acetate–petroleum ether mixture and obtained as a white powder, m.p. 258–259°.

Anal. Calcd. for $C_7H_4O_7$: C, 42.01; H, 2.01. Found: C, 42.38; H, 2.31.

The trimethyl ester, obtained in 80% yield by esterification of the acid with methanol and sulfuric acid, was recrystallized from ether–petroleum ether mixture; m.p. 79.5–80° (lit.[8] 76°).

Anal. Calcd. for $C_{10}H_{10}O_7$: C, 49.59; H, 4.16. Found: C, 49.56; H, 4.22.

Diethyl α,α-Diethoxy-α′-formylglutarate.—This was obtained in 60% yield as a crude light brown oil from the reaction of 1 mole of diethyl α,α-diethoxyglutarate and 1.3 moles of ethyl formate with 1 g. atom of sodium shot in dry ether. The reaction was carried out and worked up as described above for the preparation of diethyl α,α-diethoxy-α′-ethoxalylglutarate. Unreacted diethyl α,α-diethoxy-glutarate, 30%, was recovered.

Diethyl 2,4-Furandicarboxylate.—To 50 ml. of concentrated sulfuric acid was added with stirring and cooling 18 g. (0.06 mole) of crude diethyl α,α-diethoxy-α′-formylglutarate. The temperature was kept at 45–50°. After five minutes, the solution was cooled to 20° and poured slowly and with stirring onto 500 g. of ice. The resulting mixture was extracted with two 300-ml. portions of ether. The ether solution was washed with aqueous sodium bicarbonate, dried and evaporated leaving a pale yellow oil that crystallized. The yield was 6.9 g. (55%). A sample recrystallized from petroleum ether was obtained as a white powder, m.p. 43–44°.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.70; H, 5.89.

A sample of the ester was saponified by heating with sodium hydroxide solution. Acidification of the solution caused precipitation of 2,4-furandicarboxylic acid, m.p. 274–275° (lit.[8] 266°).

2,4-Thiophenedicarboxylic Acid.—A mixture of 18 g. of crude diethyl α,α-diethoxy-α′-formylglutarate, 13 g. of phosphorus pentasulfide and 80 ml. of toluene was stirred and heated under reflux for 1.5 hours. The toluene solution was washed with two 50-ml. portions of cold 1 *N* sodium hydroxide solution, dried and evaporated. The residue was distilled under reduced pressure to give 11 g. of liquid, b.p. 120–160° (0.5 mm.). This was heated on the steam-bath for two hours with a solution of 5 g. of sodium hydroxide in 10 ml. of water and 25 ml. of ethanol. The solution was evaporated to dryness under reduced pressure. Water, 50 ml., was added, and the resulting solution was acidified with hydrochloric acid causing the precipitation of 4.5 g. (45% yield) of the dicarboxylic acid as a light yellow powder. It was readily recrystallized from water. On the hot stage it remained unmelted up to 300° (lit.[9] m.p. 280° dec.). Above 200° it began to sublime and above 250° it appeared to slowly undergo decarboxylation without melting.

Anal. Calcd. for $C_6H_4O_4S$: C, 41.86; H, 2.34. Found: C, 41.54; H, 2.59.

The dimethyl ester was prepared in excellent yield by esterification with methanol and sulfuric acid. It was recrystallized from petroleum ether; m.p. 123° (lit.[9] 120–121°).

Anal. Calcd. for $C_8H_8O_4S$: S, 16.00. Found: S, 15.92.

2,4-Pyrroledicarboxylic Acid.—A solution of 18 g. (0.06 mole) of crude diethyl α,α-diethoxy-α′-formylglutarate in 100 ml. of dry ether was treated with 12 g. of cold 14% absolute ethanolic ammonia. After the exothermic reaction had subsided, the solution was allowed to stand for about ten minutes and then the solvents were removed by gently warming under reduced pressure. The residual sirup was cooled in an ice-bath, and 50 ml. of concentrated sulfuric acid was added. After about ten minutes at 50° this solution was cooled to 10° and poured slowly into 75 ml. of ice-cold, absolute ethanol. To the resulting solution was added 200 ml. of ethyl acetate followed by 500 ml. of ice-water. The ethyl acetate layer was separated, and the aqueous layer extracted with three additional 100-ml. portions of ethyl acetate. The combined extract was washed with sodium bicarbonate solution, dried and evaporated leaving about 8 g. of brown oil. Since this did not crystallize, it was saponified with aqueous sodium hydroxide. Acidification of the solution (50 ml.) caused precipitation of a brown crystalline solid, which, after two days, was collected and air-dried. The yield was 3.0 g. (42%). A sample recrystallized from water was obtained as a tan powder. It melted and decomposed in a capillary at about 295°, but on a hot stage it remained unmelted up to 300°.

Anal. Calcd. for $C_6H_5NO_4$: C, 46.46; H, 3.25; N, 9.06. Found: C, 46.65; H, 3.58; N, 8.66.

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[8] F. Feist, *Ber.*, **34**, 1994 (1901).

[9] N. Zelinsky, *ibid.*, **20**, 2017 (1887).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Identity of Some 5-Substituted 1,2,4-Triazolones[1]

BY HENRY G. MAUTNER[2] AND W. D. KUMLER

RECEIVED FEBRUARY 11, 1955

The identity of "N$^\beta$-cyano acid hydrazides" was investigated by means of infrared and ultraviolet spectroscopy, and by the measurement of dissociation constants. These compounds were found to be 5-substituted 1,2,4-Δ^4-triazolones. An acidic isomer of these substances was identified as a 5-substituted 1,2,4-Δ^5-triazolone.

Some time ago it was discovered by Bougault[3,4] that the treatment of the semicarbazones of α-keto acids with iodine and sodium hydroxide resulted in the formation of crystalline products, which will hereafter be referred to as I. These substances sublime easily, form addition products with acid and react with ammoniacal silver nitrate to form mono-silver salts. Acetylation and benzoylation yielded mono-substituted products, which retain the ability to form mono-silver salts. Bougault and Popovici[5] identified I as 5-substituted 1,2,4-triazolones (A).

Girard[6,7] found that treatment of I with boiling alkali resulted in the formation of crystalline weak acids, isomeric with I, which will be referred to as II. These compounds, which have very high melting points and sublime easily, form di-silver salts, and react with acetic anhydride to form monoacetyl derivatives. Girard showed that this group of substances was identical with the hydroxytriazoles obtained by Young and Witham[8] by oxidizing aldehyde semicarbazones with ferric

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[1] The material reported here represents part of a thesis presented by Henry G. Mautner in partial fulfillment of the requirements for the Ph.D. degree in pharmaceutical chemistry.

[2] Fellow of the American Foundation for Pharmaceutical Education 1954–1955.

[3] J. Bougault, *Bull. soc. chim.*, **21**, 183 (1917); **25**, 385 (1919).

[4] J. Bougault, *Compt. rend.*, **163**, 237 (1916).

[5] J. Bougault and L. Popovici, *ibid.*, **189**, 188 (1929).

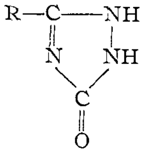
[6] M. Girard, *Ann. chim. phys.*, [11], **16**, 326 (1941).

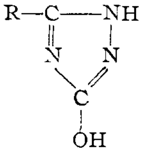
[7] M. Girard, *Compt. rend.*, **212**, 547 (1941).

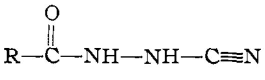
[8] G. Young and E. Witham, *J. Chem. Soc.*, **77**, 228 (1900).

perchlorate. Girard, therefore, identified II as 5-substituted 3-hydroxy-1,2,4-triazoles (B).

Gehlen[9] recently discovered that the treatment of acid hydrazides with cyanogen bromide in cold potassium bicarbonate resulted in the formation of I. He also found that II could be obtained by treating N^{β}-carbamyl acid hydrazides (1-acylsemicarbazides) with boiling alkali. From these facts he concluded that the compounds referred to as I are N^{β}-cyano acid hydrazides (C), and that compounds II are 5-substituted 1,2,4-triazolones (A).


A


B


$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NH-NH-C\equiv N$$
C

We recently prepared "N^{β}-cyanoacetohydrazide" (I_a) and "N^{β}-cyanobenzohydrazide" (I_b) by Gehlen's method. These compounds were found to be completely inert to the addition of hydrogen sulfide, although a wide variety of conditions was utilized. It was also found, as previously reported by Gehlen, that these compounds could not be hydrolyzed by concentrated acid to yield N^{β}-carbamyl acid hydrazides. This seemed astonishing, since it is known[10] that 1-phenyl-2-cyanohydrazine hydrochloride will form 1-phenyl-2-carbamylhydrazine on being poured into cold water, while both 1-phenyl-1-cyanohydrazine and 1-phenyl-2-cyanohydrazine will easily form their respective thiosemicarbazides. It was decided, therefore, to investigate the structures of I and II.

While I_a would be expected to be a weak acid, it was found to be a weak base, with a K_b of 2.3×10^{-12}, while its K_a was too low to be determined. The K_b observed is quite close to the basicity which structure A would be expected to exhibit, the K_b of 1,2,4-triazole being 2×10^{-12}.[11]

The infrared spectra of I_a and I_b were investigated and compared with the spectrum of 1-phenyl-1-cyanohydrazine. While the latter compound showed a sharp peak at 4.5 μ, a region identified with the cyanide group,[12] the "N^{β}-cyano acid hydrazides" showed no evidence of nitrile bands whatever; however, they showed well defined bands in the C=O and C=N regions (Fig. 1).

The ultraviolet spectra of the acetyl and benzoyl compounds were now investigated for evidence of conjugation, which should be present in structure A, but absent in structure C. Both compounds were found to exhibit peaks in the ultraviolet region compatible with conjugation.

It appears, therefore, that the structure A assigned to I by Bougault and Popovici[3] is correct; this structure is also in agreement with the ability of these compounds to form mono-silver salts, and mono-acetyl derivatives, which retain the ability to form silver salts. The substances investigated here, therefore, were 5-methyl- and 5-phenyl-1,2,4-Δ^4-triazolone, respectively.

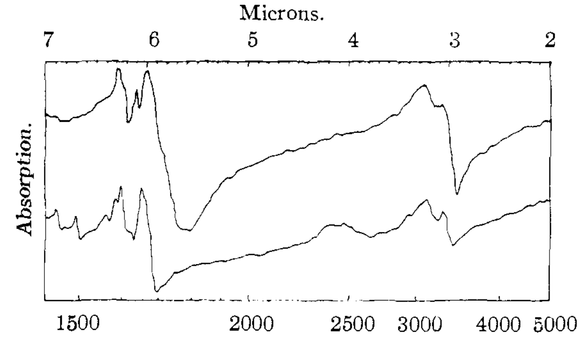


Fig. 1.—(Upper) I_a, 5-methyl-1,2,4-Δ^4-triazolone; (lower) I_b, 5-phenyl-1,2,4-Δ^4-triazolone.

Next a representative compound of type II was prepared by treating I_a with boiling potassium hydroxide, and also by treating N^{β}-carbamylacetohydrazide with boiling base.

The K_a of the resulting substance was found to be 3.7×10^{-10}, which is fairly close to the K_a of succinimide 2.2×10^{-10}.[13] It is probable that the structure assigned to II by Girard[6] B would be more acidic, while structure A assigned to II by Gehlen[9] would show weakly basic properties.

The infrared spectrum of II (Fig. 2) shows that II has a strong ketone band, while there are no peaks which show the presence of a free hydroxyl group. The bands observed at 3.1 and 3.3 μ are in the expected region for –NH, and are comparable with the bands observed in this region in compounds of group I, in which the presence of a hydroxyl group may be excluded. It was also found that the addition of ferric chloride to a solution of II gave no color.

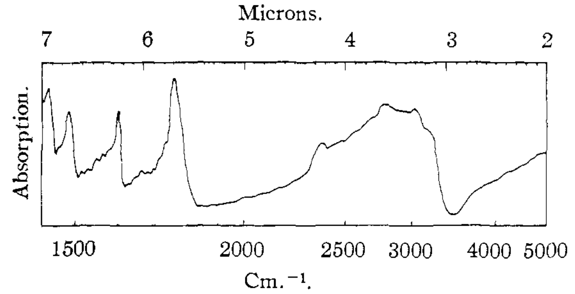
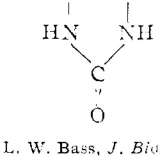


Fig. 2.—II, 5-methyl-1,2,4-Δ^5-triazolone.

The ultraviolet spectrum showed no absorption, indicating the presumable absence of conjugation.

From these observations, in addition to the chemical facts previously noted—such as the ability of II to form di-silver salts—it may be deduced that II is a cyclic ketone with non-conjugated double bonds. The structure 5-methyl-1,2,4-Δ^5-triazolone may, therefore, be assigned to it



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(9) H. Gehlen, *Ann.*, **563**, 185 (1949).

(10) G. Pellizzari and D. Tivoli, *Gazz. chim. ital.*, **22**, [I] 226 (1892).

(11) A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 405.

(12) F. A. Miller in H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 145.

(13) P. A. Levene and L. W. Bass, *J. Biol. Chem.*, **70**, 235 (1926).

Gehlen's[9] recalculated yield data suggest that the electron donating effect of the R part of the acyl groups in N$^{\beta}$-carbamyl acid hydrazides (phenylacetyl 50%, isobutyryl 48%, acetyl 33%, benzoyl 9%) and of the R groups in 5-substituted triazolones of type I (phenylethyl 50%, methyl 20%, phenyl 15%) is related to the yield of II obtained on refluxing the starting material with boiling potassium hydroxide for one hour.

The path of the formation of I by the addition of cyanogen bromide to acid hydrazides still remains to be elucidated. Presumably N$^{\beta}$-cyano acid hydrazides are formed as unstable intermediates, which then cyclize. However, we did not observe such a cyclization when N$^{\beta}$-carbamylacetohydrazide and N$^{\beta}$-carbamylbenzohydrazide were treated with a quantity of potassium bicarbonate equivalent to that used in the cyanogen bromide addition, while carbamylbenzohydrazide would not even react in the presence of cold sodium hydroxide. Therefore, the nitriles must cyclize without the semicarbazides being formed as intermediates.

Experimental

Preparation of Materials.—Compounds I_a, I_b and II were prepared by Gehlen's[9] procedure. Our results for m.p. and analysis confirmed his.

I_a was obtained in 55% yield in the presence of potassium bicarbonate, while in the absence of base an unpurifiable sirupy mass was obtained. The yield of I_b was 92% in the presence, 52% in the absence of base.

Measurement of Ionization Constants.—The K_b of I_b could not be determined because of the extreme insolubility of this compound. The K_b for 5-methyl-1,2,4-Δ^4-triazolone was determined as follows. A sample was dissolved in water from which carbon dioxide had been expelled, and titrated to the 30, 50 and 70% neutralization values, the *p*H being determined at each titration by means of a Cambridge *p*H meter (model L). The K_b was calculated by means of the equation

$$K_b = \frac{\frac{K_w}{(H^+)}\left[\frac{K_w}{(H^+)} + Cl^- - (H^+)\right]}{M - \left[\frac{K_w}{(H^+)} + Cl^- - (H^+)\right]}$$

Duplicate measurements were made. A K_b of $2.3 \pm 0.2 \times 10^{-12}$ was observed.

The K_a of 5-methyl-1,2,4-Δ^5-triazolone (II) was determined in the aforementioned fashion using a Cenco titration *p*H meter. Duplicate determinations gave a value of $3.7 \pm 0.3 \times 10^{-10}$.

Ultraviolet spectra were determined using a Cary recording spectrophotometer model 11 PMS, with quartz cells. Solutions were made up in volumetric flasks from weighed quantities of the compounds. The following values were obtained

	Compound	$\lambda_{max.}$	ϵ
I_a	5-Methyl-1,2,4-Δ^4-triazolone	221	5,450
I_b	5-Phenyl-1,2,4-Δ^4-triazolone	278	15,150
II	5-Methyl-1,2,4-Δ^5-triazolone	End-absorption only	

Infrared spectra were measured with a Perkin-Elmer model 21 infrared spectrophotometer with sodium chloride optics using perfluorokerosene mulls. The compounds investigated were too insoluble in carbon tetrachloride and carbon disulfide for their spectra to be determined in solution.

Treatment of N$^{\beta}$-Carbamylacetohydrazide with Base.—One gram of N$^{\beta}$-carbamylacetohydrazide was dissolved in a solution of 0.7 g. of potassium bicarbonate in 5.5 cc. of water. The solution was left to stand at room temperature for 18 hours and then evaporated to dryness. The residue was extracted with hot ethanol, from which a white solid separated on cooling, which did not sublime and which showed no m.p. depression with N$^{\beta}$-carbamylacetohydrazide.

Treatment of N$^{\beta}$-Carbamylbenzohydrazide with Base.—Two grams of N$^{\beta}$-carbamylbenzohydrazide was finely powdered in a mortar, and suspended in a solution of 1.4 g. of potassium bicarbonate in 24 cc. of water. The mixture was placed in a mechanical shaker for 22 hours. The solution was filtered; a mixed m.p. of the starting material and the product showed no depression.

One gram of N$^{\beta}$-carbamylbenzohydrazide was dissolved in 30 cc. of 5% sodium hydroxide. After one hour at room temperature, the solution was cooled to 0° and treated with concentrated hydrochloric acid. Small white crystals separated, which were recrystallized from ethyl alcohol. The product, which did not sublime, showed no m.p. depression with authentic N$^{\beta}$-carbamylbenzohydrazide, and the infrared spectra were found to be identical.

Acknowledgment.—We wish to thank Dr. Louis A. Strait and Mr. M. K. Hrenoff for measuring the absorption spectra. We are also indebted to Dr. Henry Rapoport for his valuable advice during the investigation.

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