TABLE I

2-SUBSTITUTED-THIAZOLIDINE-4-CARBOXYLIC ACIDS

| R | M. p. °C.[a] | Yield, % | Formula | Analyses,[b] % Calculated C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| 1'-Ethylpentyl | 163–164 | 97 | $C_{11}H_{21}NO_2S$ | 57.10 | 9.15 | | 56.71 | 8.72 | |
| 2'-Thienyl | 145–146 | 94 | $C_8H_9NO_2S_2$ | 44.63 | 4.21 | | 44.25 | 4.17 | |
| Methylene-3',4'-dioxyphenyl | 167–168 dec. | 99 | $C_{11}H_{11}NO_4S$ | 52.16 | 4.38 | | 52.60 | 4.40 | |
| Benzyl | 165–166 dec. | 90 | $C_{11}H_{13}NO_2S$ | 59.17 | 5.87 | | 58.97 | 5.98 | |
| 4'-Methoxyphenyl | 156–158 dec. | 95 | $C_{11}H_{13}NO_3S$ | 55.21 | 5.48 | | 54.74 | 5.67 | |
| 2'-Phenylethyl | 159–160 dec. | 94 | $C_{12}H_{15}NO_2S$ | 60.73 | 6.37 | | 61.06 | 6.27 | |
| 4'-Hydroxy-3'-methoxyphenyl | 164–166 dec. | 95 | $C_{11}H_{13}NO_4S$ | | | 5.49 | | | 5.53 |
| 4'-Hydroxyphenyl | 167–169 dec. | 93 | $C_{10}H_{11}NO_3S$ | | | 6.22 | | | 6.54 |
| 2'-Hydroxyphenyl | 164–166 | 99 | $C_{10}H_{11}NO_3S$ | | | 6.22 | | | 6.04 |
| 1'-Ethylpropyl | 173–175 | 43 | $C_9H_{17}NO_2S$ | | | 6.89 | | | 6.70 |
| 3',4'-Diethoxyphenyl | 149–151 dec. | 96 | $C_{14}H_{19}NO_4S$ | | | 4.71 | | | 4.65 |
| *n*-Hexyl | 150–152 | 99 | $C_{10}H_{19}NO_2S$ | | | 6.45 | | | 6.28 |
| *i*-Propyl | 180–182 | 41 | $C_7H_{13}NO_2S$ | | | 7.99 | | | 7.70 |

[a] Melting points were taken on a Fisher–Johns apparatus. [b] Carbon and hydrogen analyses by Oakwold Laboratories, Alexandria, Va.; nitrogen analyses by H. Soloway.

colorless crystals which melt, in most cases, with decomposition, have solubility properties reminiscent of α-amino acids, and show a tendency to revert to the original components on solution in polar solvents.

### Experimental

The method of Schubert[2] was used in all cases, and the results obtained are listed in Table I.

**2-(2'-Thienyl)-thiazolidine-4-carboxylic acid.**—L(+)-Cysteine hydrochloride[6] (5 g., 0.028 mole) and 3 g. (0.035 mole) of potassium acetate were dissolved in 43 ml. of distilled water. To this solution was added 3.56 g. (0.0318 mole) of freshly distilled thiophene-2-aldehyde in 45 ml. of 95% ethanol. On shaking vigorously, precipitation occurred. After refrigeration overnight, the crystalline product was separated by filtration, washed with 20 ml. of cold ethanol, and recrystallized from the same solvent, giving a 94% yield of product melting at 145–146°.

(6) Purchased from General Biochemicals, Inc., Chagrin Falls, Ohio.

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RECEIVED NOVEMBER 21, 1947

# NEW COMPOUNDS

### 6-β-Hydroxyethoxy-4-(3'-diethylaminomethyl-4'-hydroxyanilino)-quinoline

2-Diethylaminomethyl-4-aminophenol dihydrochloride[1] (13.3 g.) and 6-β-hydroxyethoxy-4-chloroquinoline[2] (11.2 g.) were refluxed in isopropyl alcohol (550 cc.) for twenty-four hours. The dihydrochloride of 6-β-hydroxyethoxy-4-(3'-diethylaminomethyl-4'-hydroxyanilino)-quinoline precipitated and was filtered from the hot reaction mixture. Suspending the precipitate in fresh, hot isopropyl alcohol, then filtering, gave 20 g. of dihydrochloride. This material (20 g.) was dissolved in water (150 cc.), ether (200 cc.) was added, and the mixture was made alkaline with potassium carbonate with shaking. The free base was filtered off, triturated in a mortar with water, and crystallized from acetone (16 volumes). When dried to a melting point of 144–145° the compound contained one-half mole of water; yield, 40%. The substance was a tan powder, soluble in acetone, slightly soluble in benzene or chloroform, and very slightly soluble in ether.

*Anal.* Calcd. for $C_{22}H_{27}O_3N_3 \cdot 0.5H_2O$: C, 67.67; H, 7.23; N, 10.74; $H_2O$, 2.31. Found: C, 67.41; H, 7.25; N, 10.87; $H_2O$, 2.33.

(1) Kindly presented by Parke, Davis and Company.

(2) Ramsey and Gretcher, THIS JOURNAL, 69, 1659 (1947).

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### Substituted Amides of *p*-Cyclohexylbenzoic Acid

A number of substituted amides of *p*-cyclohexylbenzoic acid were prepared by a reaction of the acid chloride with the corresponding amine in benzene solution. The standard method described by Shriner and Fuson[1] was employed. However, as the amounts of amine employed in each instance was double to triple the molar quantity specified

TABLE I

SUBSTITUTED AMIDES OF *p*-CYCLOHEXYLBENZOIC ACID

| N-*p*-cyclohexylbenzoyl | M. p., °C. | Solvent | Yield, % | Empirical formula | N Analyses, % Found | Calcd. |
|---|---|---|---|---|---|---|
| Aniline | 198–198.5 | *b, c, d* | 39 | $C_{19}H_{21}NO$ | 5.08 | 5.01 |
| *p*-Toluidine | 205.0 | *b* | 52 | $C_{20}H_{23}NO$ | 4.59 | 4.78 |
| *m*-Toluidine | 149.5–150.0 | *d* | 23 | $C_{20}H_{23}NO$ | 4.55 | 4.78 |
| *o*-Toluidine | 153.0 | *a* | 67 | $C_{20}H_{23}NO$ | 4.86 | 4.78 |
| *p*-Bromoaniline | 250.5 | *a, b* | 46 | $C_{19}H_{20}NOBr$ | 3.76 | 3.91 |
| *m*-Bromoaniline | 164.0 | *b* | 39 | $C_{19}H_{20}NOBr$ | 3.83 | 3.91 |
| *o*-Bromoaniline | 106.0–106.2 | *b* | 50 | $C_{19}H_{20}NOBr$ | 3.78 | 3.91 |
| 3-Bromo-4-amino-toluene | 123.5–124.0 | *a* | 80 | $C_{20}H_{22}NOBr$ | 3.67 | 3.76 |
| 5-Bromo-2-amino-toluene | 223.5 | *b, c* | 60 | $C_{20}H_{22}NOBr$ | 3.63 | 3.76 |
| 3-Nitro-4-amino-toluene | 134.0 | *c* | 86 | $C_{20}H_{22}N_2O_3$ | 7.75 | 8.28 |

[a] Ethyl acetate. [b] Benzene. [c] 1,4-Dioxane. [d] Ethyl alcohol. [e] *n*-Propyl alcohol.

(1) Ralph L. Shriner and Reynold C. Fuson, "The Systematic Identification of Organic Compounds," 2nd Ed., John Wiley & Sons, Inc., New York, N. Y., 1940, pp. 132–133.

by these authors, it was found desirable to wash the benzene solution of the crude amide with several times the amount of 5% hydrochloric acid called for by them.

The crude amides were dissolved in hot ethyl or *n*-propyl alcohol, diluted in several instances with water. The solutions were filtered hot after the addition of activated carbon together with kieselguhr, and the filtrates chilled to obtain the recrystallized products. A substantial quantity of a second crop of satisfactory purity was obtained by concentration of the mother liquors from the recrystallization of the derivatives of *p*-bromoaniline and 3-bromo-4-aminotoluene. The melting points reported are the best values obtained after recrystallization from a variety of solvents.

The derivatives and their properties are listed in Table I. All melting points are corrected.

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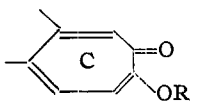
# COMMUNICATIONS TO THE EDITOR

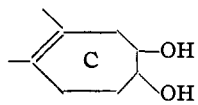
## THE STRUCTURE OF RING C OF COLCHICINE[1]

*Sir:*

It has been suggested,[2] without experimental support, that ring C of colchicine is seven-membered (I, R = $CH_3$). We have obtained evidence which favors the Dewar and definitely excludes the Windaus[3] formulation.




I

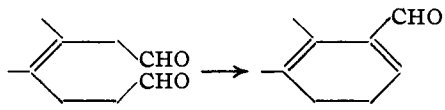



II

Colchiceine (I, R = H) (m. p. 175.5–176°; calcd. for $C_{21}H_{23}O_6N$: C, 65.45; H, 5.97; N, 3.66. Found: C, 65.65; H, 6.06; N, 3.45; benzoate, m. p. 207–209°, calcd. for $C_{28}H_{27}O_7N$: C, 68.70; H, 5.90; N, 2.86. Found: C, 68.87; H, 5.90; N, 2.78), prepared from purified colchicine,[4] was reduced with Raney nickel in methanol at room temperature and atmospheric pressure for one day, taking up three moles of hydrogen. The product was first crystallized from methanol, yielding about 26% of crude hexahydrocolchiceine[5] (II), m. p. 195.5–197°. Repeated crystallization from methanol–ether afforded the pure compound, m. p. 205.5–206° (calcd. for $C_{21}H_{29}O_6N$: C, 64.39; H, 7.47; N, 3.58. Found: C, 63.68; H, 7.39; N, 3.65; diacetate, m. p. 167°; calcd. for $C_{25}H_{33}O_8N$: C, 63.14; H, 6.99; N, 2.95. Found: C, 63.01; H, 6.83; N, 3.37).

Hexahydrocolchiceine was oxidized with periodic acid in 50% aqueous methanol at *p*H 4. At a lower *p*H side reactions appeared to take place. In a typical experiment hexahydrocolchiceine, m. p. 201–202°, $[\alpha]^{21.5}D$ −205 ± 1° (*c* = 1.544, methanol), $[\alpha]^{19}D$ −162 ± 1° (*c* = 1.436, 50% aqueous methanol) gave an uptake of 0.86 mole periodate after ten minutes, 0.92 mole after ninety minutes, unchanged after eighteen hours. At the end of the reaction, the rotation of the reaction mixture (50% aqueous methanol) had fallen to $[\alpha]^{19}D$ −109 ± 1° (*c* = 1.401). These results indicate the presence of one 1,2-glycol group in hexahydrocolchiceine.

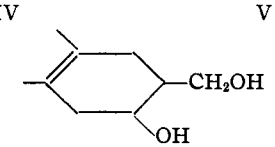
A chloroform extract of the reaction mixture yielded a yellow mobile sirup (III), strong Schiff and Tollens reactions, and reduced Fehling solution. On standing, it slowly lost its aldehydic properties. Efforts to obtain a semicarbazone or dimedone derivative have been unsuccessful, but an alcoholic solution of III with 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid gave amorphous mono-2,4-dinitrophenylhydrazone, m. p. 103–107° (dec.) (after chromatography on alumina) (calcd. for $C_{27}H_{29}O_8N_5$: C, 58.77; H, 5.30; N, 12.7. Found: C, 59.65; H, 5.39; N, 12.84). The oxidation of II presumably gives the dialdehyde (IV) which cyclises spontaneously to the monoaldehyde (V), or the dehydrogenation product from V.




IV




V




VI

On the Windaus structure, hexahydrocolchiceine would be a 1,3-glycol (VI) and no oxidation should occur with periodate; the above results are in agreement with (I).

Work is continuing on this and other reduction products of colchicine and its derivatives.

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RECEIVED MARCH 25, 1948

(1) Aided by a grant from the National Institute of Health.

(2) Dewar, *Nature*, **155**, 141 (1945).

(3) Windaus, *Ann.*, **439**, 59 (1924).

(4) Ashley and Harris, *J. Chem. Soc.*, 677 (1944).

(5) Bursian, *Ber.*, **71**, 245 (1938).