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Original Scientific Paper

Reduction of Some 2-Thiazoline Benzamide and Carbamate Derivatives with Lithium Aluminum Hydride*

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This paper reports the reduction with lithium aluminum hydride of 2-benzamido-5-methyl-2-thiazoline (Va) and 2-benzamido-5,5-dimethyl-2-thiazoline (Vb) to give the corresponding 2-benzylamino-2-thiazolines (VIa, b), and of ethyl *N*-(5-methyl-2-thiazoline-2-yl)-carbamate (IIa) and ethyl *N*-(5,5-dimethyl-2-thiazoline-2-yl)-carbamate (IIb) to give the corresponding 2-methylamino-2-thiazolines (IIIa, b). No evidence of ring reduction or cleavage was observed either at room temperature or in refluxing ether or tetrahydrofuran. The structure of the products was confirmed by independent syntheses. Characteristic infrared bands are described.

The 2-benzamido- and 2-carbamate derivatives of 5-methyl- and 5,5-dimethyl-2-thiazolines (Va, b; IIa, b) were prepared and reduced by lithium aluminum hydride as part of a project to prepare biologically active thiazoline and thiazolidine derivatives related to penicilin.

In the present work the benzamide derivatives, 2-benzamido-5-methyl-2-thiazoline (Va) and 2-benzamido-5,5-dimethyl-2-thiazoline (Vb) or the carbamate derivatives, ethyl *N*-(5-methyl-2-thiazolin-2-yl) carbamate (IIa) and ethyl *N*-(5,5-dimethyl-2-thiazolin-2-yl) carbamate (IIb) were treated with twice the molar quantity of lithium aluminum hydride in ether or in tetrahydrofuran at reflux temperature for time periods ranging from one to two hours. After decomposition of the excess hydride the products were obtained as ether extracts of the aqueous alkaline solutions. As a point of interest, similar treatment of the free thiazolines (Ia, b) gave an ether extract which contained no starting material and no compound capable of forming a picrate derivative.

No evidence was found for either cleavage or addition of hydrogen to the thiazoline ring by lithium aluminum hydride reduction. Characteristically the carbamate group was reduced to a methylamino group[1,2] (III) and the benzamide to a benzylamino group[3,4] (VI). Isolation of the pure picrate derivative from the crude reaction product was considered as evidence that appreciable amounts of any other basic substances were not formed.

As indicated in the reaction scheme the 2-aminothiazolines (I) were formed by ring closure of the proper allyl thioureas. For Ia the closure was effected[5] with concentrated hydrochloric acid at 100°. Treatment of methallyl

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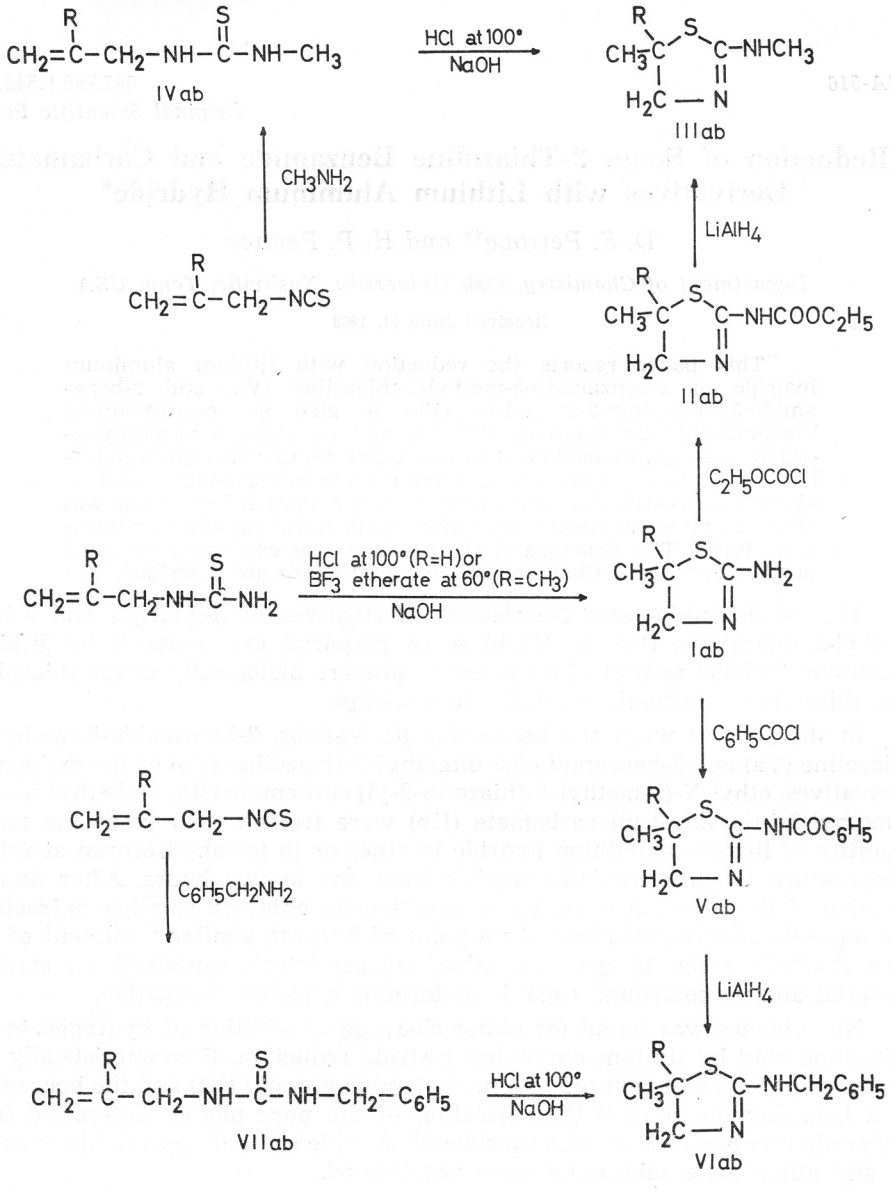

IVab
HCl at 100°
NaOH
IIIab
CH3NH2
LiAlH4
IIab
C2H5OCOCl
HCl at 100°(R=H)or
BF3 etherate at 60°(R=CH3)
NaOH
Iab
C6H5COCl
Vab
C6H5CH2NH2
LiAlH4
VIIab
HCl at 100°
NaOH
VIab

a, R = H
b, R = CH_3

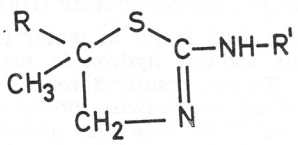
thiourea with concentrated hydrochloric acid at 140° for eight hours as reported[6] did not give a pure sample of the hydrochloride of Ib. In this case the ring closure was carried out conveniently with boron trifluoride etherate in acetonitrile at 60° to give a 54% yield of the hydrochloride. While boron trifluoride was also used for some of the other closures, hydrochloric acid seemed generally preferable.

The acylated products, II and V, were prepared in aqueous, slightly alkaline, medium by use of ethyl chloroformate and benzoyl chloride, respectively. Literature reports[7] indicate that frequently, particularly in benzene--pyridine solution, disubstituted derivatives are obtained. No difficulty was encountered in preparing the monosubstituted carbamate derivatives. However, the crude benzamides generally had a wide melting range, indicative of a mixture, and in the case of the attempted preparation of Vb it was found that recrystallization of the product gave a disubstituted derivative. However, the pure monosubstituted derivative was easily obtained by digesting the crude mixture with boiling ligroin (b. p. 60—90°). In this case the melting points of the mono- and di-substituted products were quite close to each other (115——117°, mono-; 120—121°, di-) which added to the difficulty of distinguishing between them.

The independent preparation of the benzylamino- and methyl-aminothiazolines (III and VI) were also carried out by ring closure of the appropriate allyl- and methallylthioureas, which in turn were prepared from the isothiocyanates and methylamine[8] or benzylamine[9]. The identity of the products with those obtained by reduction confirms not only the structures of the reduced products, but also the position of acylation of the carbamates (II) and the benzamides (V).

TABLE I

Infrared bands for



R′	R	I(cm.$^{-1}$)	II(cm.$^{-1}$)	III(cm.$^{-1}$)
C_2H_5OCO	H	1860	1228	1080
CH_3	H	1645	1260	1023
C_2H_5OCO	CH_3	1695	1253	1085
CH_3	CH_3	1650	1250, 1230	1025
C_6H_5CO	H	1620	1270	1025
$C_6H_5CH_2$	H	1645	1350, 1190	1029
C_6H_5CO	CH_3	1665	1292	1010
$C_6H_5CH_2$	CH_3	1640	1230	1032

Infrared spectra of all of the products were examined in an attempt to find characteristic bands for the series. Otting and Drawert[10] have assigned bands in three regions to the 2-thiazoline ring systems. Roggero and Mitzger[11] have found other characteristic bands as well. Others[12,13] have examined the infrared spectra of some 2-aminothiazolines, mainly to determine which tautomeric structures predominate. In Table I are listed bands for the thiazolines prepared in this work in the three regions chosen by Otting and

Drawert.[10] The bands in region I are typical of the C = N stretching vibration and are among the strongest bands in the spectra. These show little movement and can be readily distinguished from the carbonyl or aromatic bands in the same region. The bands in region II are generally of medium intensity and are stronger than those reported by Otting and Drawert for compounds without a 2-amino function. Also, these bands are somewhat difficult to locate in the presence of aromatic bands. Bands in region III are readily assigned to the vibrations of the heterocyclic ring[14].

EXPERIMENTAL

The infrared spectra were recorded on a Beckman IR 7 spectrophotometer in CCl_4 and CS_2 solution.

2-Amino-5-methyl-2-thiazoline hydrochloride (Ia) was prepared by the procedure described by Gabriel[5].

2-Amino-5,5-dimethyl-2-thiazoline (Ib)

To 5 g. (0.04 mole) of methallythiourea in 50 ml. of acetonitrile, 5 ml. of boron trifluoride etherate was added gradually with cooling. The container was then tightly stoppered and heated on a water bath for 10 minutes at 60°. The resulting mixture was poured into an evaporating dish and the volatile material allowed to evaporate at room temperature. After 24 hrs. the residue was treated successively with 25 ml. of water, 25 ml. of 20% aqueous sodium hydroxide, then extracted with ether and the ethereal solution dried over anhydrous magnesium sulphate. The ether was evaporated and the residue was distilled *in vacuo*. Yield 3.41 g. (65.4%), b. p. 94—96°, $n_D^{25} = 1.5406$.

Anal. $C_5H_{10}N_2S$ (130.21) calc'd.: C 46.12; H 7.74; N 21.52%
found: C 46.01; H 7.74; N 21.30%

The hydrochloride of Ib was prepared by addition of ethereal HCl to the base dissolved in ether. The salt was recrystallized from acetone, m. p. 126—128°.

Ethyl N-*(5-methyl-2-thiazoline-2-yl)-carbamate* (IIa)

To a solution of Ia (3.05 g. 0.02 mole) in water (10 ml.), containing a drop of phenolphthalein, 10% aqueous sodium hydroxide was added dropwise until the solution turned slightly pink. To the resulting reaction mixture, 2.7 g. (0.025 mole) of ethylchloroformate was added portionwise under cooling and stirring. At the same time 10% aqueous sodium hydroxide was added at such a rate to keep the mixture just barely basic. The stirring was continued for 5 minutes under cooling and then for additional 10 minutes at the room temperature. The precipitate was filtered and recrystallized several times from a mixture of benzene and ligroin, yielding 0.96 g. (26%) of pure product (m. p. 112—114°).

Anal. $C_7H_{12}O_7N_2S$ (188.25) calc'd.: C 44.65; H 6.42; N 14.88%
found: C 44.70; H 6.51; N 14.70%

Employing the same procedure as that used for the preparation of IIa, the following compounds were obtained:

Ethyl N-*(5,5-dimethyl-2-thiazoline-2-yl)carbamate* (IIb)

From 2-amino-5,5-dimethyl-2-thiazoline hydrochloride (1.66 g. 0.01 mole) and ethylchloroformate (1.35 g. 0.0125 mole), yield 0.84 g. (42%), m. p. 166—168°.

Anal. $C_8H_{14}N_2O_2S$ (202.22) calc'd.: C 47.50; H 6.98; N 13.85%
found: C 47.66; H 6.99; N 13.92%

2-Benzamido-5-methyl-2-thiazoline (Va)

From Ia (3.05 g. 0.02 mole) and benzoyl chloride (2.81 g. 0.02 mole), yield 3.01 g. (70%), m. p. 158—159°.

Anal. $C_{11}H_{12}N_2OS$ (220.29) calc'd.: C 59.97; H 5.50; N 12.71%
found: C 60.11; H 5.54; N 12.50%

2-Benzamido-5,5-dimethyl-2-thiazoline (Vb)

From hydrochloride of Ib (3.33 g. 0.02 mole) and benzoyl chloride (2.81 g. 0.02 mole), yield of crude product 4.68 g. (100%). Recrystallization from a mixture of benzene and ligroin gave a product which melted at 115—117°.

Anal. $C_{12}H_{14}N_2OS$ (234.32) calc'd.: C 61.50; H 6.02; N 11.96%
found: C 61.55; H 6.19; N 11.63%

2-Methylamino-5-methyl-2-thiazoline (IIIa)

a. *Reduction of IIa with lithium aluminum hydride.* — To a solution of 5.64 g. (0.03 mole) of IIa in 60 ml. of anhydrous ether 2.28 g. (0.06 mole) of lithium aluminum hydride dissolved in 60 ml. of anhydrous ether was added portionwise while cooling and stirring. The resulting mixture was refluxed for one hour (two hours if tetrahydrofuran is used as a solvent) and then cooled in an ice bath. The excess of hydride was decomposed by gradually adding 120 ml. of 2 *N* HCl. The aqueous layer was separated, treated with 100 ml. 50% aqueous potassium hydroxide and then extracted with ether. The ethereal solution was dried over anhydrous magnesium sulphate for 24 hrs. and after the removal of the ether, the residue was recrystallized from ligroin. Yield 1.8 g. (46.6%) m. p. 56.5—58.5°.

Anal. $C_5H_{10}N_2S$ (130.22) calc'd.: C 46.14; H 7.74; N 21.52%
found: C 46.17; H 7.65; N 21.55%

b. *Preparation of IIIa by ring closure.* — A mixture of 1 g. of allylmethylthiourea (IVa) and 3 ml. of concentrated hydrochloric acid was placed in a tightly stoppered testtube, and heated on a water bath for one hour and then poured into an evaporating dish. After the solution was evaporated on a water bath, the residue was treated with 10 ml. of 20% aqueous sodium hydroxide and then extracted with ether. The ethereal solution was evaporated until the product crystallized. The yield of the crude product (m. p. 53—56°) was 0.6 g. (60%). After recrystallization from ligroin the product was, in all its properties (such as the melting point, mixed melting point, and IR spectrum) identical with IIIa obtained from IIa by reduction.

Allylmethylthiourea (IVa), was prepared by adding 5 g. of allylisothiocyanate to 50 ml. of methylamine with cooling[8]. The reaction mixture was allowed to stand at room temperature for 24 hrs., and the precipitate was collected. The yield of the crude product (m. p. 43—47°) was 3.25 g. (50%).

In a manner similar to that described for IIa, by reduction of the corresponding benzamido and carbamate thiazolines with a double molar quantity of lithium aluminum hydride, the following compounds were prepared:

2-Methylamino-5,5-dimethyl-2-thiazoline (IIIb)

From 4.04 g. (0.02 mole) of IIb. Yield 2.4 g. (85%) m. p. 121—123°.

Anal. $C_6H_{12}N_2S$ (144.24) calc'd.: C 49.96; H 8.38; N 19.41%
found: C 49.99; H 8.43; N 19.45%

2-Benzylamino-5-methyl-2-thiazoline (VIa)

From 4.4 g. (0.02 mole) of Va. Yield 1.1 g. (27.07%) m. p. 61—62°.

Anal. $C_{11}H_{14}N_2S$ (206.30) calc'd.: C 64.04; H 6.84; N 13.58%
found: C 64.08: H 6.98; N 13.51%

2-Benzylamino-5,5-dimethyl-2-thiazoline (VIb)

From 3.8 g. (0.016 mole) of Vb. Yield 0.7 g. (20%), m. p. 126—127.5°.

Anal. $C_{12}H_{16}N_2S$ (220.33) calc'd.: C 65.41; H 7.32; N 12.72%
found: C 65.42; H 7.58; N 12.61%

The preparation of IIIb, VIa, and VIb was also carried out by ring closure of methallymethylthiourea (IVb), allylbenzylthiourea (VIIa) and methallylbenzylthiourea (VIIb) respectively, in a manner similar to that described for IIIa. These compounds were identical with those obtained by reduction as indicated by their melting points and mixed melting points, and by their identical IR spectra.

Methallylmethylthiourea (IVb)

Obtained in a manner similar to that described for IVa, by adding 5 g. of methallylisothiocyanate to 50 ml. of methylamine. The crude product was recrystallized from water. Yield 4.5 g. (71%) m. p. 64—66°.

Anal. $C_6H_{12}N_2S$ (144.24) calc'd.: C 49.96; H 8.38; N 19.41%
found: C 50.09; H 8.43; N 19.33%

Allylbenzylthiourea (VIIa) was prepared by the procedure of Weller *et al.*[9].

Methallylbenzylthiourea (VIIb)

Prepared according to the method of Weller *et al.*[9] by adding 3.39 g. (0.03 mole) of methallylisothiocyanate to 3.21 g. (0.03 mole) of benzylamine under cooling and stirring. The resulting mixture was allowed to warm up to room temperature and was then heated on a water bath at 60° for 10 minutes. After cooling, the precipitate was collected and recrystallized from a mixture of benzene and ligroin. Yield 6.46 g. (98%) m. p. 76—77°

Anal. $C_{12}H_{16}N_2S$ (220.33) calc'd.: C 65.41; H 7.32; N 12.73%
found: C 65.73; H 7.54; N 12,81%

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ИЗВОД

Редукција на некои 2-тиазолин бензамидни и карбаматни деривати со помош на литиум алуминиум хидрид

Д. С. Петрова и Х. П. Пеннер

Беше извршена редукција со помош на литиум алуминиум хидрид на 2-бензамидо-5-метил-2-тиазолин (Va) и на 2-бензамидо-5,5-диметил-2-тиазолин (Vb) при што се добија соответните 2-бензиламино-2-тиазолини (VIa,b) и исто така и на етил *N*-(5-метил-2-тиазолин-2-ил)карбамат (IIa) и етил *N*-(5,5-диметил-2-тиазолин-2-ил)-карбамат (IIb) за да се добиат соответните 2-метиламино-2-тиазолини (IIIa,b). При тоа не беше забележена ни редукција ни кинење на прстенот ниту на собна температура ниту на температура на рефлуксирање со етер или тетрахидрофуран.

Структурата на продуктите беше потврдена со независни синтези. Дискутирани се карактеристичните ленти во инфрацрвените спектри.

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