UDC 547.497.1

100. **Risaburo Nakai, Michiyasu Sugii, and Hideo Nakao**: The Use of Radioactive Element. II.* Decomposition of 1,4-Dibenzoylthiosemicarbazide and 1,4-Dibenzoylsemicarbazide with Alkali.

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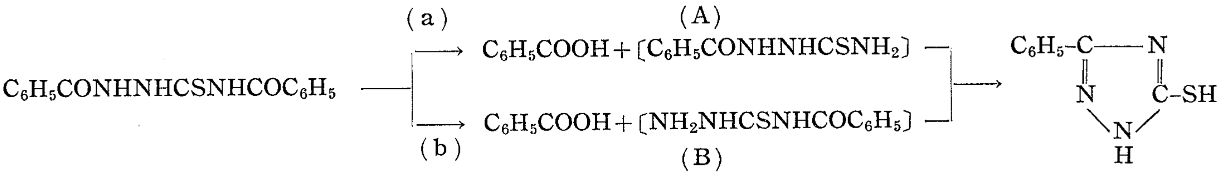
It has been reported by Hoggarth$^{1)}$ that 1,4-dibenzoylthiosemicarbazide gave 3-phenyl-5-mercapto-1,2,4-triazole and benzoic acid on treating with ethanolic solution of sodium ethoxide. There are two possible routes in this reaction, since 3-phenyl-5-mercapto-1,2,4-triazole is prepared from both 1-benzoylthiosemicarbazide (A) and 4-benzoylthiosemicarbazide (B). Both monobenzoyl compounds are presumed as intermediate products of this reaction, while they are not isolated from the reaction mixture. Wojahn$^{2)}$ reported that 1,4-dibutyroylthiosemicarbazide was converted to 3-butyl-5-mercapto-1,2,4-triazole via 1-butyroylthiosemicarbazide with 10% sodium hydroxide solution. However, he did not give any satisfactory explanation for the reaction route.



A determination of reaction route (a) or (b) is possible by using 1,4-dibenzoylthiosemicarbazide[1-*carbonyl*-^{14}C] (II), since the different routes of reaction will lead to isotopically distinguishable products. The reaction of 1,4-dibenzoylsemicarbazide[1-*carbonyl*-^{14}C] (V) with alkali was also examined and it was found to be analogous to that of 1,4-dibenzoylthiosemicarbazide (II).

These labeled compounds were synthesized by reaction of benzohydrazide[*carbonyl*-^{14}C] (I) with benzoyl isothiocyanate and benzoyl isocyanate, respectively. When treated with 10% sodium hydroxide solution, (II) decomposed into benzoic acid (III) and 3-phenyl-5-mercapto-1,2,4-triazole[3-^{14}C] (IV). When treated with 20% sodium hydroxide solution, (V) decomposed into benzoic acid (VI) and 3-phenyl-5-hydroxy-1,2,4-triazole[3-^{14}C] (VII) (Chart 1).

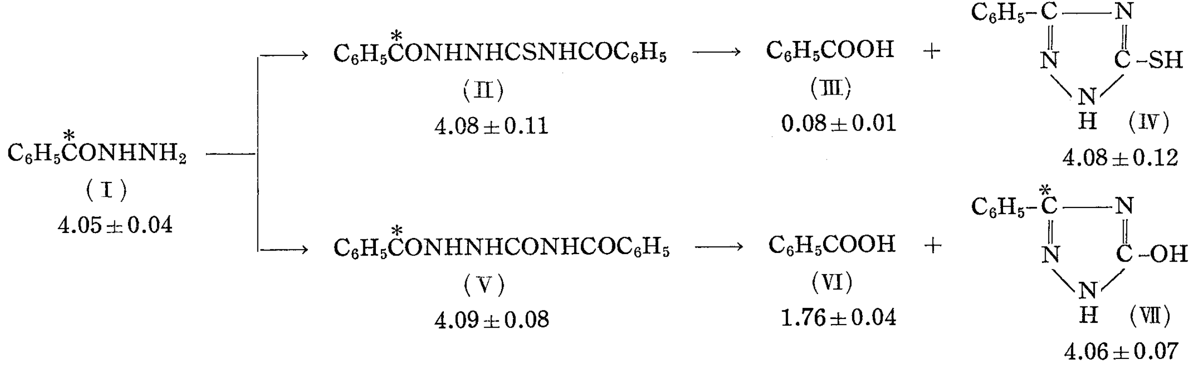


Chart 1.

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* Part I: J. Pharm. Soc. Japan, **75**, 1014(1955).

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1) E. Hoggarth: J. Chem. Soc., **1950**, 615; **1949**, 1160, 1164.

2) H. Wojahn: Arch. Pharm., **285**, 124(1952).

The specific radioactivities (μc/mM) of the products measured at each step are shown under the formulae in Chart 1.

The specific radioactivity of (IV) was equal to that of (II), whereas (III) showed a small but distinct specific radioactivity, in spite of careful purification by repeated sublimation and recrystallization. Thus the main reaction is route (a) and a small quantity of radioactive benzoic acid (ca. 4%) should be formed by further degradation of the intermediate product (A) rather than by route (b), since the formation of inactive triazole by route (b) would cause some decrease in specific radioactivity of (IV). This interpretation is supported by the following observations :

(1) When treated with 10% sodium hydroxide solution, (II) gave a small quantity of ammonia in addition to (III) and (IV).

(2) The non-labeled specimen of (A), synthesized by the method of Hoggarth,[3] was treated with alkali in the same manner as mentioned above and gave mainly triazole derivative, with a small amount of benzoic acid and ammonia. The liberation of ammonia is interpreted as the action of alkali on thiosemicarbazide, formed by hydrolysis of the compound (A). This side reaction explains the formation of a small amount of radioactive benzoic acid.

When non-labeled specimen of (V) was heated with 10% sodium hydroxide solution, 1-benzoylsemicarbazide (VIII) and benzoic acid were formed, whereas (II) under similar conditions cyclized into a triazole ring. Under a stronger basic condition (20% sodium hydroxide solution), however, (V) gave (VI), (VII), and ammonia. Accordingly it is conceivable that (VII) was formed from 1-benzoylsemicarbazide〔*carbonyl*-^{14}C〕. Further evidences that a part of the latter decomposes into radioactive benzoic acid and ammonia are described below.

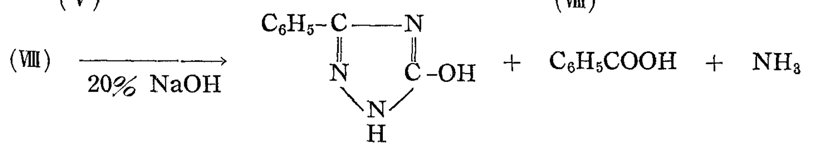
(1) When treated with 20% sodium hydroxide solution, non-labeled specimen of (VIII) gave a triazole derivative, benzoic acid, and ammonia.

(2) The specific radioactivity of (VII) was equal to that of (V).

(3) The yield of (VI) was larger (144%) than that of the theoretical value, calculated from the main reaction.

(4) The amount of ammonia (2.3% : 36%) was roughly proportional to the magnitude of specific radioactivity of benzoic acid (III) (0.08 μc/mM) and (VI) (1.76 μc/mM).

$$\underset{\text{(V)}}{C_6H_5CONHNHCONHCOC_6H_5} \xrightarrow[\text{10\% NaOH}]{} \underset{\text{(VIII)}}{C_6H_5CONHNHCONH_2} + C_6H_5COOH$$



These results would lead to the following conclusions : In the action of alkali on 1,4-dibenzoylthiosemicarbazide〔1-*carbonyl*-^{14}C〕 or 1,4-dibenzoylsemicarbazide〔1-*carbonyl*-^{14}C〕, inactive benzoic acid and 1-benzoylthiosemicarbazide〔*carbonyl*-^{14}C〕 or 1-benzoylsemicarbazide〔*carbonyl*-^{14}C〕 are formed in the first step as a result of hydrolysis and the latter further cyclizes mainly to give 3-phenyl-5-mercapto-1,2,4-triazole〔3-^{14}C〕 or 3-phenyl-5-hydroxy-1, 2, 4-triazole〔3-^{14}C〕 with loss of water. Meanwhile, a part of the intermediate is hydrolysed to radioactive benzoic acid and thiosemicarbazide or semicarbazide, which affords ammonia by alkali with ease. Thus, specific radioactivity of the isolated benzoic acid, which is composed of inactive and active one, shows the magnitude of a side reaction.

The essential reaction routes of 1,4-dibenzoylthiosemicarbazide〔1-*carbonyl*-^{14}C〕 and 1,4-dibenzoylsemicarbazide〔1-*carbonyl*-^{14}C〕 with alkali are shown in Chart 2.

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[3] E. Hoggarth : J. Chem. Soc., **1949**, 1165.

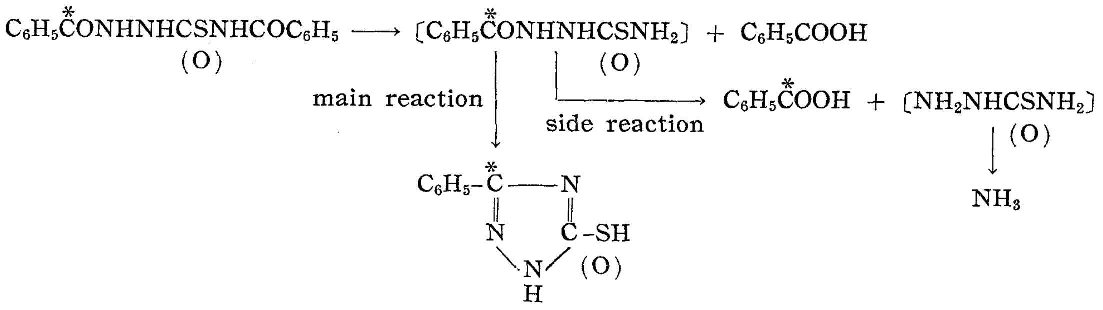

Chart 2.

Experimental

Benzohydrazide[*carbonyl*-^{14}C] (I)—Ethyl benzoate[*carboxyl*-^{14}C] was prepared from 5.3 g. of benzoic acid[*carboxyl*-^{14}C] (4 μc/m*M*), 25 cc. of dehyd. EtOH, and 0.8 cc. of conc. H_2SO_4 by the general method. Yield, 4.9 g. (75%). It was treated with 4.9 cc. of hydrazine hydrate (84%) as usual. Yield, 4 g. (90%). After recrystallization from benzene-EtOH mixture (4 : 1), 3.1 g. of colorless needles melting at 112° was obtained and the radioactivity was 4.05 ± 0.04 μc/m*M*.

1,4-Dibenzoylthiosemicarbazide[1-*carbonyl*-^{14}C] (II)—To a solution of 1.56 g. of (I) in 36 cc. of dehyd. EtOH, 1.5 cc. of benzoyl isothiocyanate was added dropwise with shaking. After 1 hr. at room temperature, the reaction vessel was cooled in an ice bath and precipitated crystals were collected, washed with EtOH and Et_2O. Yield, 2.81 g. (82%). After recrystallization from EtOH 2.4 g. of square plates, m.p. 173° (literature, 173°), was obtained. The radioactivity was 4.08 ± 0.11 μc/m*M*.

Reaction of (II) with 10% NaOH : Benzoic Acid (III)—A mixture of 2.18 g. of (II) and 20 cc. of 10% NaOH was refluxed in N_2 stream for 3 hrs. The yellow color of the reaction mixture was discharged. The effluent gas was washed in 10 cc. of 0.2*N* H_2SO_4 and NH_3 absorbed was determined colorimetrically by the Nessler reagent (NH_3, 2.9 mg., 2.3%). After cool, the reaction mixture was acidified with 10% HCl, the precipitated crystals were collected, and washed with cold water. Yield, 1.9 g. The product was sublimed at 60~65° and at 7 mm. Hg. It formed colorless needles, m.p. 118~120°. Yield, 0.69 g. (78%). The sublimate was further purified by two recrystallizations from boiling water and two sublimations. It yielded 0.4 g. of pure benzoic acid, m.p. 121°. The radioactivity was 0.08 ± 0.01 μc/m*M*.

3-Phenyl-5-mercapto-1,2,4-triazole[3-^{14}C] (IV)—The residual part (1.16 g.) from sublimations of (III) was recrystallized twice from 50% EtOH and yielded 0.8 g. (62%) of colorless needles, m.p. 255~256° (literature, 255~256°). The radioactivity was 4.08 ± 0.12 μc/m*M*.

Reaction of 1-Benzoylthiosemicarbazide with 10% NaOH—A mixture of 1.0 g. of 1-benzoylthiosemicarbazide and 10 cc. of 10% NaOH was refluxed in N_2 stream for 3 hrs. The effluent gas was washed in 10 cc. of 0.2*N* H_2SO_4 and NH_3 absorbed was determined as described in the foregoing (NH_3, 2 mg., 2.3%). After cool, the reaction mixture was acidified with 10% HCl, the precipitated crystals were collected, and washed with cold water. Yield, 0.8 g. The mother liquor was extracted with Et_2O. After evaporation of Et_2O, a small amount of residue was combined with the crystalline product and sublimed. Yield of benzoic acid, m.p. 120°, 8 mg. (1.3%). The residual part of sublimation was recrystallized twice from 50% EtOH and 0.4 g. (44%) of 3-phenyl-5-mercapto-1,2,4-triazole, m.p. 255~256°, was obtained.

1,4-Dibenzoylsemicarbazide[1-*carbonyl*-^{14}C] (V)—To a solution of 1.37 g. of (I) in 14 cc. of dioxane, 1.47 g. of benzoyl isocyanate was added dropwise with shaking. After cooling in an ice bath, the precipitated crystals were collected, and washed with benzene and Et_2O. Yield, 2.23 g. (79%). After two recrystallizations from EtOH-dioxane mixture (10 : 1), 1.14 g. of minute plates, m.p. 216~218°, was obtained. The radioactivity was 4.09 ± 0.08 μc/m*M*. *Anal.* Calcd. for $C_{15}H_{13}O_3N_3$: C, 63.59; H, 4.63; N, 14.83. Found : C, 63.62; H, 4.70; N, 15.02.

Reaction of Non-labeled Specimen of (V) with 10% NaOH—A mixture of 1.0 g. of non-labeled specimen of (V) and 10 cc. of 10% NaOH was refluxed for 3 hrs. After cool, the reaction mixture was acidified with 10% HCl, the precipitated crystals (0.8 g.) were collected and treated, as described for (III). After two sublimations, 0.47 g. (109%) of benzoic acid,† m.p. 120~121° was obtained. The residual part of sublimation was recrystallized from EtOH and 0.2 g. (32%) of colorless needles, m.p. 220~222°, was obtained. It showed no depression in m.p. when mixed with an authentic sample of 1-benzoylsemicarbazide.[4]

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† It was accompanied by decomposition of monobenzoylsemicarbazide.

[4] A. Darapsky : J. prakt. Chem., [2], **76**, 451(1907).

Reaction of (V) with 20% NaOH: Benzoic Acid (VI)—A mixture of 1.05 g. of (V) and 10 cc. of 20% NaOH was refluxed in N_2 stream for 3 hrs. The effluent gas was washed in 20 cc. of 0.2*N* H_2SO_4 and NH_3 absorbed was titrated with 0.2*N* NaOH (NH_3, 22.8 mg., 36%). After cool, the reaction mixture was acidified with 10% HCl, the precipitated crystals were collected, and washed with cold water. Yield, 0.94 g. The crystalline product was sublimed twice as described for (III). Yield of benzoic acid, 0.65 g. (144%). The radioactivity was 1.76±0.04 μc/m*M*.

3-Phenyl-5-hydroxy-1,2,4-triazole[3-^{14}C] (VII)—The residual part from sublimation of (VI) was recrystallized twice from EtOH and yielded 0.1 g. (16.8%) of colorless needles, m.p. 315~317°. *Anal.* Calcd. for $C_8H_7ON_3$: C, 59.62; H, 4.38; N, 26.08. Found: C, 59.80; H, 4.51; N, 25.93. The radioactivity was 4.06±0.07 μc/m*M*.

Reaction of 1-Benzoylsemicarbazide with 20% NaOH—A mixture of 1.0 g. of 1-benzoylsemicarbazide and 10 cc. of 20% NaOH was refluxed in N_2 stream for 3 hrs. The reaction mixture was treated as described for (VI) and (VII). Products obtained were 38.5 mg. (41%) of NH_3, 0.2 g. (30%) of benzoic acid, and 0.3 g. (33%) of 3-phenyl-5-hydroxy-1,2,4-triazole.

Radioactivity Determinations—For the determination of specific radioactivity, all specimens were ignited by a dry combustion method[5] and converted to $Ba^{14}CO_3$. The activity was counted at infinite thickness with a G-M counter tube and compared with the count of a standard $Ba^{14}CO_3$.

Summary

1,4-Dibenzoylthiosemicarbazide (II) is converted by the action of alkali principally into 3-phenyl-5-mercapto-1,2,4-triazole (IV) and benzoic acid. The reaction route was studied by using ^{14}C-tracer technique. It was thereby found that (II) affords 1-benzoylthiosemicarbazide (A) and benzoic acid in the first step and (A) further cyclizes to (IV), while a part of (A) decomposes into benzoic acid and ammonia. 1,4-Dibenzoylsemicarbazide also behaves in analogous manner.

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[5] M. Calvin, *et al.*: "Isotopic Carbon," John Wiley & Sons, Inc., N. Y., 82(1949).