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The Alkylation of 5-Benzoylamino-1,3,4-thiadiazoline-2-one

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Submitted in honour of the sixtieth birthday of our teacher, Professor *Arne Fredga*

The methylation of 5-benzoylamino-1,3,4-thiadiazoline-2-one has been studied. It was found that methylation using methyl iodide produced 3-methyl-5-benzoylamino-1,3,4-thiadiazoline-2-one, in contrast to the opinion of Sugii [10]. Using dimethyl sulfate a mixture of 3-methyl-5-benzoylamino-1,3,4-thiadiazoline-2-one and 4-methyl-5-benzoylimino-1,3,4-thiadiazolidine-2-one was obtained. 2-Methoxy-5-benzoylamino-1,3,4-thiadiazole was also synthesized.

Several authors have studied the alkylation of heterocycles which contain a ring nitrogen and an oxygen atom, where the oxygen atom is in a position allowing tautomerism between the oxy and oxo forms. O-Alkylation generally requires the use of diazomethane as the methylation agent [1–3]. When methyl halides or dimethyl sulfate are used, usually the N-methyl derivatives are obtained [3–6], sometimes mixed with the O-alkyl compounds [7,8]. However Ponzio [9] has reported the O-alkylation of 3-phenyl-1,2,4-oxadiazoline-5-one and Sugii [10*] has reported the analogous reaction of 5-acylamino-1,3,4-thiadiazoline-2-one. None of these authors appear to have proved their structures, and since we have found that other thiadiazolones give N-methyl derivatives, a control of Sugii's results seemed justified.

Methylation of 5-benzoylamino-1,3,4-thiadiazoline-2-one (VI) may give five mono-methyl derivatives (I—V) **

We have repeated Sugii's synthesis and have obtained a product with the same melting point. The IR spectrum of this substance (Fig. 1), however, has two carbonyl frequencies (1655 cm^{-1}, 1630 cm^{-1}) but only one strong absorption band in the 1300 cm^{-1} region. This band (1298 cm^{-1}) corresponds to the amide structure of the molecule. There is no other band around 1300 cm^{-1} to indicate a methoxyl group.

* Note that the corresponding abstract in *Chem. Abstr.* **53** (1959) 10033 is incorrect.

** The hydroxythiadiazole structures have been excluded, since it has been shown that similar compounds are present in the oxoform both in solution and in the solid state [14].

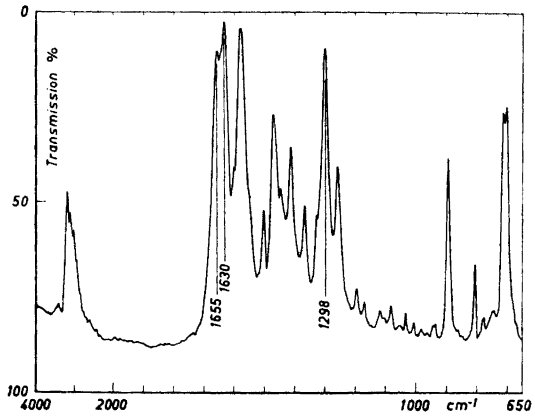
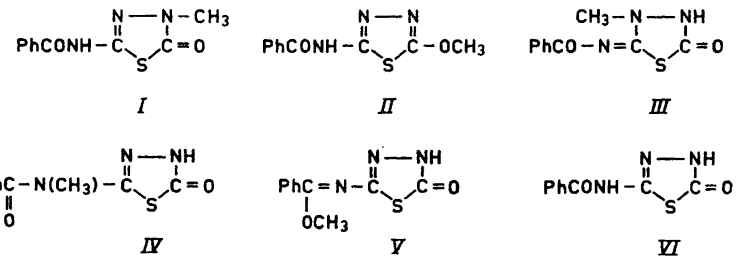


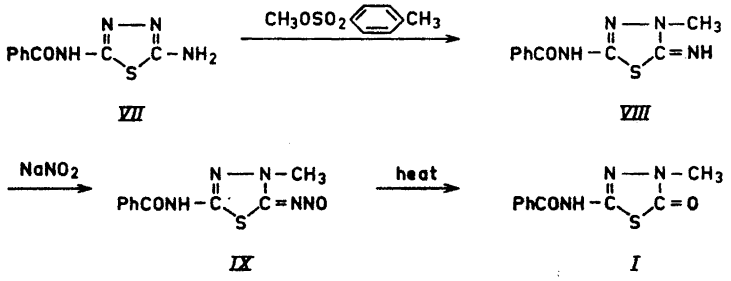
Fig. 1. IR absorption of 3-methyl-5-benzoylamino-1,3,4-thiadiazoline-2-one (I).



I *II* *III*

IV *V* *VI*

In accordance with this a Zeisel methoxyl determination gives a negative result. Therefore, the 3-methyl derivative (I) was synthesized in a manner which proves its structure (scheme 1). Nitrosation of the methyl derivative (VIII) gave a nitroso compound (IX) which on heating was converted to a thiadiazolone (I), in agreement with the general behaviour of 3-alkyl-2-imino-1,3,4-thiadiazolines [18]. A 4-methyl derivative should give a diazonium salt rather than a nitroso compound.



VII *VIII*

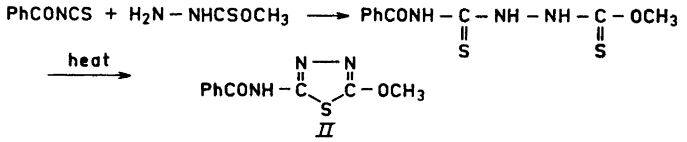
IX *I*

Scheme 1.

The substance obtained was identical to Sugii's substance, which thus is shown to be 3-methyl-5-benzoylamino-1,3,4-thiadiazoline-2-one (I).

The preparation of 2-amino-5-benzoylamino-1,3,4-thiadiazole (VII) is described by Sugii [12]. In our hands this method gave mixtures which were hard to separate. Therefore, the ring closure was performed by oxidation with hydrogen peroxide, which gave only the expected benzoyl compound.

In order to obtain a final proof of the preceding result we prepared 2-methoxy-5-benzoylamino-1,3,4-thiadiazole by ring closure of 1-methoxythiocarbonyl-4-benzoyl-3-thiosemicarbazide (scheme 2).



Scheme 2.

The IR spectrum of the compound (II) (Fig. 2) has the expected carbonyl peak at 1670 cm^{-1} and, in addition, two strong absorption bands in the 1300 cm^{-1} region. Here the band at 1310 cm^{-1} may be correlated with the amide structure of the molecule. The other frequency (1279 cm^{-1}) corresponds to a methoxyl group.

In our hands the methylation of 5-benzoylamino-1,3,4-thiadiazoline-2-one (VII) with methyl iodide gave a comparatively low yield. Therefore, an attempt was made to perform the reaction with dimethyl sulfate. We obtained a mixture of at least two substances containing (I) and a substance (A) with the same composition as (I) but differing from this substance and also from (II). By paper chromatography the presence of small amounts of (II) was also indicated.

Determination of the equivalent weight (potentiometrically) and of the molecular weight (ebullioscopically, acetone) shows that substance (A) behaves

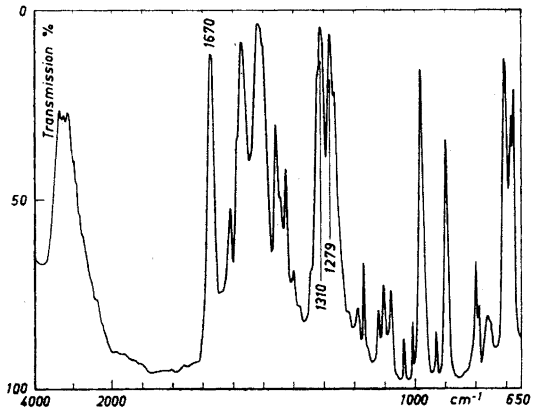


Fig. 2. IR absorption of 2-methoxy-5-benzoylamino-1,3,4-thiadiazole (II).

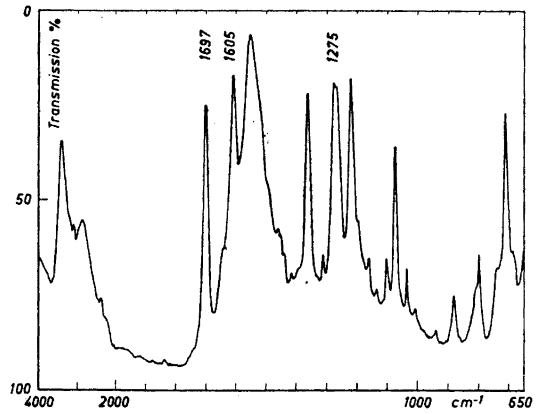


Fig. 3. IR absorption of 4-methyl-5-benzoylimino-1,3,4-thiadiazolidine-2-one (III).

like a monobasic acid with a molecular weight around 230. A Zeisel methoxyl group determination gave about one-half a methoxy group per molecule. This result is confusing, but Karpitschka has reported that sometimes N-methyl groups are split under conditions of a Zeisel test [13]. This may be the case in our determination.

Methoxyl groups exhibit an IR absorption around 1300 cm^{-1}. Actually, substance (A) absorbs at 1275 cm^{-1} (Fig. 3). However, this band disappears when (A) is converted into its sodium salt (Fig. 4). Therefore, it is more likely that this band is caused by an amide structure. A methoxy group absorption should be maintained in the IR spectrum of the salt as is shown by substance (II) (Figs. 2 and 5).

A further inspection of the IR spectrum reveals that compound (A) (Fig. 3) has only one band (1697 cm^{-1}) characteristic of an amide carbonyl grouping,

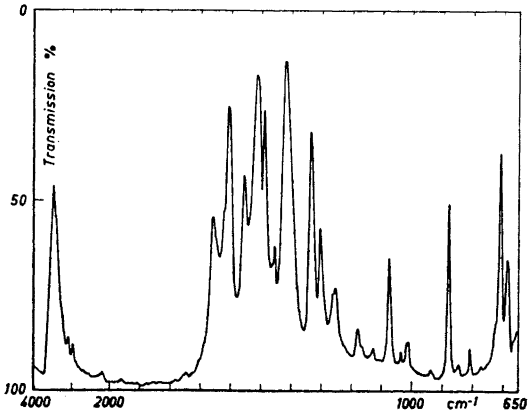


Fig. 4. IR absorption of sodium salt of 4-methyl-5-benzoylimino-1,3,4-thiadiazolidine-2-one.

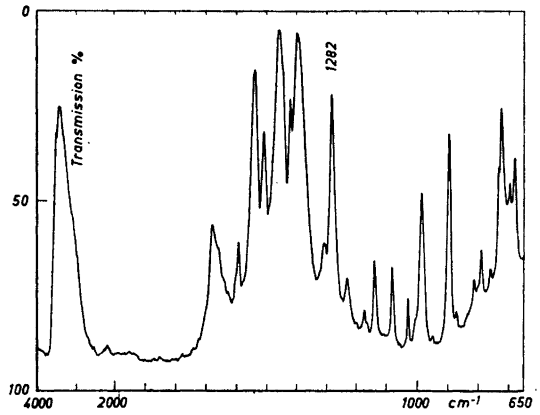


Fig. 5. IR absorption of sodium salt of 2-methoxy-5-benzoylamino-1,3,4-thiadiazole.

whereas (I) (Fig. 1) and (VI) (Fig. 6) exhibit two absorptions (at 1655 and 1630; and at 1668 and 1646 cm^{-1}, respectively). Furthermore substance (A) absorbs at 1605 cm^{-1}, which can be attributed to the presence of an imide structure [14] in the molecule.

Thus, the IR spectra indicate that substance (A) lacks a methoxy group but, instead, possesses an imido group. These fact speak in favour of formula (III) for compound (A).

The UV absorption maxima of the substances (I), (II), (VI), and (A) are collected in Table 1. In an acid medium the substances (I), (II) and (VI), which have amide structures, absorb at 277—282 mμ, whereas substance (A) absorbs at 310 mμ which is characteristic of imido configurations. A similar behaviour has been reported for other heterocycles [14].

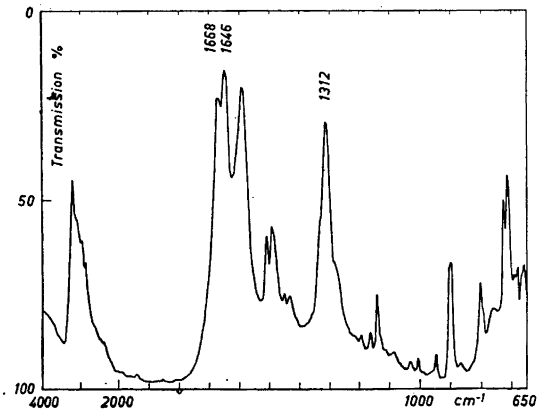
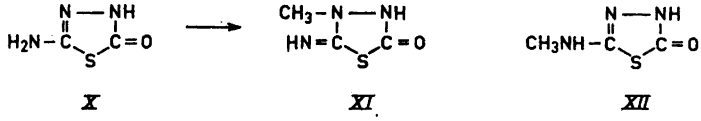


Fig. 6. IR absorption of 5-benzoylamino-1,3,4-thiadiazoline-2-one (VI).

Acid hydrolysis of (A) yields a substance which is identical to the substance (XI) which can be obtained by methylation of 5-amino-1,3,4-thiadiazoline-2-one with methyl *p*-toluenesulfonate (scheme 3). Substance (XI) does not have the same melting-point as 5-methylamino-1,3,4-thiadiazoline-2-one (XII) synthesized by Guha [16].



X XI XII

Scheme 3.

The opinion that the alkylation reaction in scheme 3 gives the 4-methyl-5-imino-1,3,4-thiadiazolidine-2-one is supported by the general behaviour of aminothiadiazoles in such reactions [15]; also the nonidentity of (A), (I) and (II) excludes O- or 3-N-substitution.

Thus, the collected chemical and spectral data of substance (A) definitely show it to be 4-methyl-5-benzoylimino-1,3,4-thiadiazolidine-2-one (III). On hydrolysis the molecule (V) should give a non-methylated amino-thiadiazolinone.

EXPERIMENTAL

2-Amino-5-benzoylamino-1,3,4-thiadiazole (VII). 14.8 g (0.058 mole) of 1-benzoyldithiobiurea [12] was stirred with 50 ml of water. 150 ml of 3 % hydrogen peroxide was added and the mixture refluxed for 1 h. After cooling, the mixture was filtered and the precipitate was dissolved in 2 N sodium hydroxide. 1.8 g of undissolved sulfur was filtered off. The filtrate was treated with charcoal, filtered, and acidified with 2 N hydrochloric acid. 11.7 g (91 %) of a colourless substance was obtained. M.p. 277—278.5°C (decomp.). (Found: C 48.9; H 4.0; N 25.3; S 15.0. Calc. for $C_9H_8N_4OS$ (220.2): C 49.1; H 3.7; N 25.4; S 14.6.)

2-Imino-3-methyl-5-benzoylamino-1,3,4-thiadiazoline (VIII). 12.7 g (0.058 mole) of 2-amino-5-benzoylamino-1,3,4-thiadiazole and 21.5 g (0.116 mole) of methyl *p*-toluenesulfonate were mixed and heated in an oil bath at 240°C for 15 min. After cooling, the solidified melt was stirred with acetone and filtered. The precipitate was dissolved in 100 ml of ethanol, the solution treated with charcoal and allowed to cool. 10.8 g (40 %) of 2-imino-3-methyl-5-benzoylamino-1,3,4-thiadiazolinium *p*-toluenesulfonate was obtained as colourless crystals melting at 255.5—260°C.

Table 1. The UV absorption spectra in dimethylformamide-water.

Substance	Maxima (mμ) at pH 2.6	Maxima (mμ) at pH 11.2
3-Methyl-5-benzoylamino-1,3,4-thiadiazoline-2-one (I)	282	315
2-Methoxy-5-benzoylamino-1,3,4-thiadiazole (II)	277	311
4-Methyl-5-benzoylimino-1,3,4-thiadiazolidine-2-one (A)	252, 310	252, 338
5-Benzoylamino-1,3,4-thiadiazoline-2-one (VI)	253, 279	249, 326

The salt was stirred with water, and 2 N sodium hydroxide was added until pH 9 was obtained. The precipitate formed was filtered off and dried. Yield 5.3 g (39 % total yield) of VIII. M.p. 255—257°C (decomp.) (Found: C 51.3; H 4.3; N 24.0; S 13.8. Calc. for $C_{10}H_{10}N_4OS$ (234.3): C 51.3; H 4.3; N 23.9; S 13.7.)

2-Nitrosimino-3-methyl-5-benzoylamino-1,3,4-thiadiazoline (IX). 1.0 g (0.004 mole) of 2-imino-3-methyl-5-benzoylamino-1,3,4-thiadiazoline was dissolved in 30 ml of glacial acetic acid. A solution of 0.36 g (0.005 mole) of sodium nitrite in 5 ml of water was added slowly. The solution turned yellow and after 15 min a yellow substance was precipitated. The mixture was stirred for 1 h at room temperature and filtered. 0.15 g (13 %) of the 2-nitrosimino compound was obtained. The substance decomposes at 200°C.

From the mother liquor 0.7 g of the starting material was recovered after evaporation of the solvent.

3-Methyl-5-benzoylamino-1,3,4-thiadiazoline-2-one (I). 0.15 g (0.6 mmole) of (IX) was refluxed in about 10 ml of chlorobenzene for 30 min. The colour changed from deep yellow to pale yellow. The solution was chilled and 0.1 g (75 %) of an almost colourless substance was collected by filtration. M.p. 257—261°C. After recrystallization from glacial acetic acid 0.06 g of (I), melting at 263.5—267°C, was obtained. Mixed with a substance prepared according to Sugii [10] it showed no melting point depression. (Found: C 50.8; H 3.9; N 18.1; S 13.5. Calc. for $C_{10}H_9N_3O_2S$ (235.2): C 51.1; H 3.9; N 17.9; S 13.6.)

1-Methoxythiocarbonyl-4-benzoyl-3-thiosemicarbazide. 13.3 g (0.125 mole) of methoxythiocarbonylhydrazine was stirred in 100 ml of benzene. A solution of 20.2 g (0.125 mole) of benzoylisothiocyanate in 50 ml of benzene was added carefully. The hydrazine compound was dissolved and the solution became warm. After a while a slightly yellow substance was precipitated. The mixture was stirred for 4 h and finally filtered. Yield 27.5 g (82 %). M.p. 108—109.5°C. (Found: C 44.7; H 4.3; N 15.8; S 23.5. Calc. for $C_{10}H_{11}N_3O_2S_2$ (269.3): C 44.6; H 4.1; N 15.6; S 23.8.)

2-Methoxy-5-benzoylamino-1,3,4-thiadiazole (II). 20 g (0.074 mole) of 1-methoxythiocarbonyl-4-benzoyl-3-thiosemicarbazide was refluxed in chlorobenzene for 3 h. Evolution of hydrogen sulfide was easily recognized. After cooling 14.3 g of colourless crystals were obtained. M.p. 201—215°C. Recrystallization in a mixture of ethanol and acetone. Yield 11.9 g (69 %) of (II). M.p. 217.5—219.5°C. (Found: C 51.2; H 4.2; N 17.9; O 13.8; S 13.5. Calc. for $C_{10}H_9N_3O_2S$ (235.2): C 51.1; H 3.9; N 17.9; O 13.6; S 13.6.)

Acid hydrolysis of 2-methoxy-5-benzoylamino-1,3,4-thiadiazole (II). 1 g of the methoxy compound was refluxed with a mixture of 16 ml of 6 N ethanolic hydrogen chloride and 5 ml of water on a water bath for 1.5 h. The hot mixture was filtered and the precipitate collected. 0.7 g of a subtance, decomposing at 263—271°C, was obtained. The product showed no melting point depression with 5-benzoylamino-1,3,4-thiadiazoline-2-one (VI), prepared according to Sugii [10]. In addition the infrared spectra of the two substances were identical.

Methylation of 5-benzoylamino-1,3,4-thiadiazoline-2-one (VI) with dimethyl sulfate. 4.5 g (0.02 mole) of (VI) was dissolved in 25 ml of 2 N NaOH. 5.0 g (0.04 mole) of dimethyl sulfate was slowly added. After 10 min a precipitate was formed and the mixture turned warm. After stirring for an hour the mixture was filtered. The precipitate (a) and the filtrate (b) were treated as follows:

(a) The precipitate (weight after drying 4.5 g) was stirred with water and the pH was adjusted to 3 with 2 N hydrochloric acid. The mixture was filtered and the precipitate was washed with water and dried. 3.3 g of a substance melting at 136—160°C, was obtained. It was extracted with boiling benzene and 2.5 g of undissolved substance was finally recrystallized from 40 ml of ethanol. 2 g of substance (A) (shown to be (III)), melting at 179.5—181°C was collected. (Found: C 51.2; H 4.0; N 17.7; S 13.7. Calc. for $C_{10}H_9N_3O_2S$ (235.2): C 51.1; H 3.9; N 17.9; S 13.6.)

The solvent was removed from the benzene extract. 0.65 g of a substance melting at 144—165°C was obtained. Chromatography on paper in a 2-butanone-water-methylamine system gave two large spots, one corresponding to (II) and the other unidentified, and further one small spot corresponding to substance (A).

(b) The filtrate was acidified to pH 3 with 2 N hydrogen chloride and filtered. 1.0 g of (I), melting at 257—260°C, was obtained. After recrystallization from glacial acetic acid, the substance melted at 257—260°C, and it showed no melting point depression with the substance prepared according to scheme 1.

Hydrolysis of substance (A). 1 g of substance (A) was refluxed for 1.5 h in ethanolic hydrogen chloride. The solution was chilled and filtered, and 0.45 g of the solid starting material was recovered. The filtrate was evaporated to dryness and 0.3 g of a solid product extracted with boiling acetone. 0.15 g remained undissolved, and it decomposed at 246–249°C. (Found: C 21.9; H 3.7; N 24.9; S 18.9; Cl 21.2. Calc. for $C_3H_6N_3ClOS$ (167.6): C 21.5; H 3.6; N 25.1; Cl 21.2; S 19.1.)

The salt was dissolved in water and NaOH was added to pH 7. The solution was evaporated to dryness and the remainder extracted with hot ethanol. The filtered extract was evaporated to dryness. The resulting base melted with decomposition at 248–249°C and had an IR spectrum identical with (XI), prepared as described below.

4-Methyl-5-imino-1,3,4-thiadiazolidine-2-one (XI). 0.95 g (0.008 mole) of 5-amino-1,3,4-thiadiazoline-2-one [17] was mixed with 3 g of methyl *p*-toluenesulfonate and slowly heated in an oil bath to 125°C. The melt was chilled and extracted with ether, the ether layer decanted, and the undissolved oil was dissolved in acetone. Dry ethanolic hydrogen chloride was added, and the colourless hydrochloride of (XI) was collected and recrystallized from ethanol-ether. 0.25 g was obtained, which decomposed at 250–252°C.

0.2 g of the salt was dissolved in water and the base isolated as described in the previous synthesis. 0.15 g of the base, decomposing at 251.5–253.5°C, was obtained. This substance gave no melting point depression with the substance obtained in the hydrolysis experiment.

Infrared spectra. A Unicam SP 100 spectrophotometer with sodium chloride optics was used. All of the substances were examined with the potassium bromide disc technique.

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