[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

ACYLATED 2-IMINOTHIAZOLINES

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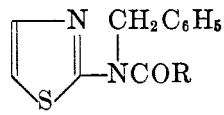
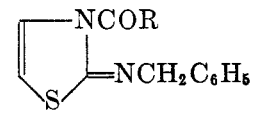
Received December 26, 1952

Although N,N-disubstituted-2-aminothiazoles may be prepared in good yield by treating secondary 2-thiazolylamines with alkyl or aralkyl halides in the presence of lithium amide (1, 2), only a small amount of 2-benzylaminothiazole was isolated after interaction of 2-aminothiazole with benzyl chloride and lithium amide (1). This reaction was repeated with 2-acetamidothiazole in the expectation that N-benzyl-N-(2-thiazolyl)acetamide (I; R = methyl) might be formed in better yield, thus offering a superior route, *via* hydrolytic cleavage of the acyl grouping, for the preparation of 2-benzylaminothiazole. Whereas treatment of the potassium derivative of 2-acetamido-4-methylthiazole with methyl iodide[2] (3) and the sodium derivative of 2-formylaminopyridine with alkyl halides (4) have given only extranuclear N-alkylated compounds, our product (II) was identical with that obtained by acetylating 2-imino-3-benzylthiazoline (III). In the absence of lithium amide, no product could be isolated. Similar results were obtained by Shephard, Bratton, and Blanchard (5) who, in alkylating the sodium salt of 2-sulfanilamidothiazole, isolated only nuclear N-alkylated compounds.

This observation suggested the possibility that acylated 2-benzylaminothiazoles may have the 2-benzylimino-3-acylthiazoline (IV) rather than the N-benzyl-N-(2-thiazolyl)amide (I) structure. We have investigated two methods which seemed applicable in establishing the configuration of these compounds but neither proved successful.



I

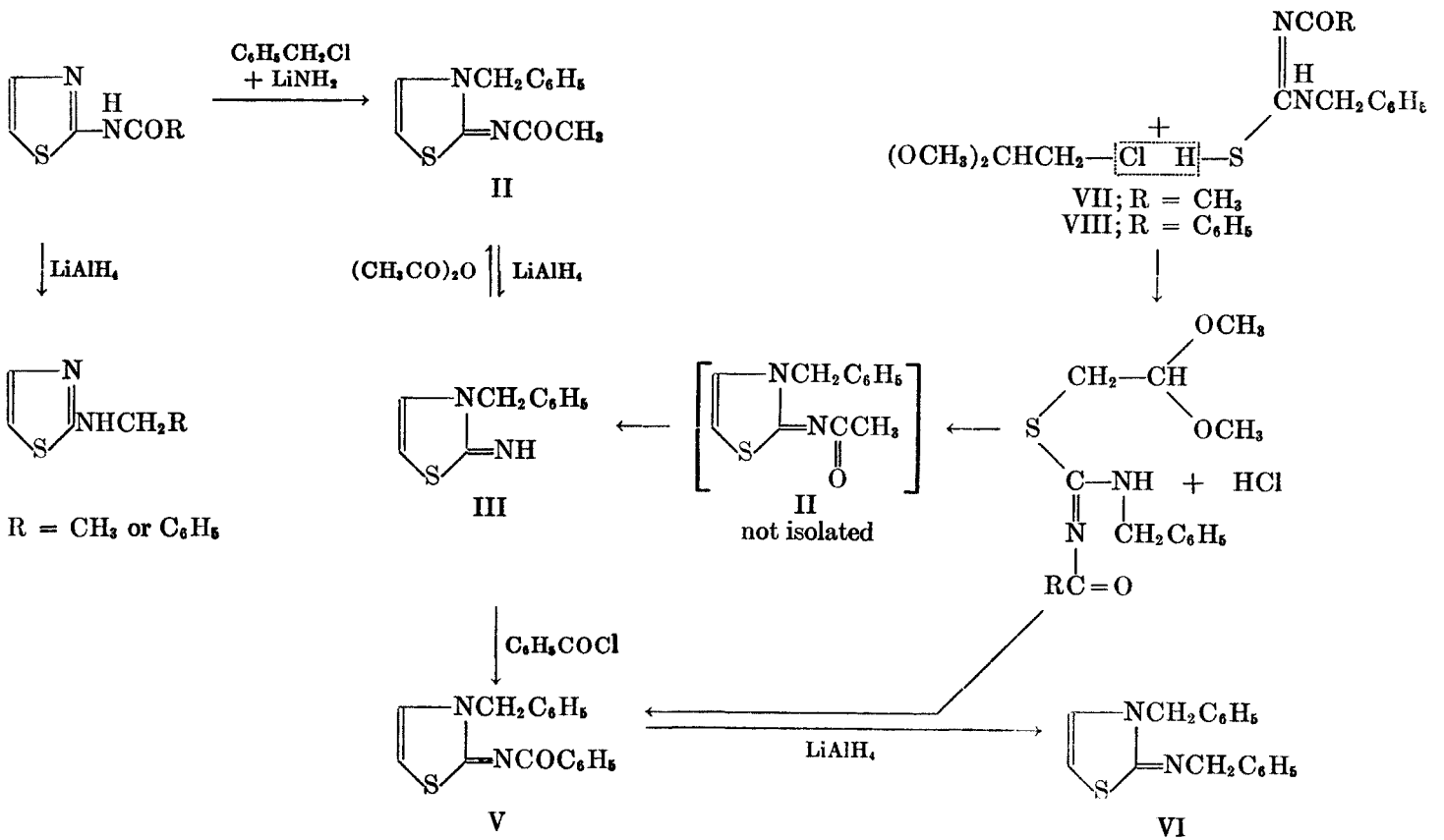


IV

Prior work had shown that high yields of 2-aralkylaminothiazoles (2) may be obtained by reduction of 2-acylaminothiazoles with lithium aluminum hydride (6). Accordingly, the benzoyl and acetyl derivatives of 2-benzylaminothiazole were treated with this reagent in an attempt to form either the known (1) disubstituted 2-thiazolylamines or 2-iminothiazolines. However, both compounds underwent acyl cleavage to give only 2-benzylaminothiazole. Subsequent work revealed that 2-acetylimino-3-benzylthiazoline (II) also loses its acetyl group in this reaction although the benzoyl analog (V) is reduced to 2-benzylimino-3-

[1] From a thesis submitted by Chester L. Parris to the Graduate Faculty of Brooklyn College, June 1951, in partial fulfillment of the requirements for the Master of Arts degree.

[2] By a similar procedure Wagner-Jauregg and Helmert, *Ber.*, **75**, 935 (1942), prepared 2-ethylaminobenzothiazole (m.p. 88–89°) but did not establish that this compound differed from their 2-imino-3-ethylbenzothiazoline (m.p. 83–87°).


C6H5CH2Cl + LiNH2
LiAlH4
(CH3CO)2O
LiAlH4
C6H5COCl
LiAlH4
R = CH3 or C6H5
II
III
II not isolated
V
VI
VII; R = CH3
VIII; R = C6H5
HCl

benzylthiazoline. These examples of hydrogenolysis of an acyl group during reaction with lithium aluminum hydride are apparently not unique (6).

Another route investigated involved the synthesis of substituted 2-aminothiazoles by the reaction of a thiourea with dimethyl chloroacetal. Since both N-benzylthiourea (7) and N-acetylthiourea have each been found to form only 2-substituted-aminothiazoles in this reaction, it seemed possible that 2-benzylimino-3-acetylthiourea might be isolated from a reaction-mixture of dimethyl chloroacetal and N-benzyl-N′-acetylthiourea (VII). However the sole product obtained was 2-imino-3-benzylthiazoline (III), indicating that the isomeric 2-acetylimino-3-benzylthiazoline (II) was formed and was hydrolytically cleaved under the conditions of the reaction. In an analogous reaction with N-benzyl-N′-benzoylthiourea (VIII) no loss of the benzoyl group occurred. Since the product isolated was 2-benzoylimino-3-benzylthiazole (V), it would appear that the acylated thioureas behave in these cyclization reactions as though they possess the tautomeric structures VII and VIII.

Acknowledgement. This project was supported in part by a research grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

EXPERIMENTAL

Melting points are corrected; boiling points are not. 2-Benzamidothiazole (8, 9), m.p. 150.5–151° after recrystallization from isopropyl alcohol, was obtained in 94% yield by the method previously described for 2-(*p*-chlorobenzamido)thiazole (2). 2-Acetamidothiazole (8, 10), m.p. 205–206° after recrystallization from ethanol, was formed in 90% yield by refluxing 2-aminothiazole with two moles of acetic anhydride for 1.5 hours. It was also prepared in 22% yield from N-acetylthiourea (11) and dimethyl chloroacetal (Method B). N-Benzyl-N′-acetylthiourea (VII) (12), m.p. 127.5–129.5° after recrystallization from isopropyl alcohol, was obtained in 95% yield from N-benzylthiourea (7) and acetic anhydride.

Acetyl derivative of 2-benzylaminothiazole. A mixture of 14.9 g. (0.0785 mole) of 2-benzylaminothiazole (7) and 50 ml. of acetic anhydride was refluxed for 3 hours. This was then poured into ice-water, giving an oil which solidified rapidly. The solid was separated, washed with water, and air-dried. The crude product, weighing 17.6 g. (97%) and melting at 69–72°, was recrystallized 3 times from aqueous methanol, m.p. 71.5–72.5°.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: N, 12.01. Found: N, 12.05.

Benzoyl derivative of 2-benzylaminothiazole. Method A. To a stirred solution of 27.1 g. (0.143 mole) of 2-benzylaminothiazole (7) in 150 ml. of pyridine and 50 ml. of ether, was added 21.9 g. (0.156 mole) of benzoyl chloride while maintaining the temperature of the reaction mixture at 1–3°. After addition was complete, the mixture was refluxed gently for 10 minutes and then poured into ice-water. The product was collected and washed with water, dilute sodium carbonate solution, and again with water until the washings were neutral to litmus. After recrystallization from isopropyl alcohol, there was obtained 23.5 g. (56%) of a product melting at 105–108°. The melting point remained constant at 126.5–127° after four more recrystallizations from this solvent.

Anal. Calc'd for $C_{17}H_{14}N_2OS$: N, 9.52. Found: N, 9.46.

2-Benzoylimino-3-benzylthiazoline (V) (8). *Method B.* A mixture of 13.5 g. (0.05 mole) of N-benzyl-N′-benzoylthiourea (VIII) (1), 7.5 g. (0.06 mole) of dimethyl chloroacetal, and 50 ml. of water was heated on a steam-bath for 54 hours. On cooling, the dark oily layer which had formed solidified. This was removed, washed well with water, and recrystallized from ethanol. The product, weighing 8.5 g. (58%) and melting at 98–101°, melted at 100–101°

after a second recrystallization from ethanol. The amide (V) was also prepared in 58% yield by benzoylating 2-imino-3-benzylthiazoline (III) (1) (Method A). A mixture of the products obtained by both methods showed no depression in melting point.

In a similar manner (Method B) a mixture of 20.8 g. (0.1 mole) of N-benzyl-N'-acetylthiourea (VII), 15.0 g. (0.12 mole) of dimethyl chloroacetal, and 100 ml. of water, heated for 24 hours on a steam-bath, gave 10.0 g. (53%) of a light tan product, m.p. 181.5–183°. The melting point was not depressed on mixing with an authentic sample of 2-imino-3-benzylthiazoline hydrochloride (III) (1).

2-Acetylimino-3-benzylthiazoline (II). A solution of 24.0 g. (0.19 mole) of benzyl chloride in 25 ml. of benzene was added to a mixture of 21.3 g. (0.15 mole) of 2-acetaminothiazole, 4.5 g. (0.19 mole) of lithium amide (of 98% purity), and 250 ml. of dry xylene which had been refluxed 7 hours. The reaction mixture was refluxed 17 hours longer and the insoluble material was then removed and washed with ether. The filtrate was extracted repeatedly with dilute hydrochloric acid. The combined acid extracts, after being washed twice with ether, were made alkaline with dilute sodium hydroxide. The precipitate which formed at this point was collected, washed with water, and air-dried. The amide, weighing 13.5 g. (39%) and melting at 96.5–98.5°, was recrystallized three times from isopropyl alcohol, m.p. 101.5–102°.

This substance was also prepared by the dropwise addition of a solution of 40 g. (1.0 mole) of sodium hydroxide in 75 ml. of water to a vigorously stirred mixture of 33.0 g. (0.146 mole) of 2-imino-3-benzylthiazoline hydrochloride, 50 ml. of acetic anhydride, and 75 ml. each of ether and water, the temperature being maintained below 10° during the addition. A voluminous precipitate appeared when the mixture became alkaline. The ether was removed by distillation and the precipitate was separated, washed with water, and air-dried. The product, weighing 30.6 g. (90%), melted at 98–100° after recrystallization from ethanol and showed no depression in melting point on admixture with a sample prepared by alkylating 2-acetaminothiazole.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: N, 12.01. Found: N, 12.17.

Lithium aluminum hydride reactions. The method described recently for the preparation of 2-(*p*-chlorobenzyl)aminothiazole (2) was followed. The identity of all products obtained in this manner was confirmed by the fact that no depression in melting point was observed on mixing with authentic samples (1, 7). From 2-benzamidothiazole and acetylated and benzoylated 2-benzylaminothiazoles there were obtained 85%, 75%, and 89% yields, respectively, of 2-benzylaminothiazole, m.p. 127–129°. 2-Ethylaminothiazole, prepared in 77% yield from 2-acetamidothiazole, melted at 52.5–53.5° after three recrystallizations from hexane. The picrate, prepared in ether and recrystallized from acetone, melted at 182.5–183.5°. 2-Benzylimino-3-benzylthiazoline, m.p. 220–220.5° after recrystallization from ethanol, was isolated in 81% yield from 2-benzoylimino-3-benzylthiazoline while 2-imino-3-benzylthiazoline, m.p. 181–182° after recrystallization from the same solvent, was obtained in 42% yield from 2-acetylimino-3-benzylthiazoline.

SUMMARY

2-Acetylaminothiazole, on alkylation with benzyl chloride in the presence of lithium amide, gave the nuclear N-alkylated product (II) rather than the expected N-benzyl-N-(2-thiazolyl)acetamide (I). Attempts to establish the position of the acyl substituents in acylated 2-benzylaminothiazoles by lithium aluminum hydride reduction resulted in cleavage of these groups. From symmetrically-substituted thioureas and dimethyl chloroacetal the desired acylated 2-benzylaminothiazoles (IV) could not be obtained.

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