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Total Syntheses of Holomycin, Thiolutin, and Aureothricin

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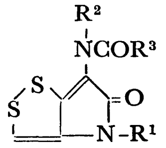
The reactions of 4-benzylthio-5-benzylthiomethyl-3-hydroxy-2-oxo-2,5-dihydrofuran with ammonia and primary amines gave 3-amino-4-benzylthio-5-benzylthiomethyl-3-pyrrolin-2-one derivatives. 3-Acylamino-4-benzylthio-5-benzylthiomethylene-3-pyrrolin-2-one derivatives, including the intermediate of the synthesis of holomycin by Büchi, were prepared by the treatment of the 3-acylaminolactams derived from the 3-aminolactams with chloranil or DDQ. Thiolutin and aureothricin were also synthesized from 3-acetamido- and 3-propionamido-4-benzylthio-5-benzylthiomethylene-1-methyl-3-pyrrolin-2-one respectively.

Holomycin (**1**),[1] thiolutin (**2**),[2] aureothricin (**3**),[2] and isobutyropyrrothine (**4**)[3] are antibiotics produced by certain *Streptomyces* species. Their structures have been shown by degradative studies to have pyrrolinonodithiole nucleus.[1,2] Furthermore, two antibiotics (**5** and **6**) bearing a formamide group at the side chain were also isolated.[4] These substances are effective against Gram-positive and Gram-negative bacteria, fungi, and ameboid parasites. The total syntheses of **1** and **2** was first reported by Schmidt and Geiger.[5] Somewhat later, an alternate total synthesis of **1** was presented by Büchi and Lukas.[6]



1; $R^1=R^2=H$, $R^3=CH_3$
2; $R^1=CH_3$, $R^2=H$, $R^3=CH_3$
3; $R^1=CH_3$, $R^2=H$, $R^3=CH_2CH_3$
4; $R^1=CH_3$, $R^2=H$, $R^3=CH(CH_3)_2$
5; $R^1=R^2=R^3=H$
6; $R^1=H$, $R^2=CH_3$, $R^3=H$

Scheme 1.

In the course of studies of the sulfonium ylides, we have developed a synthesis of a new lactone, 4-benzylthio-5-benzylthiomethyl-3-hydroxy-2-oxo-2,5-dihydrofuran (**7**), which is expected to be a useful intermediate for the synthesis of **1**—**3**.[7] This paper will describe how a new route for the synthesis of **1**—**3** was successfully established in three stages from **7**; this route involves the formation of five-membered lactams, dehydrogenation, and the final ring closure to the desired antibiotics.

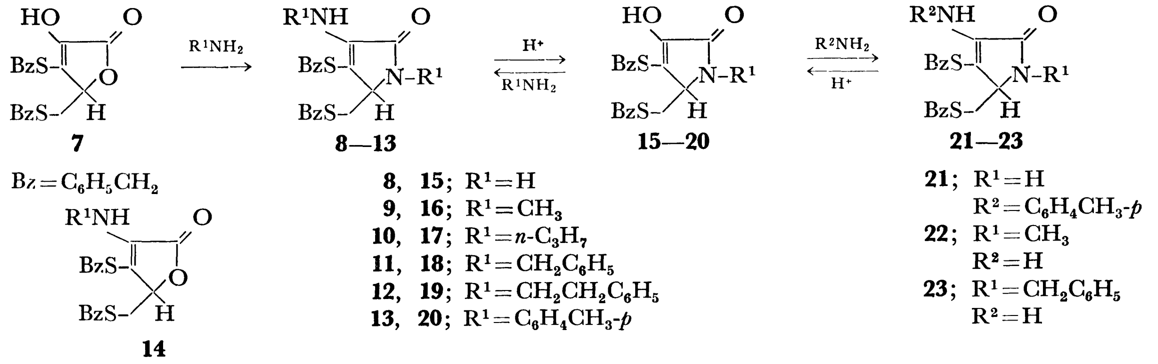
Formation of Five-membered Lactams. The reaction of **7** with methylamine and acetic acid in refluxing ethanol gave 4-benzylthio-5-benzylthiomethyl-1-methyl-3-methylamino-3-pyrrolin-2-one (**9**) (mp 106—108 °C), which was then purified by a chromatographic separation on silica gel G. The IR spectrum showed absorptions at 3310, 1693, and 1645 cm^{-1} due to NH stretching, five-membered lactam carbonyl, and a double bond respectively. The NMR spectrum ($CDCl_3$) exhibited signals at δ 2.80 (3H, s, N–CH_3), 2.90 (2H, m, the methylene protons attached to C_5), 2.93 (3H, s, N–CH_3), 3.65 (1H, m, the methine proton at C_5), 3.64 (2H, s, S–CH_2–Ph), 3.68 (2H, s, S–CH_2–Ph), 3.9—4.6 (1H, D_2O-exchangeable, NH), 7.21 and 7.29 (two phenyl groups). By the reaction of **7** with methylamine in water or ethanol in a sealed tube at 80 °C, **9** was also obtained in a comparable yield. The prolonged reaction in the absence of acetic acid resulted in the decomposition of **7**. Similarly, 3-aminolactams (**8** and **10**—**13**) were synthesized from **7** (see Table 1).

However, the attempted isolation of 3-aminolactone (**14**), another product anticipated in this reaction, was unsuccessful.[8]

Contrary to ordinary methods for the transformation of lactones into lactams, the formation of 3-aminolactams (**8**—**13**) from **7** proceeded under relatively mild conditions. The low yield in the reaction with *p*-toluidine may be due to the low basicity or the steric

Table 1. Reactions of **7** with ammonia and primary amines

R^1NH_2	Solvent	Temp (°C)	Time (hr)	Product		
				No	yield (%)	mp (°C)
CH_3COONH_4	—	120	1	**8**	29	syrup
NH_3	EtOH	70—75	5	**8**	29	
NH_3	H_2O	80	1	**8**	22	
$CH_3COO^-\cdot CH_3NH_3^+$	EtOH	refl.	2	**9**	38	107—108
CH_3NH_2	EtOH	80	0.5	**9**	33	
CH_3NH_2	H_2O	80	0.5	**9**	31	
n-$C_3H_7NH_2$	n-$C_3H_7NH_2$	refl.	20	**10**	50	syrup
$C_6H_5CH_2NH_2$	Benzene	refl.	1	**11**	52	121—122
$C_6H_5CH_2NH_2$	—	90—100	1	**11**	39	
$C_6H_5CH_2CH_2NH_2$	Benzene	refl.	3	**12**	56	syrup
p-$CH_3C_6H_4NH_2$	Benzene	refl.	23	**13**	18	132—133



$Bz = C_6H_5CH_2$

8, **15**; $R^1 = H$
9, **16**; $R^1 = CH_3$
10, **17**; $R^1 = n\text{-}C_3H_7$
11, **18**; $R^1 = CH_2C_6H_5$
12, **19**; $R^1 = CH_2CH_2C_6H_5$
13, **20**; $R^1 = C_6H_4CH_3\text{-}p$

21; $R^1 = H$, $R^2 = C_6H_4CH_3\text{-}p$
22; $R^1 = CH_3$, $R^2 = H$
23; $R^1 = CH_2C_6H_5$, $R^2 = H$

Scheme 2.

Table 2. Dehydrogenations of 3-acylamino-5-benzylthiomethyl-3-pyrrolin-2-ones

No	Reagent	Yield(%)	Mp(°C)	*cis*/*trans*[a]
30	Chloranil	62	178—179	[b]
30	DDQ	67		[b]
30	$SOCl_2$	7		[b]
31	Chloranil	82	130—135	1 : 5
31	DDQ	81		1 : 5
32	Chloranil	92	120—125	2 : 5
32	DDQ	79		2 : 5
33	Chloranil	76	149—152	1 : 2 or 2 : 1[c]
34	Chloranil	70	164—166	[b]

a) Determined by NMR spectrometric analysis of the mixture. b) The single isomer. c) The geometric configuration was not determined.

Table 3. Physical data of geometric isomers of **31** and **32**

Compd	Mp(°C)	λ_{max}^{MeOH} nm(ε)	NMR(δ, in $CDCl_3$)	
			S-CH=	N-CH_3
31a(*cis*)	137—138	365(21000)	6.05	3.01
31b(*trans*)	132—134	363(26200)	6.28	3.37
32a(*cis*)	154—156	368(21600)	6.02	3.03
32b(*trans*)	128—129	362(26100)	6.29	3.39

hindrance.

The treatment of **9** with hydrochloric acid in boiling ethanol afforded 4-benzylthio-5-benzylthiomethyl-3-hydroxy-3-pyrrolin-2-one (**16**) as colorless needles (mp 123—124 °C); they turned blue with ferric chloride. Under similar conditions, 3-aminolactams (**8** and **10**—**13**) were converted readily into the corresponding 3-hydroxy derivatives in good yields.

3-Hydroxy lactam (**16**) was refluxed in ethanol with ammonium acetate to give 3-amino-4-benzylthio-5-benzylthiomethyl-1-methyl-3-pyrrolin-2-one (**22**) in an 84% yield; the substance turned violet upon treatment with ninhydrin. Analogous reactions of 3-hydroxy derivatives yielded the corresponding 3-aminolactams.

Thus, the introduction of the desired substituents of 3-amino group was achieved through the hydrolysis of 3-aminolactams, followed by the condensation of the resulting 3-hydroxylactams with appropriate amines.

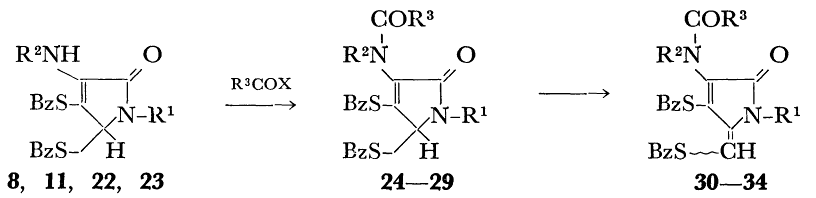
In contrast to the assumption that the reactivity of the 3-amino group in a conjugated system would be low, the acylation of the 3-aminolactams proceeded easily, yielding the acyl derivatives. The treatment of **22** with acetic anhydride in boiling benzene furnished 3-acetamido-4-benzylthio-5-benzylthiomethyl-1-methyl-3-pyrrolin-2-one (**25**) in an 86% yield (mp 140—142 °C). By a similar treatment of 3-aminolactams, several 3-acylamino derivatives were obtained in good yields.

Dehydrogenation. The reaction of **24** with chloranil and DDQ in refluxing benzene afforded the dehydrogenated product (**30**) as yellow needles (mp 178—179 °C) in 63 and 67% yields respectively. The melting point and the spectral properties were consistent with those of 3-acetamido-4-benzylthio-5-benzylthiomethylene-3-pyrrolin-2-one, as reported by Büchi[6] in his holomycin synthesis. On the contrary, the reaction with thionyl chloride, which had been successfully used by Büchi[6] for the dehydrogenation of the side chain of 3-acetyl-4-hydroxy-5-benzylthiomethyl-3-pyrrolin-2-one, gave **30** only in a 7% yield. The resulting product in both the reactions was a single isomer, though its geometric configuration was not clarified.

The dehydrogenation of **26** with chloranil or DDQ in boiling benzene or *t*-butyl alcohol gave a mixture of *cis* and *trans* isomers (**32a** and **32b**) as yellow microcrystals (mp 120—125 °C). Separation by preparative thin-layer chromatography on silica gel G gave **32a** (mp 154—156 °C) and **32b** (mp 128—129 °C). On the basis of the elemental analyses and spectral data (see Table 3), both of them were confirmed to be the geometric isomers with an exocyclic methylene group. Considering the deshielding effect of the phenyl groups, the lower-shifted signals of the vinylic proton and the *N*-methyl protons in the NMR spectrum of **32b** suggest that both the benzylthio groups are *trans*. From the peak areas of the vinylic and *N*-methyl protons, **32** was found to be a mixture of *cis* and *trans* isomers in the ratio of 1 : 5.

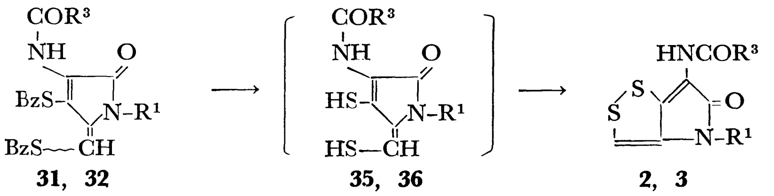
Although the interconversion of **32a** and **32b** was attempted under various conditions, no useful method for the isomerization was obtained.

Under similar conditions, **31** and **33** were obtained in good yields as mixtures of geometric isomers (see Table 2). The mixture (**31**) was treated by preparative thin-layer chromatography (silica gel G) to separate the *cis* and *trans* isomers, but attempts to sepearte



24, **30**: $R^1=R^2=H$, $R^3=CH_3$
25, **31**; $R^1=CH_3$, $R^2=H$, $R^3=CH_3$
26, **32**; $R^1=CH_3$, $R^2=H$, $R^3=CH_2CH_3$
27, **33**; $R^1=CH_2C_6H_5$, $R^2=H$, $R^3=CH_3$
28, **34**; $R^1=CH_2C_6H_5$, $R^2=H$, $R^3=C_6H_5$
29; $R^1=R^2=CH_2C_6H_5$, $R^3=CH_3$

Scheme 3.



35; $R^1=R^2=CH_3$
36; $R^1=CH_3$, $R^2=CH_2CH_3$

Scheme 4.

the isomers (**33**) were unsuccessful.

The dehydrogenation of **28** yielded one (**34**) of the isomers, though its geometric configuration remained unclear.

Together with the interconversion between 3-aminolactams (*e. g.* **9** and **22**), the success in the dehydrogenation of the side chain with chloranil or DDQ made this synthetic line an advantageous method.

Debenzylation and Ring Closure. At the final stage of the synthesis, the reductive debenzylation of both benzylthio groups was carried out by a slight modification of Büchi's method[6] using 4 equivalent of lithium in liquid ammonia. The subsequent air-oxidation of the crude dithiol (**35**) thus obtained in aqueous methanol at pH 2 afforded aureothricin (**3**) as yellow needles (mp 260—270 °C (dec)). The similar treatment of **31** gave thiolutin (**2**) (mp 270—275 °C (dec)). The NMR spectra of **2** and **3** were consistent with the structural assignment made. The IR, UV spectra, and the thin-layer chromatographic behavior were identical with those of the natural antibiotics.

Experimental

All the melting points are uncorrected. The IR spectra were obtained on a Shimadzu IR-27G spectrophotometer. The NMR spectra were recorded on a Hitachi R-20A instrument, using TMS as the internal standard. The UV spectra were determined with a Hitachi EPS-3F spectrophotometer. The elemental analyses of the new compounds are listed in Table 8.

*Preparation of 3-Amino-4-benzylthio-5-benzylthiomethyl-3-pyrrolin-2-one Derivatives (**8**-**13**).* The reactions were achieved in the following two fashions. The results and spectral data are listed in Tables 1 and 4 respectively.

a) By Reaction in the Presence of Acetic Acid: To a cooled solution of **7** (10.0 g) and methylamine (8.5 g) in ethanol (50 ml) was added acetic acid (16 ml) with stirring. After refluxing for 2 hr, the reaction mixture was evaporated and the residue was extracted with ethyl acetate. The extract was washed with 1% hydrochloric acid, with a 5% sodium bicarbonate solution, and with water, and then dried over sodium sulfate. After the removal of the solvent, the tarry residue was chromatographed on silica gel G, using chloroform as the eluent, to give 4.10 g (38%) of **9** as colorless needles, (mp 106—108 °C); it was subsequently recrystallized from 2-propanol.

b) By Reaction in the Absence of Acetic Acid: A solution of **7** (3.58 g) and methylamine (0.93 g) in water (5 ml) was heated in a sealed tube for 30 min and then poured into water. The mixture was extracted with ethyl acetate, and the organic layer was worked up to afford 1.20 g (31%) of **9** by a procedure similar to that described above.

Hydrolysis of 3-Aminolactams. A solution of **9** (1.50 g) in ethanol (25 ml) was refluxed with 10% hydrochloric acid (5 ml) for 1 hr and then evaporated. The residue was extracted with ethyl acetate, and the extract was washed with water, dried over sodium sulfate, and evaporated. The recrystallization of the residue from 2-propanol gave 1.41 g (96%) of **16** as colorless needles (mp 123—124 °C).

In a similar manner, **8** and **10**—**13** were treated with hydrochloric acid to afford hydrolysis products: **15**, 71%, yellow syrup; **17**, 64%, mp 96—98 °C; **18**, 94%, mp 128—129 °C; **19**, 71%, mp 130—131 °C; **20**, 83%, mp 129—130 °C. The spectral data are shown in Table 5.

Conversion of 3-Hydroxylactams into 3-Aminolactams. a) By Reaction with Ammonium Acetate: A solution of **16** (4.14 g) and ammonium acetate (4.0 g) in ethanol (50 ml) was refluxed for 2 hr and then evaporated to give a syrup, which was subsequently extracted with ether. The extract was washed with water, dried and evaporated to dryness. The addition of cyclohexane to the residue, followed by recrystallization from isopropyl ether, afforded 3.05 g (84%) of **22** as colorless needles (mp 69—71 °C). The product gave a violet color with ninhydrin.

Similarly, **18** reacted with ammonium acetate to furnish **23** (mp 66—67 °C) in an 81% yield.

Table 4. Spectral data of 3-aminolactams (**8**—**13** and **21**—**23**)

No	ν_{max}^{Nujol} cm^{-1} [a]	NMR(δ, in CDCl$_3$)
8	3450—3150, 1700, 1650	2.02(1H, q), 2.91(1H, q), 3.6(1H, m), 3.65(2H, s), 3.69(2H, s), 3.8(2H, broad s)[c], 6.7(1H, broad s)[c], 7.20(5H, s), 7.27(5H, s)
9	3310, 1693, 1645	2.80(3H, s), 2.90(2H, m), 2.93(3H, s), 3.65(1H, m), 3.64(2H, s), 3.68(2H, s), 3.9—4.6(1H)[c], 7.21(5H, s), 7.29(5H, s)
10	3300, 1685, 1637	0.6—1.2(6H, m), 1.2—1.8(4H, m), 2.5—3.0(3H, m), 3.1—3.9(4H, m), 3.1—3.9(1H)[c], 3.60(2H, s), 3.68(2H, s), 7.19(5H, s), 7.28(5H, s)
11	3210, 1690, 1638	2.75(2H, m), 3.30—3.55(1H, m), 3.46(2H, s), 3.51(2H, s), 3.70(1H, d), 4.3(1H, broad s)[c], 4.57(2H, d), 5.08(1H, d), 6.7—7.2(20H, m)
12	3330, 1685, 1637	2.50—2.95(8H, m), 3.35—3.65(2H, m), 3.60(4H, s), 3.4—4.2(1H)[c], 3.7—4.2(1H, m), 6.8—7.5(20H, m)
13	3360, 1697, 1680(sh)[b]	2.34(6H, s), 2.66(1H, q), 3.00(1H, q), 3.45(2H, s), 3.48(2H, s), 6.6(1H, broad s)[c], 6.8—7.4(18H, m)
21	3380, 1710, 1632, 1610	1.96(1H, q), 2.32(3H, s), 2.92(1H, q), 3.30(2H, s), 3.68(2H, s), 3.76(1H, m), 5.5—6.1(1H)[c], 6.8—7.3(14H, m), 6.8—7.3(1H)[c]
22	3460, 3320, 1690, 1645	2.81(3H, s), 2.76(2H, d), 3.59(1H, t), 3.61(2H, s), 3.70(2H, s), 4.08(2H, broad s)[c], 7.27(5H, s), 7.23(5H, s)
23	3450, 3310, 1692, 1650	2.71(2H, d), 3.51(1H, t), 3.56(2H, s), 3.66(2H, d), 3.76(1H, d), 4.25(2H, broad s)[c], 5.09(1H, d), 6.9—7.5(15H, m)

a) Syrupy substances were measured as a film. b) Sh, shoulder absorption. c) D$_2$O-exchangeable peak.

Table 5. Spectral data of 3-hydroxylactams(**15**—**20**)

No	ν_{max}^{Nujol} cm^{-1}	NMR(δ, in CDCl$_3$)
15	3250, 1690(broad)[a]	1.87(1H, q), 2.79(1H, q), 3.5—3.8(1H, m), 3.60(2H, s), 4.05(2H, s), 5.5—6.5(1H)[c], 7.17(5H, s), 7.21(5H, s), 7.4(1H, broad s)[c]
16	3200, 1685, 1660	3.17(2H, m), 2.85(3H, s), 3.50—3.75(1H, m), 3.62(2H, s), 4.14(2H, s), 7.28(10H, s), 9.0(1H, broad s)[c]
17	3170, 1660(broad)	0.88(3H, m), 1.1—1.7(3H, m), 2.64(2H, m), 2.95(1H, m), 3.61(2H, s), 3.4—3.9(1H, m), 4.12(2H, s), 7.25(10H, s), 8.8(1H, broad s)[c]
18	3240, 1667	2.65(2H, d), 3.57(2H, s), 3.54(1H, t), 3.84(1H, d), 4.09(2H, s), 5.12(1H, d), 6.8—7.5(15H, m), 8.1—8.9(1H)[c]
19	3150(broad), 1680, 1660	2.2—3.0(4H, m), 3.1—3.5(2H, m), 3.57(2H, s), 3.7—4.2(1H, m), 4.06(2H, s), 6.9—7.4(15H, m), 8.4—9.2(1H)[c] .
20	3310, 1655(sh)[b], 1650	2.34(3H, s), 2.73(1H, d), 2.77(1H, d), 4.25(2H, d), 4.40(1H, q), 6.9—7.5(14H, m), 8.22(1H, broad s)[c]

a) Measured as a film. b) Sh, shoulder absorption. c) D$_2$O-exchangeable peak.

Table 6. Spectral data of 3-acylaminolactams (**24**—**29**)

No	ν_{max}^{Nujol} cm^{-1}	NMR(δ, in CDCl$_3$)
24	3200, 1680(broad)[a], 1625	2.09(3H, s), 2.35(1H, q), 3.02(1H, q), 3.73(2H, s), 3.79(2H, s), 4.09(1H, q), 7.1—7.4(1H)[c], 7.23(5H, s), 7.27(5H, s), 8.22(1H, s)[c]
25	3160, 1690(sh)[b], 1655	2.13(3H, s), 2.8(2H, m), 2.87(3H, s), 3.86(2H, s), 3.90(2H, s), 4.05(1H, m), 7.1—7.5(10H, m), 8.58(1H, s)[c]
26	3150, 1685(sh)[b], 1650(broad)	1.17(3H, t), 2.40(2H, q), 2.8(2H, m), 2.89(3H, s), 3.77(2H, s), 3.88(2H, s), 4.02(1H, m) 7.1—7.5(10H, s), 8.30(1H, s)[c]
27	3270, 1668, 1663	2.13(3H, s), 2.80(2H, d), 3.71(2H, d), 3.77(2H, s) 4.00(1H, t), 3.85(1H, d), 5.12(1H, d), 6.8—7.5(15H, m), 8.50(1H. s)[c]
28	3200(broad), 1660(broad)[a]	2.86(2H, d), 3.77(2H, s), 3.82(2H, s), 3.92(1H, d), 4.02(1H, t), 5.16(1H, d), 6.9—8.1(20H, m) 8.33(1H, s)[c]
29	1695, 1670	2.18(3H, s), 2.75(2H, d), 3.4—3.8(2H, m), 3.57(2H, s), 3.63(2H, s), 4.99(2H, s), 5.08(1H, d), 6.6—7.5(20H, m)

a) Measured as a film. b) Sh, shoulder absorption. c) D$_2$O-exchangeable peak.

b) By Reaction with Primary Amines: A solution of **18** (500 mg) and benzylamine (655 mg) in benzene (6 ml) was refluxed for 5 hr. After cooling, the reaction mixture was washed with 1% hydrochloric acid and with water, and dried. The removal of the solvent gave **11** (570 mg, 78%) (mp 121—122 °C), which was subsequently recrystallized from ethanol. In this way, **15** was allowed to react with *p*-toluidine for 7 hr to afford **21** as colorless needles in a 23% yield (mp 110—111 °C).

The spectral data are shown in Table 4.

*Preparation of 3-Acylamino-3-pyrrolin-2-one Derivatives. a) Preparation of **24***: A solution of **8** (2.12 g) and acetic anhydride (6 ml) in benzene (20 ml) was refluxed for 2 hr and evaporated to dryness. The residue was extracted with ethyl acetate, and the extract was washed with a 5% sodium bicarbonate solution and with water, and dried. The removal of the solvent left a syrup; this syrup was then chromatographed over silica gel G, using benzene-ethyl acetate (4 : 1) as the eluent, to give 1.33 g (56%) of **24** as a pale yellow syrup. The structure of **24** was confirmed by the spectral properties shown in Table 6.

*b) Preparation of **25**—**27** and **29***: A solution of **22** (2.92 g) and acetic anhydride (6 ml) in benzene (20 ml) was refluxed for 2 hr and then evaporated to give a syrup, which was subsequently crystallized by the addition of ether. Filtration and recrystallization from ethanol afforded 2.78 g (86%) of **25** as colorless needles (mp 140—142 °C). By the procedure described above, **26** (72%, mp 142—144 °C), **27** (88%, mp 128—129 °C), and **29** (88%, mp 95—96 °C) were obtained. The spectral data are listed in Table 6.

*c) Preparation of **28***: A solution of **23** (1.0 g) and benzoyl chloride (1.0 g) in benzene (5 ml) was stirred for 2 hr at room temperature. By the procedure described in the preparation of **24**, the resulting reaction mixture afforded 0.87 g (71%) of **28** as a pale yellow syrup. The structural assignment was made on the basis of spectral properties shown in Table 6.

Dehydrogenations of 3-Acylamino-5-benzylthiomethyl-3-pyrrolin-2-one Derivatives. a) With Chloranil or DDQ: A solution of **24** (0.63 g, 1.6 mmol) and chloranil (0.43 g, 1.8 mmol) in benzene (6 ml) was refluxed for 30 min and then diluted with methylene chloride. The solution was washed with 1% aqueous sodium hydroxide and with water, and dried. The removal of the solvent and recrystallization of the residue from ethanol gave 0.39 g (62%) of **30** as pale yellow needles: mp 178—179 °C; λ_{max}^{EtOH} 361 nm (ε 23500); M$^+$ ion at *m/e* 396. The IR and NMR spectra shown in Table 7 were consistent with the published data.[6] When DDQ was employed, **24** (0.40 g) yielded 0.27 g (67%) of **30**.

Similarly, **25**—**28** were treated with chloranil or DDQ to afford the corresponding exocyclic methlene compounds (**31**—**34**). The reactions in *t*-butanol also gave the dehydrogenated products in yields comparable to those in benzene. The results and the spectral properties are shown in Tables 2 and 7.

b) With Thionyl Chloride: Thionyl chloride (0.32 g, 3.8 mmol) was added to a cooled solution of **24** (1.50 g, 3.8 mmol) in chloroform (15 ml) with stirring. The resulting dark solution was allowed to stand overnight, and then washed with water and dried. After the evaporation of the solvent, the residue was chromatographed on silica gel G, using benzene-ethyl acetate (1 : 1) as the eluent, to give 103 mg (7%) of **30**. The reaction of 1-substituted lactams (**25**—**28**) with thionyl chloride led to the formation of unidentified products.

Separation of Geometric Isomers. The mixture (**32**, 500 mg) was treated by thin-layer chromatography (benzene-ethyl acetate, 1 : 1 on silica gel G) to give **32a** (70 mg, yellow leaflets) and **32b** (255 mg, yellow needles), which were recrystallized from 2-propanol. Similarly, the mixture (**31**, 300 mg) was separated into **31a** (60 mg, yellow leaflets) and **31b** (145 mg, yellow needles). The spectral properties are shown in Table 3.

*Thiolutin (**2**) and Aureothricin (**3**).* A solution of **31** (215 mg, 0.53 mmol) in tetrahydrofuran (2 ml) was introduced to liquid ammonia (20 ml). To the solution was added small pieces of lithium (15 mg, 2.2 mg. atom) with vigorous stirring. After 5 min, ammonium chloride (0.2 g) was added to the resulting orange-colored suspension. Evaporation left a yellow solid which was subsequently dissolved in methanol (20 ml). The solution was adjusted to pH 2 with 10% hydrochloric acid. After air was bubbled through the solution for 3 hr, evaporation gave a solid which was chromatographed on alumina, using chloroform-ethyl acetate (4 : 1), to give a yellow powder. Recrystallization from *n*-butanol afforded 13 mg (11%) of thiolutin (**2**) as yellow needles: mp 270—275 °C (dec); IR (KBr) 3270, 3060, 1670, 1640, 1605, 1550, 1235, 825 and 740 cm^{-1}; λ_{max}^{MeOH} 250, 312, 390 nm (6200, 5200, 11100); NMR (DMSO-d_6) δ

Table 7. Spectral data of 5-benzylthiomethylene-3-pyrrolin-2-ones (**30**—**34**)

No	ν_{max}^{KBr} cm^{-1}	NMR(δ, in CDCl$_3$)
30	3250, 1690, 1660	2.08(3H, s), 3.83(2H, s), 3.91(2H, s), 6.08(1H, s), 7.15(5H, m), 7.26(5H, s), 7.50(1H, broad s)[b], 8.24(1H, broad s)[b]
31a	3230, 1690, 1665	2.09(3H, s), 3.01(3H, s), 4.02(4H, s), 6.05(1H, s), 7.2(5H, m), 7.35(5H, s), 8.05(1H, s)[b]
31b	3280, 1700, 1670	2.08(3H, s), 3.37(3H, s), 3.80(2H, s), 3.93(2H, s), 6.28(1H, s), 7.2(5H, m), 7.33(5H, s), 7.91(1H, s)[b]
32a	3200, 1693, 1655	1.17(3H, t), 2.27(2H, q), 3.03(3H, s), 4.00(2H, s), 4.03(2H, s), 6.02(1H, s), 7.2(5H, m), 7.35(5H, s), 7.62(1H, s)[b]
32b	3270, 1680(broad)	1.17(3H, t), 2.35(2H, q), 3.39(3H, s), 3.80(2H, s), 3.96(2H, s), 6.29(1H, s), 7.2(5H, m), 7.36(5H, s), 8.71(1H, s)[b]
33[a]	3350, 3280, 1675(broad)	2.05(3H, s), 3.74(s), 3.82(s) and 3.94(s)(4H), 4.72(s) and 5.11(s)(2H, 2 : 1), 5.96(s) and 6.24(s)(1H, 2 : 1), 6.8—7.6(10H, m), 7.76(s)[b] and 7.81(s)[b] (1H)
34	3230, 1667, 1648	2.83(2H, s), 3.92(2H, s), 4.74(2H, s), 5.97(1H, s), 6.7—7.8(20H, m), 7.72(1H, s)[b]

a) The IR and NMR spectra of the isomeric mixture are shown, b) D$_2$O-exchangeable peak,

Table 8. Elemental analyses of new compounds

No	Formula	Calcd(%)				Found(%)			
		C	H	N	S	C	H	N	S
9	$C_{21}H_{24}N_2OS_2$	65.59	6.29	7.29	16.68	65.71	6.36	7.25	16.77
11	$C_{33}H_{32}N_2OS_2$	73.84	6.00	5.21	11.94	73.52	5.96	5.17	11.83
13	$C_{33}H_{32}N_2OS_2$	73.84	6.00	5.21	11.94	73.99	6.10	5.10	11.87
16	$C_{20}H_{21}NO_2S_2$	64.53	5.69	3.76	17.26	64.68	5.80	3.42	17.22
17	$C_{22}H_{25}NO_2S_2$	66.12	6.30	3.50	16.04	66.06	6.39	3.29	15.79
18	$C_{26}H_{25}NO_2S_2$	69.76	5.62	3.12	14.32	69.47	5.75	3.29	14.42
19	$C_{27}H_{27}NO_2S_2$	70.24	5.89	3.03	13.89	70.30	6.09	3.18	13.61
20	$C_{26}H_{25}NO_2S_2$	69.76	5.62	3.12	14.32	69.76	5.74	3.02	14.30
21	$C_{26}H_{26}N_2OS_2$	69.91	5.86	6.27	14.35	70.03	5.95	6.25	14.22
22	$C_{20}H_{22}N_2OS_2$	64.82	5.98	7.56	17.30	64.65	6.12	7.75	17.46
23	$C_{26}H_{26}N_2OS_2$	69.91	5.86	6.27	14.35	69.82	5.79	6.38	14.29
25	$C_{22}H_{24}N_2O_2S_2$	64.04	5.86	6.79	15.54	63.54	5.87	6.87	15.25
26	$C_{23}H_{26}N_2O_2S_2$	64.75	6.14	6.56	15.03	64.52	6.34	6.37	15.03
27	$C_{28}H_{28}N_2O_2S_2$	68.81	5.77	5.73	13.12	68.61	5.88	5.81	13.06
29	$C_{35}H_{34}N_2O_2S_2$	72.62	5.92	4.84	11.07	72.72	5.98	4.74	11.00
30	$C_{21}H_{20}N_2O_2S_2$	63.59	5.08	7.06	16.14	63.57	5.06	7.03	16.10
31a	$C_{22}H_{22}N_2O_2S_2$	64.36	5.40	6.80	15.63	64.16	5.60	7.02	15.60
31b	$C_{22}H_{22}N_2O_2S_2$	64.36	5.40	6.80	15.63	64.34	5.58	6.65	15.66
32a	$C_{23}H_{24}N_2O_2S_2$	65.06	5.70	6.60	15.10	64.81	5.79	6.64	15.03
32b	$C_{23}H_{24}N_2O_2S_2$	65.06	5.70	6.60	15.10	65.23	5.88	6.54	15.03
33	$C_{28}H_{26}N_2O_2S_2$	69.10	5.38	5.75	13.17	68.90	5.48	5.77	12.94
34	$C_{33}H_{28}N_2O_2S_2$	72.23	5.14	5.10	11.68	71.96	5.29	5.07	11.62

2.05 (3H, s), 3.92 (3H, s), 7.19 (1H, s) and 9.85 (1H, broad s).

By a similar procedure, **32** (1.04 g) yielded 37 mg (6%) of aureothricin (**3**) as yellow needles: mp 260—270 °C (dec); IR (KBr) 3250, 3050, 1670, 1640, 1605, 1545, 1230, 815 and 730 cm^{-1}; λ_{max}^{MeOH} 246, 313, 390 nm (6300, 4000, 11100); NMR (DMSO-d_6) δ 1.02 (3H, t), 2.40 (2H, q), 3.25 (3H, s), 7.28 (1H, s) and 9.8 (1H, broad s).

Both substances showed no depression on a mixed-melting-point determination with an authentic sample. The IR, UV spectra, and the thin-layer chromatographic behavior on silica gel G and alumina using benzene-ethyl acetate (1 : 1), benzene-methanol (9 : 1) and chloroform-ethyl acetate (4 : 1) could not distinguish between the synthetic and natural antibiotics (**2** and **3**).

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