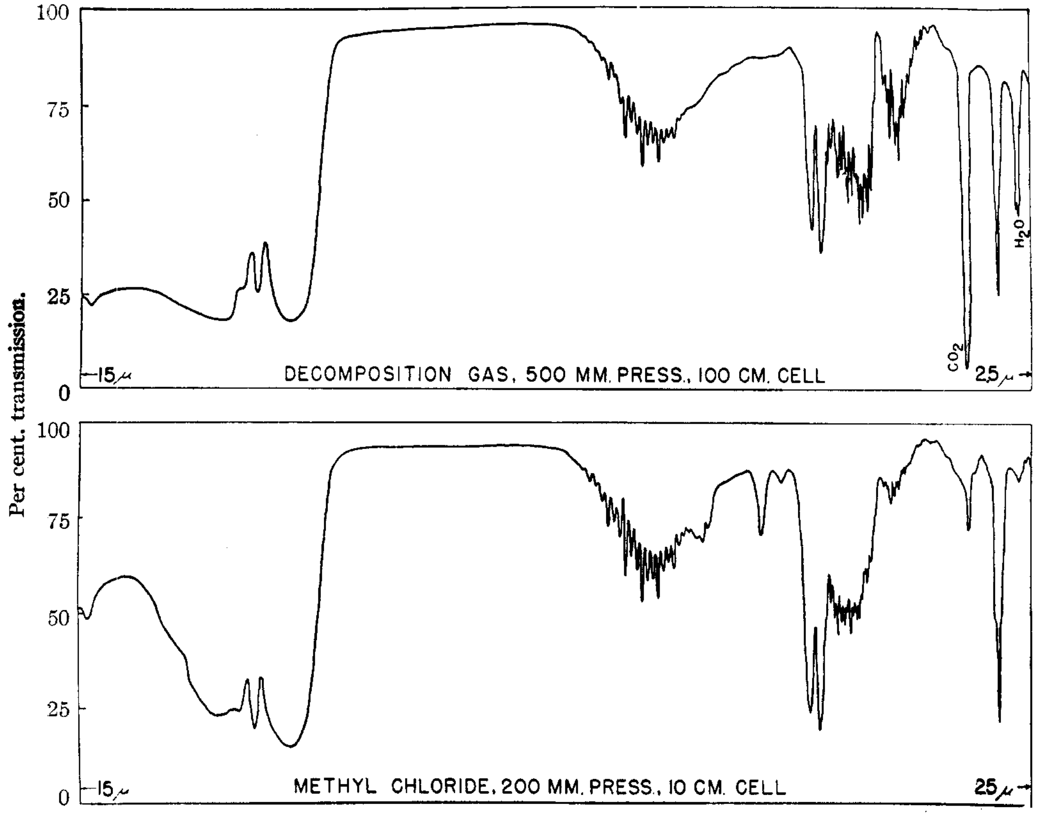

Fig. 1.—Comparison of spectra of methyl chloride and gas sample obtained from decomposition of *o*-methoxybenzene diazonium chloride.

composition reactions occurring simultaneously, one a slow single-step reaction to give guaiacol, and the other a pair of consecutive reactions to give catechol. They regretted that they did not find methyl chloride or methyl alcohol to substantiate their hypothesis.

We have obtained some evidence that their hypothesis is correct by infrared spectral analysis of the evolved nitrogen in the following manner: A solution of the diazonium salt was prepared from *o*-anisidine with 2.5 equivalents of hydrochloric acid and 1 equivalent of sodium nitrite. This solution was heated for about six hours at 90–95° and the evolved gas was passed through Drierite and soda-lime (to remove carbon dioxide used in sweeping air out of the apparatus) and collected over mercury. The gas was transferred to an infrared absorption cell which had an optical path length of one meter. With the gas at a pressure of 500 mm. the spectrum was recorded between 2.5 and 15 microns. The characteristic absorption spectrum of methyl chloride clearly was evident as shown in Fig. 1. A quantitative determination showed that the mole fraction of methyl chloride was 0.026. No other products were detected.

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## 2-Substituted-thiazolidine-4-carboxylic Acids

BY HAROLD SOLOWAY,[1] FRANK KIPNIS, JOHN ORNFELT AND PAUL E. SPOERRI

Schubert[2] has reported on the interaction of a number of aldehydes with cysteine to produce substituted thiazolidine carboxylic acids. Other workers[3] have extended the reaction and Ratner and Clarke[4] found that the mechanism consisted in hemimercaptal formation, followed by dehydration and cyclization.

Recently, with the discovery that penicillin contained a thiazolidine moiety within the molecule, interest was revived in this class of heterocyclics, and further syntheses have been announced.[5]

The present work reports on the interaction of a representative group of aldehydes with cysteine to produce thirteen new 2-substituted-thiazolidine-4-carboxylic acids. The new compounds form

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(1) Abstracted from a thesis by Harold Soloway submitted to the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

(2) Schubert, *J. Biol. Chem.*, **111**, 671 (1935); **114**, 341 (1936); **121**, 539 (1937); **130**, 601 (1939).

(3) Génévois and Cayrol, *Bull. soc. chim.*, [5] **6**, 1223 (1939); Woodward and Schroeder, THIS JOURNAL, **59**, 1690 (1937); Micheel and Emde, *Ber.*, **72**, 1728 (1939).

(4) Ratner and Clarke, THIS JOURNAL, **59**, 200 (1937).

(5) British Patent 584,918 (1947); Neher, Wettstein and Miescher, *Helv. Chim. Acta*, **29**, 1815 (1946); Brack, *ibid.*, **30**, 1 (1947).

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°.

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

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# 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.

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

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

## 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-aminotoluene | 123.5–124.0 | *a* | 80 | $C_{20}H_{22}NOBr$ | 3.67 | 3.76 |
| 5-Bromo-2-aminotoluene | 223.5 | *b*, *c* | 60 | $C_{20}H_{22}NOBr$ | 3.63 | 3.76 |
| 3-Nitro-4-aminotoluene | 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.

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(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.