anhydride (6.8 g) and the azlactone (III) (1.79 g, 0.005 mol) or the hydantoin (IV) (1.49 g, 0.005 mol) was gently refluxed in an oil bath for 6 hr. The subsequent treatment was almost similar to that stated in the standard procedure.[3b] The yield of the amino acid as monohydrate was 1.2 g (96%) starting from the azlactone and 1.05 g (84%) from the hydantoin. On recrystallization in five hundred times its weight of boiling water, the amino acid afforded colorless elongated plates, mp 287°C (decomp). It exhibited a violet red color with ninhydrin and a green color with ferric chloride.

The pK_2, 4.5; pK_3, 10.5, isoelectric point. 7.5, IR spectra $\nu_{cm^{-1}}^{KBr}$ 3480, 2920, 1630, 1575; 1520; 1435, 1410, 1350 and 1170. Paper chromatogram by descending technique R_f 0.3 (Solvent: Butanol-acetic acid-water, 4 : 1 : 2).

Found: C, 57.63; H, 5.54; N, 11.24%. Calcd for $C_{12}H_{12}O_3N_2 \cdot H_2O$*[2]: C, 57.60; H, 5.60; N, 11.20%.

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*[2] Vacuum dried at room temperature over potassium hydroxide.