24.6 g.), using the previously described procedure[22] for similar alkylations, gave 23.5 g. (78.8%) of 2-*n*-butyl-4-methylpyridine, b.p. 205–208°, which gave a picrate, m.p. 98.6–99.0° (lit. 88.5–90.5°[17]).

Anal. Calcd. for $C_{16}H_{18}N_4O_7$: N, 14.81. Found: N, 14.85.

V. *Synthesis of an authentic sample of α-(4-methyl-2-pyridyl)valerophenone.* The interaction of phenyllithium (0.2 mole), 2-*n*-butyl-4-methylpyridine (0.2 mole, 29.8 g.), and methyl benzoate (0.1 mole, 13.6 g.), using the previously described procedure for similar acylations,[2,4] gave 15.1 g. (59.7%) of α-(4-methyl-2-pyridyl)valerophenone, b.p. 168–170° at 1.5 mm.

Anal. Calcd. for $C_{17}H_{19}NO$: N, 5.53. Found: N, 6.05.

This ketone gave a dark, blue-green color with iron(III) chloride solution and gave a picrate, m.p. 109.2–109.6° (from 95% ethanol).

Anal. Calcd. for $C_{23}H_{22}N_4O_8$: N, 11.61. Found: N, 11.56.

VI. *The use of sodium amide to effect the benzoylation of 4-alkylpyridines.* (a) *4-Picoline.* Undiluted 4-picoline (0.4 mole, 37.2 g.) was added to a suspension of sodium amide [prepared from 0.4 mole (9.2 g.) of sodium in 300 ml. of anhydrous liquid ammonia] and the mixture was stirred for 15 to 20 min. To the suspension of 4-picolylsodium thus obtained, methyl benzoate (0.2 mole, 27.2 g.), dissolved in 30 ml. of anhydrous ether, was added over a period of 25 to 35 min. and stirring was continued for one more hour. The reaction was quenched by the addition of excess solid ammonium chloride and the liquid ammonia was replaced by adding ether and warming on a water bath. When the liquid ammonia had evaporated, as indicated by the refluxing of the ether, the reaction mixture was poured onto a mixture of ice and hydrochloric acid and processed in the regular fashion.[2,4] The solvent was distilled from the dried ether extracts and on cooling a semi-solid mass was obtained. This was filtered and gave 26.4 g. of 4-phenacylpyridine, m.p. 112–113.4°. The mother liquor was distilled to give 4.0 g. of 4-picoline, b.p. 140–145°, and 6.9 g. of a solid mixture of benzamide and 4-phenacylpyridine, b.p. 135–160° at 1.1 mm. This mixture was washed with several portions of cold anhydrous ether and filtered to separate the ketone from the amide. On the funnel there remained 3.6 g. of benzamide, m.p. 126.4–127.6° alone and when mixed with an authentic sample. The combined ether washings were distilled to given an additional 2.7 g. of 4-phenacylpyridine, b.p. 135–150° at 1.1 mm., m.p. 112–113.5°. The total yield of the ketone was 29.1 g. (73.8%).

(b) *4-Ethylpyridine.* The last reaction was repeated except that sodium amide (0.2 mole), 4-ethylpyridine (0.2 mole, 21.5 g.), and methyl benzoate (0.1 mole, 13.6 g.) were used. On processing the reaction mixture there was obtained 18.8 g. of crude product, b.p. 130–147° at 1 mm. This material, which crystallized on standing, was filtered and washed with several portions of anhydrous ether. Benzamide (0.5 g., m.p. 126.5–127.5°) remained on the funnel. The solvent was removed from the combined ether washings to give 17.9 g. (84.8%) of α-(4-pyridyl)propiophenone, m.p. 62.4–63.0° (from 30–60° petroleum ether).

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.57; H, 5.75; N, 6.82.

The ketone gave a picrate, m.p. 150.1–150.9° (from 95% ethanol).

Anal. Calcd. for $C_{20}H_{16}N_4O_8$: N, 12.72. Found: N, 13.08.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Thiazolidine Chemistry. II. The Preparation of 2-Substituted Thiazolidine-4-carboxylic Acids[1,2]

IRVING R. SCHMOLKA[3] AND PAUL E. SPOERRI[4]

Received March 21, 1957

Twenty-two 2-substituted thiazolidine-4-carboxylic acids have been prepared by the condensation of cysteine with aliphatic and aromatic aldehydes. Attempts to synthesize similar compounds from some α,β-unsaturated aldehydes were unsuccessful. An explanation of this failure of the reaction is discussed.

In the course of an investigation directed towards the preparation of water-soluble thiazolidine salts, the scope of the reaction of cysteine with aldehydes has been extended and an attempt made to explain its limitations. Twenty-two new (L)-2-substituted thiazolidine-4-carboxylic acids,[5] listed in Table I, were prepared using the method of Schubert.[6]

The preparation of the thiazolidines from the saturated aliphatic aldehydes indicated that increasing the chain length does not hinder the reaction. All these compounds crystallize in shining white platelets and are soluble in boiling isopropyl alcohol. The melting points decrease with increasing molecular weight. This was to be expected, since the compounds change from essentially heterocyclic carboxylic acids with a small aliphatic side chain to hydrocarbons with a small heterocyclic acid at one end.

The potassium salts of 2-undecyl and 2-hexadecylthiazolidine-4-carboxylic acids were prepared. The former was found to be soluble in water at a concentration of 0.1%, but the latter was insoluble at a 0.02% concentration, at 25°. The potassium salts were unstable and slowly decomposed on aging. This is in agreement with the reported findings

(1) Previous paper in series: H. Soloway, F. Kipnis, J. Ornfelt, and P. E. Spoerri, *J. Am. Chem. Soc.*, **70**, 1667 (1948).

(2) Abstracted in part from the M.S. thesis of Irving R. Schmolka, Polytechnic Institute of Brooklyn, June 1950. Presented in part at the first Meeting in Miniature, Metropolitan Long Island Subsection of the AMERICAN CHEMICAL SOCIETY's New York Section, March 17, 1950.

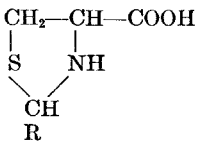
(3) Current address, Wyandotte Chemicals Corp., Wyandotte, Mich.

(4) To whom inquiries should be sent.

(5) Y. Kashida, *J. Pharm. Soc. Japan*, **69**, 185 (1949), has since reported No. 15 and No. 19, Table I.

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

TABLE I



2-SUBSTITUTED THIAZOLIDINE-4-CARBOXYLIC ACIDS

No.	R	Emp. Form.	M.P., °C.[a]	Yield	Rec. Solvent	Analyses[b] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	*n*-Pentyl	$C_9H_{17}O_2NS$	162–163 dec.	64	Isopr. Alc.	53.17	53.07	8.43	8.54	—	—
2	*n*-Heptyl	$C_{11}H_{21}O_2NS$	159–160 dec.	75	Isopr. Alc.	57.10	57.17	9.15	9.42	—	—
3	*n*-Octyl	$C_{12}H_{23}O_2NS$	158–159 dec.	45	Isopr. Alc.	—	—	—	—	5.71	5.54
4	*n*-Nonyl	$C_{13}H_{25}O_2NS$	156–157 dec.	46	Isopr. Alc.	—	—	—	—	5.40	5.39
5	*n*-Decyl	$C_{14}H_{27}O_2NS$	153–154 dec.	57	Isopr. Alc.	—	—	—	—	5.12	5.22
6	*n*-Undecyl	$C_{15}H_{29}O_2NS$	151–152 dec.	72	Isopr. Alc.	—	—	—	—	4.87	4.92
7	*n*-Tridecyl	$C_{17}H_{33}O_2NS$	148–149 dec.	65	Isopr. Alc.	—	—	—	—	4.44	4.20
8	*n*-Hexadecyl	$C_{20}H_{39}O_2NS$	142–143 dec.	76	Isopr. Alc.	67.17	67.16	10.99	10.61	3.92	4.23
9	2′-Chlorophenyl	$C_{10}H_{10}O_2NSCl$	145–146 dec.	77	50% Acetone	49.28	49.49	4.14	4.37	5.75	5.68
10	4′-Chlorophenyl	$C_{10}H_{10}O_2NSCl$	150–151 dec.	83	50% Acetone	49.28	49.61	4.14	4.12	—	—
11	3′,4′-Dichlorophenyl	$C_{10}H_9O_2NSCl_2$	160–161 dec.	83	50% Acetone	43.18	43.49	3.26	3.41	—	—
12	2′,6′-Dichlorophenyl	$C_{10}H_9O_2NSCl_2$	159–160 dec.	89	[c]	—	—	—	—	5.04	5.06
13	2′-Hydroxy-5′-chlorophenyl	$C_{10}H_{10}O_3NSCl$	160–161 dec.	77	[c]	—	—	—	—	5.40	5.25
14	2′-Nitrophenyl	$C_{10}H_{10}O_4N_2S\cdot 1^1/_2H_2O$	103–104 dec.	76	[c]	42.70	42.10	4.66	4.80	9.96	10.02
14	2′-Nitrophenyl	$C_{10}H_{10}O_4N_2S\cdot HCl$	158–159	90	[c]	—	—	—	—	9.64	9.77
15	3′-Nitrophenyl	$C_{10}H_{10}O_4N_2S$	151–153 dec.[d]	83	[c]	—	—	—	—	11.02	10.73
16	4′-Nitrophenyl	$C_{10}H_{10}O_4N_2S$	131–133 dec.	73	[e]	—	—	—	—	11.02	11.18
17	1′-Naphthyl	$C_{14}H_{13}O_2NS$	152–153 dec.	68	[c]	—	—	—	—	5.40	5.26
18	4′-(2′-Thiazolidine-4′-carboxylic acid)-phenyl	$C_{14}H_{16}O_4N_2S_2$	162–163 dec.	85	[c]	—	—	—	—	8.23	8.00
19	4′-Dimethylaminophenyl	$C_{12}H_{16}O_2N_2S$	198–199 dec.[d]	73	50% Isopr. Alc.	—	—	—	—	11.11	11.01
20	4′-Isopropyl-α-methylphenethyl	$C_{16}H_{23}O_2NS$	152–153 dec.	69	50% Isopr. Alc.	—	—	—	—	4.78	4.72
21	2′-Hydroxy-3′-methoxyphenyl	$C_{11}H_{13}O_4NS$	142–143 dec.	33	[f]	—	—	—	—	5.49	5.20
22	3′-Ethoxy-4′-hydroxyphenyl	$C_{12}H_{15}O_4NS$	176–177 dec.	88	Ethyl Alc.	—	—	—	—	5.20	5.10

[a] Melting points are uncorrected. [b] Microanalyses by R. Schachat and H. Biletch of the Polytechnic Institute of Brooklyn. [c] No recrystallizing solvent found other than alkali. Therefore the material was washed and thoroughly dried. [d] Ref. (5) reports 154–156° for No. 15 and 195–197° for No. 19. [e] Dissolved in hot ethyl alcohol and reprecipitated with carbon tetrachloride. [f] Dissolved in hot diethyl ether and reprecipitated with *n*-heptane.

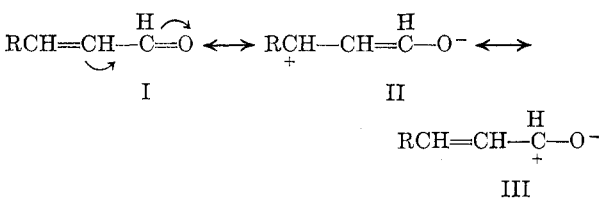
concerning the sodium salt of a similar compound.[7]

The formation of thiazolidine carboxylic acids from aromatic aldehydes containing nitro or chloro substituents demonstrated that these groups do not hinder the cyclization. The chlorinated products are stable, white, crystalline materials, whereas the nitrophenyl substituted thiazolidines are colored and exhibit a great affinity for water. The existence of the dihydrate of the condensation product of cysteine and nitrosalicylaldehyde has been reported[8] and other thiazolidine carboxylic acid hydrates have been previously described.[9] Only the *o*-nitro isomer gives a positive nitroprusside test in 5% sodium bicarbonate solution.

The reaction between cysteine and naphthaldehyde shows that the cyclization proceeds equally well with a naphthalene ring as with a benzene ring. From terephthaldehyde it can be inferred that the reaction takes place equally well with a dialdehyde as with a monoaldehyde. The thiazolidine carboxylic acid formed from *p*-dimethylaminobenzaldehyde and cysteine is water soluble.

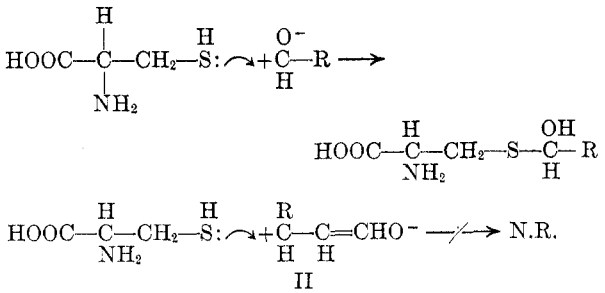
The following aldehydes did not give the normal reaction product, when using the customary method: citral, crotonaldehyde, acrolein, 2-ethyl-2-hexenal, α-amyl cinnamaldehyde, α-hexyl cinnamaldehyde, and 2,2,4,8,10,10-hexamethylundecene-5-al-5. This is in agreement with other findings[5,9-11] that an unsaturated bond α, β to the carbonyl group influences the reaction with cysteine.

The mechanism for thiazolidine carboxylic acid reaction has been shown[12] to consist in hemimercaptal formation, followed by dehydration and cyclization. In the case of unsaturated carbonyl compounds, the following structures can be written:



I II III

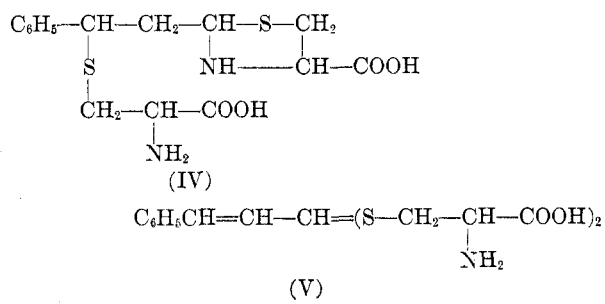
It is suggested that condensation fails to occur due to the low contribution of III, the active species necessary for hemimercaptal formation, as follows:



II

Cinnamaldehyde and *p*-chlorocinnamaldehyde did form a precipitate with cysteine hydrochloride. This phenomenon agrees with the observation made by Lieberman *et al.*[10] Since microanalyses of product from the initial experiment indicated a ratio of two moles of cysteine to one mole of aldehyde, this molar ratio was used subsequently.

Only two products appeared possible from the condensation of two moles of cysteine with one mole of cinnamaldehyde. One would be 5′-carboxy-4′-amino-2′-phenyl-3′-thiapentylthiazolidine-4-carboxylic acid (IV), formed by a 1,4 addition of one mole of cysteine to the double bond of cinnamaldehyde, followed by a reaction of this product with a second mole of cysteine to form the thiazolidine. The other would be the cinnamaldehyde mercaptal (V).



(IV)

(V)

The formation of IV would be in agreement with the postulation made by Geiger and Conn,[13] that some simple α, β unsaturated ketones react with sulfhydryl compounds by means of a 1,4 addition to produce β alkyl thioketones. The formation of V would be in agreement with the work of Holmberg,[14] who reported that cinnamaldehyde condensed with β mercaptopropionic acid to form the corresponding mercaptal. Examination of the ultraviolet and infrared absorption spectra revealed the presence of a conjugated double bond, ruling out compound (IV), and served to establish the unknown condensation product as a mercaptal.

EXPERIMENTAL

L-2-Hexadecylthiazolidine-4-carboxylic acid. The conditions employed for the preparation of this compound are essentially the same as those of Schubert.[6] The heptadecanal was

(7) I. T. Strukov, *J. Gen. Chem. (U.S.S.R.)*, **22**, 521 (1952).

(8) M. Ikawa and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 653 (1954).

(9) H. T. Clarke, J. R. Johnson, and R. Robinson, *The Chemistry of Penicillin*, pp. 940–963, Princeton University Press, Princeton, N. J., 1949. The book describes the extensive studies of thiazolidines made on the Penicillin program.

(10) S. Lieberman, P. Brazeau, and L. B. Hariton, *J. Am. Chem. Soc.*, **70**, 3094 (1948).

(11) D. Todd and S. Reich, *J. Am. Chem. Soc.*, **75**, 1895 (1953).

(12) S. Ratner and H. T. Clarke, *J. Am. Chem. Soc.*, **59**, 200 (1937).

(13) W. B. Geiger and J. E. Conn, *J. Am. Chem. Soc.*, **67**, 112 (1945).

(14) B. Holmberg, *Arkiv. Kemi., Mineral. Geol.*, **15A**, No. 8, 1 (1942).

prepared from hexadecanol *via* the chloride, the Grignard, and ethyl orthoformate. A solution of 1.7 g. (0.0067 mole) of freshly prepared heptadecanal (m.p. 36°) in 25 ml. of 95% ethanol was added to a solution of 1.0 g. (0.0057 mole) of L-cysteine hydrochloride monohydrate[15] and 0.6 g. (0.007 mole) of potassium acetate in 25 ml. of water. Upon vigorous agitation for a few minutes, precipitation occurred. After standing at room temperature for an hour the mixture was refrigerated overnight. Following filtration by gentle suction, the precipitated thiazolidine carboxylic acid was thoroughly washed with water, cold 95% ethanol, ether, and air-dried. Upon recrystallization from boiling isopropyl alcohol, there were obtained 1.54 g. (76%) of product melting at 142–143°, dec.

(15) Purchased from Mann Fine Chemicals Inc., New York, N. Y.

Cysteinyl cinnamyl mercaptal. This was prepared similarly, using a 2:1 ration of water to ethanol. The product, for which no recrystallization solvent was found, is a white powder, melting at 179.3–180.5°, dec., obtained in 81% yield.

Anal. Calcd. for $C_{15}H_{20}O_4N_2S_2$: C, 50.54; H, 5.66; N, 7.86. Found: C, 50.45; H, 5.75; N, 7.55.

Acknowledgment. Thanks are due to Monsanto Chemical Co. for samples of *o*-vanillin and bourbonal, to Heyden Chemical Corp. for 2,6-dichlorobenzaldehyde, to Shell Chemical Corp. for 2-ethyl-2-hexenal, and to Rohm & Haas Co. for 2,2,4,8,10,10-hexamethylundecene-5-al-5.

BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Flavonoid Petal Constituents of *Chrysanthemum segetum* L.

T. A. GEISSMAN AND CORNELIUS STEELINK

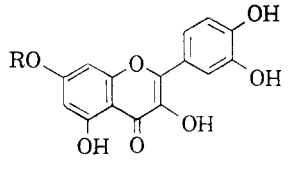
Received February 11, 1957

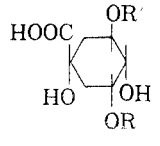
The petals of *Chrysanthemum segetum* L. contain gossypitrin (3,3′,4′,5,7,8-hexamethoxyflavone-7-glucoside), quercimeritrin, and chlorogenic and isochlorogenic acids. This is the first recorded occurrence of gossypitrin in a plant family other than the Malvaceae. The co-occurrence of gossypitrin and quercimeritrin is observed in both *C. segetum* and in *Gossypium* species, and appears to be of significance in the problem of the biogenesis of the flavonoid pigments.

Chromatographic examination on paper of the methanol extract of the bright yellow petals of *Chrysanthemum segetum* L. disclosed the presence of five distinct substances. Three of these were readily identified as quercimeritrin (quercetin-7-glucoside) (I), chlorogenic acid (II), and isochlorogenic acid (III). A fourth was isolated by methanol extraction of the fresh or dried petals and concentration of the extract, when it separated as a bright yellow crystalline substance in an amount constituting six per cent of the weight of the dried petals. Spectral and R_f data suggested that this compound was a derivative of a hexahydroxyflavone, and analyses of the glucoside, the aglucon, and their acetates were in agreement with the formulation of the pigment as a monoglucoside of a hexahydroxyflavone. The melting point of the aglucon hexaacetate was in agreement with that reported for gossypetin (IV, R = H) hexaacetate,[1] but since spectral data for gossypetin derivatives were lacking, and authentic samples were not at hand for direct comparison, the structure of the glycoside was established by degradative and synthetic procedures.

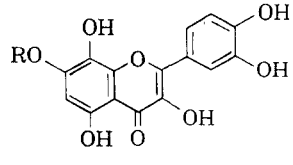
The presence of a free hydroxyl group in the 3-position of the glycoside was indicated by the characteristic shift of 60 mμ in the long wavelength absorption maximum (from 388 to 448 mμ) induced by the addition of aluminum chloride.[2] Methylation of the aglycon yielded gossypetin hexamethyl ether, identical with an authentic sample prepared by synthesis from quercetin 3,3′,4′,7-tetramethyl ether.[3]

Alkaline cleavage of the fully methylated aglycon yielded veratric acid and 2′-hydroxy-2,3′,4′,6′-tetramethoxyacetophenone.[4]





I, R = $C_6H_{11}O_5$ (glucosyl)
II, R = H, R′ = 3,4-dihydroxycinnamoyl
III, R′ = H, R = 3,4-dihydroxycinnamoyl



IV, R = H
V, R = $C_6H_{11}O_5$ (glucosyl)

The determination of the position of the sugar residue in the glycoside, and thus the establishment of the identity of the latter with gossypitrin (V),

(1) A. G. Perkin, *J. Chem. Soc.*, **95**, 2181 (1909).
(2) T. A. Geissman and L. Jurd, unpublished results.
(3) P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **25A**, 379 (1946).
(4) A. G. Perkin, *J. Chem. Soc.*, **103**, 653 (1913)