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Microbiologically Active 4-Thiazolidones

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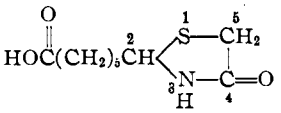
Analogs and derivatives of the antibiotic (−)-2-(5-carboxypentyl)-4-thiazolidone (I) have been prepared and assayed for *in vitro* antitubercular activity.

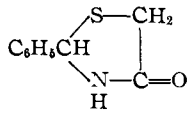
In a recent communication,[1] the structure (−)2-(5-carboxypentyl)-4-thiazolidone (I) was established for a new antibiotic. Its unusually high



I

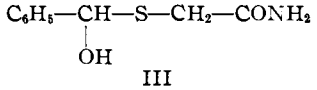
in vitro activity against *Mycobacterium tuberculosis* led to the preparation and testing of three types of closely related compounds: (1) 2-substituted-4-thiazolidones, (2) carboxyl derivatives of I and (3) ring substituted analogs of I.

4-Thiazolidones substituted only in the 2-position have been reported by Davies, Ramsay and Stove.[2] A product which they believed to be 2-phenyl-4-thiazolidone (II) was obtained when



II

benzaldehyde was added to a melt of mercaptoacetamide. They observed that when the compound was heated or when it was recrystallized from water, some dissociation occurred and benzaldehyde was released. The preparation of this compound was repeated in this Laboratory and its instability confirmed. Since I is much more stable, it was felt that Davies' product was the hemimercaptal (III).[3] In support of this, the condensation



III

of benzaldehyde and mercaptoacetamide under dehydrating conditions is found to lead to the formation of a more stable compound, believed to be the true thiazolidone (II). A comparison of the analytical data, active hydrogen determinations and infrared spectra in Nujol for the two compounds confirms these conclusions. In particular, the infrared spectrum of Davies' compound exhibits –OH absorption at 3400 cm.$^{-1}$ and an –NH bending band at 1610 cm.$^{-1}$, characteristic of primary and most secondary amides but not of 4-thiazolidones.[1] The infrared spectrum of the new compound, on the other hand, is entirely consistent with assignment of the 4-thiazolidone structure (II).

A general procedure developed for obtaining 2-substituted-4-thiazolidones (Table II) consists of heating the appropriate carbonyl compound with mercaptoacetamide and a catalytic amount of *p*-toluenesulfonic acid in the presence of a hydrocarbon solvent with provision for continuous removal of water as it is formed. Yields were variable, but these reaction conditions appear to be satisfactory for most aldehydes and ketones with the possible exception of α,β-unsaturated aldehydes. Infrared spectra of all of these thiazolidones in chloroform solution exhibit a carbonyl band at 1680 cm.$^{-1}$, free NH absorption near 3400 cm.$^{-1}$ and hydrogen-bonded NH absorption between 3040 and 3110 cm.$^{-1}$.

Semi-aldehyde esters of dibasic acids, which served as carbonyl components for the preparation of many of the thiazolidones, were prepared by a modified Rosenmund reduction[1] of the corresponding acid chlorides. Data on intermediate acids and acid chlorides are reported in Table II, while physical constants of the aldehydes and their respective crystalline semicarbazones are listed in Table III. Intermediates for the preparation of XVIII and XIX, each of which has a methyl group alpha to the carbethoxy group, were obtained by methylation of 2-carbethoxycyclopentanone and 2-carbethoxycyclohexanone, respectively. Ring cleavage, followed by hydrolysis, afforded semi-acid esters,[4] and these were converted to the corresponding semi-aldehyde esters.

Optically active esters and amides of I were prepared by reaction of the acid chloride of I with the appropriate alcohol or amine. On the other hand, under basic conditions optically inactive amide, hydrazide or hydroxamic acid derivatives were obtained from the (−) methyl ester. This is consistent with the observed ease of racemization of I.[1] Lithium aluminum hydride reduction of the methyl ester of I gave the corresponding alcohol. Physical constants and microbiological assays of these derivatives are recorded in Table IV.

In order to synthesize analogs of the antibiotic having substitution on the thiazolidone ring in the 5-position, α-mercaptobutyramide and α-mercaptodiethylacetamide were prepared by reaction of the corresponding α-bromoamides with potassium hydrogen sulfide. Condensation of these α-mercaptoamides with methyl pimelaldehydate led to the synthesis of IV and V.

(1) W. M. McLamore, Walter D. Celmer, Virgil V. Bogert, Frank C. Pennington, B. A. Sobin and I. A. Solomons, THIS JOURNAL, **74**, 2946 (1952).

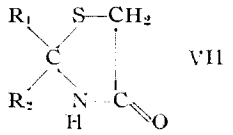
(2) W. Davies, T. H. Ramsay and E. R. Stove, *J. Chem. Soc.*, 2633 (1949).

(3) Hemimercaptals of this type have been reported (M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936)) to be formed by condensation of mercaptoacetanilide with various aldehydes. The conditions used were relatively mild, and the hemimercaptals were found to dissociate readily into their components.

(4) L. F. Fieser, M. T. Leffler and co-workers, THIS JOURNAL, **70**, 3206 (1948).

TABLE I

2,2-SUBSTITUTED 4-THIAZOLIDONES



VII

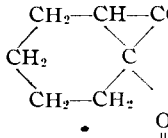
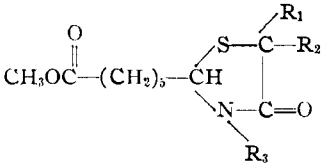
Cpd.	R_1	R_2	B. p. °C.	Mm.	M.p., °C.	Crystn. solvn.	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Microbiological activity, γ/mg. *M. Berolinense*	*M. Tuberculosis*
VIII	H	$(CH_2)_5CH_3$	157–165	0.5	45–47	Ether	$C_9H_{17}ONS$	57.73	57.89	9.15	9.04	7.47	7.34	17.11	17.21	<2	7.5
IX	H	$(CH_2)_8CH{=}CH_2$	205–215	.3	47–50	Ether	$C_{13}H_{23}ONS$	64.69	64.43	9.60	9.45	5.80	5.60	13.28	13.15	<1.9	8.5
X	H	$(CH_2)_2CO_2CH_3$	185–195	.6	74.5–76.5	Ether	$C_7H_{11}O_3NS$	44.43	44.60	5.86	5.95	7.40	7.41	16.94	16.48	<1.9	<1.7
XI	H	$(CH_2)_3CO_2CH_3$	160–175	.1	72–75	MeOH–ether	$C_8H_{13}O_3NS$	47.27	47.27	6.45	6.00	6.89	6.84	15.77	15.93	<2	2.8
XII	H	$(CH_2)_4CO_2CH_3$	190–205	.3	93.5–96	$CHCl_3$	$C_9H_{15}O_3NS$	49.74	49.79	6.96	6.91	6.45	6.40	14.76	14.99	<2.3	4.2
XIII	H	$(CH_2)_6CO_2CH_3$	205–215	.2	80.5–82.5	MeOH–ether	$C_{11}H_{19}O_3NS$	53.85	53.83	7.81	7.73	5.71	5.69	13.07	13.08	10	57
XIV	H	$(CH_2)_7CO_2CH_3$	205–230	.2	68.5–70.5	Ether	$C_{12}H_{21}O_3NS$	55.57	55.73	8.16	8.14	5.40	5.30	12.36	12.62	90	100
XV	H	$(CH_2)_8CO_2CH_3$	200–235	.5	78.5–79.5	Ether	$C_{13}H_{23}O_3NS$	57.11	57.27	8.48	8.52	5.12	5.25	11.73	12.00	7	33
XVI	H	$(CH_2)_4CO_2H$			122–125	Water	$C_8H_{13}O_3NS$	47.27	47.28	6.45	6.38	6.89	7.11	15.77	15.98	<2.2	3.8
XVII	H	$(CH_2)_7CO_2H$			128.5–129	Water	$C_{11}H_{19}O_3NS$	53.85	53.80	7.81	8.13	5.71	5.79	13.07	13.21	29	6
XVIII	H	$(CH_2)_3CH(CH_3)CO_2C_2H_5$	185–200	.2			$C_{11}H_{19}O_3NS$	53.85	53.30	7.81	7.63			13.07	12.97	<1.6	3.4
XIX	H	$(CH_2)_4CH(CH_3)CO_2C_2H_5$	180–200	.1			$C_{12}H_{21}O_3NS$	55.57	54.86	8.48	8.20	5.12	5.22	12.36	12.32	320	570
XX	CH_3	$(CH_2)_4CO_2CH_3$	175–185	.1	86.5–88	MeOH–ether	$C_{10}H_{17}O_3NS$	51.92	51.86	7.41	7.39	6.06	6.32	13.86	14.06	<1.6	4.2
XXI	CH_3	$(CH_2)_5CO_2CH_3$	180–200	.3	87–89	CCl_4–ether	$C_{11}H_{19}O_3NS$	53.85	53.39	7.81	7.75	5.71	5.83	13.07	13.13	45	800
XXII	$(CH_2)_2CO_2C_2H_5$	$(CH_2)_2CO_2C_2H_5$	210–220	.3	51–52	Ether	$C_{13}H_{21}O_5NS$	51.46	51.63	6.98	6.95	4.62	4.62	10.57	10.63	<1.8	2.5
XXIII(II)	H	C_6H_5			127.5–128.5	CCl_4	C_9H_9ONS	60.31	60.43	5.06	5.03	7.82	7.96	17.89	17.90	<1.7	...
XXIV			155–178	.2	98–100	MeOH–ether	$C_{11}H_{17}O_3NS$	54.30	54.34	7.05	7.21	5.76	5.73	13.18	13.45	<2	<1.7
XXV	H	*p*-$CH_3C(=O)NHC_6H_4$			222–223	MeOH	$C_{11}H_{22}O_2N_2S$	55.91	55.94	5.12	5.10	11.86	11.75	13.57	13.61	<2	2
XXVI	H				121–123	MeOH	$C_7H_7O_2NS$	49.69	49.64	4.17	4.26	8.28	8.15	18.95	19.01	<2	3.3

TABLE II

PROPERTIES OF ALDEHYDE INTERMEDIATES

Ester-acid derivative	n	$CH_3O_2C-(CH_2)nCO_2H$ B.p., °C.	Mm.	$n^{25}D$	Ester-acid chloride derivative	n	$CH_3O_2C-(CH_2)n-COCl$ B.p., °C.	Mm.	$n^{25}D$
Succinate[a]	2	M.p. 57–57.5	..	....	Succinate[e]	2	53–54	1.0	1.4375
Glutarate[a,f]	3	91–94	0.15	1.4360	Glutarate[f]	3	60–63	0.5	1.4431
Adipate[b]	4	...	..	1.4378	Adipate[g]	4	62	.1	1.4450
Pimelate[c,d]	5	123	.3	1.4400	Pimelate[c]	5	76–78	.3	1.4465
Suberate[c,d]	6	133	.2	1.4420	Suberate[c]	6	86	.3	1.4470
Azelate[h]	7	142	.5	1.4448	Azelate[h]	7	84–85	.03	1.4494
Sebacate	8	150	.8	M.p. 35–40	Sebacate[i]	8	109	.2	1.4480

[a] E. Fourneau and S. Sabetay, *Bull. soc. chim.*, **45**, 834 (1929). [b] Purchased from Eastman Kodak Co. [c] G. T. Morgan and E. Walton, *J. Chem. Soc.*, 290 (1935). [d] J. Kenner and F. Morton, *Ber.*, **72B**, 452 (1939). [e] Calcd. for $C_8H_7O_3Cl$: C, 39.88; H, 4.69. Found: C, 39.42; H, 4.44. [f] G. T. Morgan and E. Walton, *J. Chem. Soc.*, 276 (1932). [g] G. T. Morgan and E. Walton, *ibid.*, 91 (1933). [h] G. T. Morgan and E. Walton, *ibid.*, 902 (1936). [i] W. S. Bishop, *Org. Syntheses*, **25**, 71 (1945).



IV, $R_1 = C_2H_5$, $R_2 = R_3 = H$
V, $R_1 = R_2 = C_2H_5$, $R_3 = H$
VI, $R_1 = R_2 = H$, $R_3 = C_4H_9$

Attempts to prepare the oxazolidone and imidazolidone analogs of I by condensation of methyl pimelaldehydate with glycolamide and glycine amide, respectively, were less successful. Pure compounds could not be isolated although the crude products from some of the condensations appeared (infrared) to contain the desired analogs.

Condensation of methyl pimelaldehydate with N-*n*-butyl mercaptoacetamide to give VI apparently failed, whereas the reaction of thioglycolic acid with the aldimine from methyl pimelaldehydate and *n*-butylamine by Surrey's method[5] gave a crude product with an infrared spectrum similar to that of the methyl ester of I except for the expected absence of N–H bands in the 3000–3600 cm.$^{-1}$ region. Attempts to purify this product met with little success, apparently because of its instability under the conditions used.

Methyl pimelaldehydate readily condensed with the active methylene group in rhodanine to give 2-thiono-5-(6-carbomethoxyhexanal)-4-thiazolidone.

Microbiological activities of the 4-thiazolidones were determined against the assay organism *Mycobacterium berolinense* using the cup plate method and against *Mycobacterium tuberculosis* by a turbidimetric procedure. I was taken as a standard (1000 γ/mg.).

Surprisingly, many of the esters and amides of I show greater antibacterial activity than the antibiotic itself. Most of the esters of the substituted thiazolidones were not saponified since in two cases, XII and XIV (Table I), it was apparent that the activities of the esters were indicative of the activities of the corresponding acids. Lower and higher homologs proved to be much less active. It is of interest that the homolog of the methyl ester of I, having two additional methylene groups (XIV), is more active than the homologs XIII and XV, which have one and three additional methylene groups, respectively. It should also be noted that compounds substituted on the thiazolidone ring or aliphatic side chain have very low activity.

Of particular importance in correlating structure and microbiological activity was the preparation of two compounds, XVIII and XX, which are isomeric with esters of the antibiotic (see Table I). In each of these analogs, four carbon atoms separate the thiazolidone and ester functions, and both compounds showed little or no activity against the test organism. With the next higher homologs, XIX and XXI, respectively, antibacterial activity again was evident, thus indicating a marked dependence of activity upon this interfunctional distance. That these five carbon atoms must lie in a straight chain was demonstrated by the surprising inactivity of XXIV, a compound having a cyclic carbon skeleton.

Experimental

2-Substituted-4-thiazolidones.—With the exceptions and additions noted below, the compounds listed in Table I were prepared by the following procedure. A mixture of the aldehyde or ketone (5–10 g.), 3 equivalents of mercaptoacetamide,[6] 25–50 mg. of *p*-toluenesulfonic acid and 150–350 ml. of benzene was heated under reflux in a nitrogen atmosphere with stirring and with provision for continuous removal of water. The first 20–30 ml. of benzene that distilled was discarded, and the condensation carried out for a period of 4.5 hours. The reaction mixture was cooled, washed well with water and the organic layer dried over sodium sulfate. The benzene was removed under reduced pressure, and the residue distilled, if possible. In most of the condensations, the yield was in the range 10–50%, but no attempt was made to determine the optimum conditions for any particular condensation. Ketones gave lower yields than aldehydes.

XXV and XXVI were insoluble in benzene and in water. They were prepared by the above procedure and isolated in small amounts by repeated recrystallization of the gummy products which deposited in the reaction mixture.

XXI was obtained by condensing ε-acetylcaproic acid with mercaptoacetamide by the above procedure; the product was isolated by removing the benzene *in vacuo* and extracting the residue with sodium bicarbonate solution. Acidification of the alkaline solution followed by benzene extraction gave crude 2-methyl-2-(5-carboxypentyl)-4-thiazolidone. Methylation by the procedure indicated below for the esterification of I gave **XXI**. The ε-acetylcaproic acid was prepared by acylation of malonic ester with the semi-acid chloride of methyl pimelate and hydrolysis of the intermediate.[1,7]

XVI and XVII were prepared by hydrolysis of the corresponding esters. The esters were stirred for 4.5 hours with a 20% excess of 0.12 *N* sodium hydroxide solution, the solutions acidified with 1 *N* hydrochloric acid and the products recrystallized from water.

(5) A. R. Surrey, THIS JOURNAL, **69**, 2911 (1947).

(6) P. Klason and T. Carson, *Ber.*, **39**, 736 (1906).

(7) A. Müller and P. Kraus, *Monatsh.*, **61**, 206 (1932).

TABLE III

SEMI-ALDEHYDE ESTERS OF DIBASIC ACIDS, $CH_3O_2C-(CH_2)_n-CHO$

Ester aldehyde derivative	n	Yield, %	B.p., °C.	Mm.	$n^{25}D$	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Semicarbazones[a] M.p.,[c] °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Succinate	2	26	40	0.1	1.4230	$C_5H_8O_3$	51.72	51.33	6.94	6.98	131.5-132.5	$C_6H_{11}O_3N_3$	41.61	41.78	6.40	6.48
Glutarate[12c]	3	47	54	.15	1.4248	$C_6H_{10}O_3$	55.37	55.78	7.75	7.81	114-115	$C_7H_{13}O_3N_3$	44.91	45.05	6.70	6.87
Adipate	4	60	69	.6	1.4292	$C_7H_{12}O_3$	58.31	58.58	8.39	8.67	94.5-95	$C_8H_{15}O_3N_3$	47.75	47.73	7.51	7.50
Pimelate[1]	5	63	70	.5	1.4310	$C_8H_{14}O_3$	60.74	60.74	8.92	8.86	117-118	$C_9H_{17}O_3N_3$	50.23	50.17	7.91	7.71
Suberate	6	59	75	.25	1.4330	$C_9H_{16}O_3$	62.76	62.50	9.36	9.36	103-104	$C_{10}H_{19}O_3N_3$	52.38	52.51	8.35	8.42
Azelate[b]	7	61	100	.6	1.4365	$C_{10}H_{18}O_3$	64.49	65.27	9.74	9.85	109-111	$C_{11}H_{21}O_3N_3$	54.30	54.83	8.70	8.69
Sebacate[12d]	8	60	107	.3	1.4381	$C_{11}H_{20}O_3$	65.97	66.29	10.07	10.23	100-101	$C_{12}H_{23}O_3N_3$	56.00	55.86	9.01	8.98

[a] Semicarbazones were prepared by Noller and Adams' method.[12d] [b] W. Treibs, *Ber.*, **76B**, 670 (1943), records semicarbazone, m.p. 107-108°; Noller and Adams[12d] record semicarbazone, m.p. 104-105°. [c] Melting points were taken on a Kofler block.

TABLE IV

DERIVATIVES OF I, R—$(CH_2)_5$—CH(S—CH_2)(HN—C=O)

R	M.p.	Crystn. solvn.	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	$[\alpha]^{25}°D$ (c, 1, MeOH)	Microbiological activity, γ/mg. *M. Berolinense*	*M. Tuberculosis*
CO_2CH_3	53-54	Ether	$C_{10}H_{17}O_3NS$	51.92	51.92	7.41	7.43	6.06	6.15	13.86	13.63	−49.9	1200	3000
$CO_2C_2H_5$	47-50.5	Ether	$C_{11}H_{19}O_3NS$	53.85	53.83	7.81	7.77			13.07	13.19	−47.9	2300	1500
$CO_2(CH_2)_3CH_3$	.....	....	$C_{13}H_{23}O_3NS$	57.11	56.99	8.48	8.30	5.12	5.23	11.73	11.79	−39.2	5800	1000
$CO_2(CH_2)_{11}CH_3$	52.5-55	Hexane	$C_{21}H_{39}O_3NS$	65.41	65.48	10.20	10.23	3.63	3.73	8.32	8.43	−28	45	1200
$CO_2CH_2C_6H_5$	64-66	Hexane–EtOAc	$C_{16}H_{21}O_3NS$	62.51	62.64	6.89	7.00	4.56	4.61	10.43	10.30	−30.7	6500	2200
$CO_2C_2H_4N(C_2H_5)_2$	.....	....	$C_{15}H_{28}O_3N_2S$	56.93	57.01	8.92	8.87	8.85	8.55	10.13	9.58	−37.9	710	750
$CONH_2$	147-148	Water	$C_9H_{16}O_2N_2S$	49.97	50.18	7.46	7.28	12.96	12.77	14.82	15.09	−54	1700	2200
$CONH_2$	151.5-155	Water	$C_9H_{16}O_2N_2S$	49.97	49.93	7.46	7.53	12.96	13.08	14.82	15.23	0	1000	1500
$CONHCH_3$	132.5-133	Water	$C_{10}H_{18}O_2N_2S$	52.14	51.86	7.88	7.78					−49.7	19	380
$CONHCH_2CH(CH_3)CH_3$	111.5-113	Water	$C_{13}H_{24}O_2N_2S$	57.31	57.33	8.88	8.76					−39.8	<2	500
$CONHCH_2C_6H_5$	131-131.5	Water	$C_{16}H_{22}O_2N_2S$	62.71	62.71	7.24	7.25					−35.9	<2	900
$CONHC_4H_9$	115.5-116.5	Water–MeOH	$C_{13}H_{24}O_2N_2S$	57.31	57.45	8.88	8.88	10.29	10.40	11.77	11.84	−42.3	3.4	1500
$CONHNH_2$	126.5-128	Water	$C_9H_{17}O_2N_3S$	46.73	47.10	7.41	7.27					0	190	500
$CONHN{=}C(CH_3)CH_3$	155-156	Acetone	$C_{12}H_{21}O_2N_3S$	53.11	53.14	7.80	7.75					0	95	250
CONHOH	155 dec.	Water	$C_9H_{16}O_4N_2S$	46.53	46.26	6.94	6.72					0	230	500
CH_2OH	71.5-73	MeOH–ether	$C_9H_{17}O_2NS$	53.17	53.27	8.43	8.30	6.89	6.57	15.77	15.45	0	520	2000

Comparison of II and III.—**2-Phenyl-4-thiazolidone (II)** was prepared from benzaldehyde and mercaptoacetamide by the above procedure except that distillation was not necessary for purification. II was soluble in chloroform and showed 1.1 active hydrogens by a lithium aluminum hydride determination.[8,9]

1-Hydroxybenzylmercaptoacetamide (III) was prepared by the method of Davies, Ramsay and Stove[2] and by the method of Schubert.[3] III afforded the phenylhydrazone of benzaldehyde in 60% yield when it was refluxed with phenylhydrazine, whereas II gave no phenylhydrazone under identical conditions. III was insoluble in chloroform and showed 2.06 active hydrogens by a lithium aluminum hydride determination.[10]

Anal. Calcd. for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; S, 16.26. Found: C, 54.85; H, 5.78; N, 7.27; S, 16.14.

Preparation of Intermediate Aldehyde Esters (Table III).—The monomethyl esters of dibasic acids (Table II) were obtained by the method of Swann, Oehler and Buswell[11] except for methyl hydrogen succinate, which was prepared by treatment of succinic anhydride with an equivalent amount of methanol. A mixture of 1.0 equivalent of semi-acid ester and 1.2 equivalents of thionyl chloride was warmed until vigorous gas evolution was apparent and then allowed to stand at room temperature for two hours. Distillation gave the acid chlorides (Table II) in yields of 85–95%. The modified Rosenmund reduction[1] used for the preparation of methyl pimelaldehydate was found to be satisfactory for synthesis of lower and higher homologs. The semi-aldehyde esters exhibited the instability of this class of compounds[12]; therefore, whenever possible freshly distilled samples were used. The aldehydes could be stored unchanged for months in sealed ampoules under nitrogen at Dry Ice temperature.

For the preparation of **XIX**, 2-methyl-2-carbethoxycyclohexanone was cleaved to diethyl α-methylpimelate, which was hydrolyzed to a semi-acid ester. Conversion to the acid chloride[4] followed by a modified Rosenmund reduction gave ethyl α-methyl-ε-formylcaproate, b.p. 57–62° (0.1 mm.), $n^{26.5}D$ 1.4300.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.53; H, 9.72.

For the preparation of XVIII, 2-methyl-2-carbethoxycyclopentanone was similarly cleaved and hydrolyzed[4] to ethyl α-methyl-δ-carboxyvalerate, b.p. 143–148° (1.5 mm.).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.08; H, 8.45.

Reaction of thionyl chloride with the acid gave the acid chloride, b.p. 92° (0.5 mm.).

Anal. Calcd. for $C_9H_{15}O_3Cl$: C, 52.30; H, 7.32. Found: C, 52.73; H, 7.25.

Rosenmund reduction of the acid chloride gave ethyl α-methyl-δ-formylvalerate, b.p. 65.5–73° (0.2 mm.), $n^{24.5}D$ 1.4280.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.49; H, 9.29.

Preparation of **XX** required methyl δ-acetylvalerate, which was obtained by oxidation of *o*-methylcyclohexanol,[13] followed by esterification with methanol and sulfuric acid.

Optically Active Esters and Substituted Amides of I.—The esters and substituted amides of I listed in Table IV were prepared by the following procedure. A stirred mixture of one mole of I, 1300 ml. of dry benzene and 1.05 equivalents of thionyl chloride, added dropwise, was boiled on a steam-bath under reflux for one hour. After the mixture had cooled, 1–1.5 molar equivalents of an alcohol or 2 equivalents of an amine was added and warming continued for 15 minutes. The amides were isolated by filtration and recrystallization from water. With the esters the mixture was washed with water, 5% sodium bicarbonate solution and again with water. The benzene solution was stirred with Darco for 15 minutes and filtered. After the solvent was removed *in vacuo*, the residual solid was recrystallized; or when the ester was an oil, it was analyzed and assayed without distillation. Yields were usually better than 60%.

2-(5-Carboxamidopentyl)-4-thiazolidone.—The acid chloride of I was prepared by the above procedure, and the benzene solution carefully poured into an excess of concentrated ammonium hydroxide. The (−)amide of I was collected and recrystallized from 1% ammonium hydroxide solution.

The optically inactive amide of I was prepared by allowing the methyl ester of I to stand in an excess of concentrated ammonium hydroxide for eight days, concentrating the solution *in vacuo* and recrystallizing the residue from water.

2-(5-Carboxyhydrazidopentyl)-4-thiazolidone was prepared by treating 5.75 g. of the methyl ester of I in 25 ml. of water with 2.25 ml. of 85% hydrazine hydrate, heating the mixture under reflux for 75 minutes, removing the water *in vacuo* and recrystallizing the hydrazide from a small volume of water.

The isopropylidene derivative of the hydrazide was obtained by dissolving 100 mg. of the hydrazide in 1 ml. of boiling acetone, evaporating the mixture to dryness on a steam-bath and recrystallizing the residue from a small volume of acetone.

2-(6-Hydroxyhexyl)-4-thiazolidone.—A mixture of the methyl ester of I (5 g.) and 30 ml. of dry ether was stirred and cooled in an ice-bath while 15 ml. of 1.00 *M* lithium aluminum hydride solution was added dropwise. The resulting semi-solid mass was stirred 3 hours and then allowed to stand 2 days. The mixture was carefully treated with 70 ml. of 1 *N* hydrochloric acid, and the aqueous layer was extracted with benzene and ether to remove unreduced ester. An ethyl acetate extract then gave 0.8 g. of optically active crude alcohol, $[\alpha]^{25}D$ −54.6°. This material was stirred with 0.1 *N* sodium hydroxide solution for 4 hours to saponify any contaminating ester, the solution extracted with ethyl acetate, and the racemized product recrystallized from methanol–ether. The only carbonyl absorption in the infrared spectrum of this product was the amide band at 1680 $cm.^{-1}$.

5-Substituted Analogs of I.—The condensation of methyl pimelaldehydate with the appropriately substituted mercaptoacetamide was carried out by the general procedure indicated for the preparation of 2-substituted-4-thiazolidones. However, both the 5-ethyl (IV) and the 5,5-diethyl (V) analogs required extensive purification by short-path distillation and chromatography before they could be obtained analytically pure.

IV was recrystallized from ether–petroleum ether and obtained as white needles, m.p. 51.5–52.5°. Microbiological activity against *M. berolinense* was 55 γ/mg.

Anal. Calcd. for $C_{12}H_{21}O_3NS$: C, 55.57; H, 8.16; N, 5.40; S, 12.36. Found: C, 55.50; H, 8.24; N, 5.57; S, 12.25.

V was obtained as a light yellow oil by short-path distillation, b.p. 160° (block temperature) at 0.08 mm. Microbiological activity against *M. berolinense* was 2 γ/mg.

Anal. Calcd. for $C_{14}H_{25}O_3NS$: C, 58.50; H, 8.77; N, 4.87. Found: C, 58.04; H, 8.57; N, 4.60.

α-Mercaptobutyramide.—A solution of 13.5 g. (0.24 mole) of potassium hydroxide in 75 ml. of ethanol was saturated with hydrogen sulfide, cooled and treated with a solution of 24.9 g. (0.15 mole) of α-bromobutyramide (m.p. 109.5–110.5°)[14] in 80 ml. of ethanol. The addition required 20 minutes, and the resulting suspension of potassium bromide was kept at room temperature for 2 hours longer. During the entire period of reaction, a steady stream of hydrogen sulfide was passed through the mixture to minimize formation of the sulfide.

The reaction mixture was diluted with 200 ml. of water, extracted with 150 ml. of ether and two 150-ml. portions of chloroform and acidified with 25 ml. of hydrochloric acid. Extraction of the acid solution with three 150-ml. portions of chloroform afforded 1.2 g. of α-mercaptobutyramide. The combined ether and chloroform extracts of the alkaline

(8) See Table I for analyses.

(9) F. A. Hochstein, THIS JOURNAL, **71**, 305 (1949).

(10) The insolubility of the complex apparently made the detection of the third active hydrogen difficult.

(11) S. Swann, Jr., R. Oehler and R. J. Buswell, *Organic Syntheses*, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 276.

(12) (a) E. Baer, THIS JOURNAL, **64**, 1416 (1942); (b) G. B. Brown, M. D. Armstrong, A. W. Moyer, W. P. Anslow, Jr., B. R. Baker, M. V. Querry, S. Bernstein and S. R. Safir, *J. Org. Chem.*, **12**, 160 (1947); (c) S. A. Harris, D. E. Wolf, R. Mozingo, R. C. Anderson, N. R. Easton and K. Folkers, THIS JOURNAL, **67**, 2096 (1945); (d) C. R. Noller and R. Adams, *ibid.*, **48**, 1074 (1926).

(13) J. R. Schaeffer and A. O. Snoddy, *Org. Syntheses*, **31**, 3 (1951).

(14) Bischoff, *Ber.*, **30**, 2313 (1897).

solution were dried over sodium sulfate and evaporated. The semi-solid residue was triturated with 100 ml. of 10% potassium hydroxide, filtered and washed with water. The combined filtrate and washings were extracted twice with chloroform and acidified with 25 ml. of hydrochloric acid. Extraction of the acid solution with five 125-ml. portions of chloroform gave a further 6.3 g. of crude α-mercaptobutyramide; total yield 7.5 g. (42%); m.p. 81–91°. It was not purified further in order to avoid partial oxidation to the disulfide.

Anal. Calcd. for C_4H_9ONS: C, 40.31; H, 7.61. Found: C, 40.17; H, 7.51.

α-Mercaptodiethylacetamide.[15]—This intermediate was prepared from α-bromodiethylacetamide (58.2 g., 0.30 mole) by a slight modification of the procedure described above for preparation of α-mercaptobutyramide. Precipitation of potassium bromide was much slower in this case, presumably because of steric hindrance in the fully substituted α-bromoamide. Consequently, a much longer reaction time was required—18 hours at room temperature and 25 hours at reflux temperature. The reaction mixture was made strongly alkaline with potassium hydroxide to avoid partial extraction of the weakly acidic mercaptoamide along with the neutral products. After thorough extraction with chloroform, the alkaline solution was acidified and extracted with chloroform. The α-mercaptodiethylacetamide was obtained as a low melting solid (yield 5.7 g., 12.9%) and was not further purified.

2-Thiono-5-(6-carbomethoxyhexanal)-4-thiazolidone was obtained from methyl pimelaldehydate and rhodanine[16] as yellow crystals, m.p. 116–117°. Microbiological activity against *M. tuberculosis* was 5 γ/mg.

Anal. Calcd. for $C_{11}H_{15}O_3NS_2$: C, 48.33; H, 5.53; N, 5.12. Found: C, 48.24; H, 5.41; N, 5.15.

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(15) This compound has been reported (E. Clemmensen and A. H. C. Heitman, *Am. Chem. J.*, **40**, 298 (1908)) to melt at 147°. Because of this high melting point and because the earlier investigators took no precautions to avoid oxidation, it seems probable that their compound was actually the disulfide. The analytical results obtained by them are in better accord with the disulfide structure than with the α-mercaptodiethylacetamide formulation.

(16) P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

Some Alkyl Homologs of Theophylline

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The preparation of a number of 1,3-dialkyl- and 1,3,8-trialkylxanthines is described. The Traube synthesis, starting with a dialkylurea and cyanoacetic acid, is shown to be of general application, and many of the intermediate compounds are characterized.

The dimethylxanthines, theophylline and theobromine, have for many years been used in the treatment of certain cardiac conditions and as diuretics. While in many respects they are quite satisfactory for these purposes, they are far from ideal, since they frequently are not sufficiently potent and may be accompanied by undesirable side effects in larger doses. Since lesser alkylated xanthines are of little or no value, and since caffeine differs appreciably in therapeutic effects, it is obvious that the alkyl groups are highly significant in determining biological activity. Prior to the present investigation of the higher dialkylxanthines the preparation of only a few compounds had been recorded in the literature[1–3] and nothing had been published on their pharmacological activity. In order to permit a systematic evaluation of the effect of substituting larger alkyl groups for the methyl groups in theophylline, the present work was undertaken.

These compounds were prepared by a modification of the Traube[4] synthesis, in which a *sym*-dialkylurea is converted to the corresponding 1,3-dialkylxanthine. Since this synthesis leads readily to 8-alkylated xanthines, and since such products are not found in nature at all it seemed interesting to include them in the present study.

The Traube synthesis appears to be completely general for 1,3-dialkyl or 1,3,8-trialkylxanthines, with only obvious modification of reaction conditions needed in places. One apparent limitation to this generality of application lies in the fact that diisopropylurea was completely inert in the first step, so that it was impossible to prepare this example of a diisoalkylxanthine. The full extent of this limitation was not explored.

Preliminary pharmacological testing of some of these compounds has been completed and is published elsewhere.[5] Some of the lower members of the group, with and without an 8-alkyl substituent, were found significantly active. Activity of higher members of the series was insufficient to be interesting.

Experimental

Reagents.—*sym*-Dialkyl substituted ureas were prepared by passing 1 mole of phosgene gas into a well-stirred mixture of 2 moles of monoalkylamine, 2 moles of sodium hydroxide, 250 cc. of water and 250 cc. of benzene at 10°, or by the action of an alkyl isocyanate on a primary amine in dry ether. Other reagents were of commercial quality and used without further purification.

1,3-Dialkyl-6-aminouracils.—One mole each of a *sym*-dialkylurea and of cyanoacetic acid were heated with 2 moles of acetic anhydride and 250 cc. of acetic acid for three hours at 60°. Acetic acid and excess anhydride were then removed as far as possible under reduced pressure without raising the temperature in the reaction mixture. The residue was dissolved in about two liters of water, made alkaline with sodium carbonate and boiled for about two hours. The products crystallized on cooling giving yields ranging from 70 to 90%. For analysis, they were recrystallized from water or 50% alcohol. Their properties are given in Table I.

(1) G. Scarlat, *Bull. Soc. Sci. Bucarest*, **13**, 155, through *J. Chem. Soc.*, **88**, [I] 160 (1905).

(2) German Patent 121,224.

(3) W. Traube and W. Nithack, *Ber.*, **39**, 227 (1906).

(4) W. Traube, *ibid.*, **33**, 3035 (1900).

(5) G. V. LeRoy and J. H. Speer, *J. Pharmacol. Exptl. Therap.*, **69**, 45 (1940).