from methyl alcohol alone yielded a product of m.p. 207–208°.

Anal. Calcd. for $C_9H_{17}N_3OCl_2$: C, 42.49; H, 6.74; N, 16.53. Found: C, 42.72; H, 6.95; N, 16.51.

2-Methoxymethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (VII).—A solution of 2.2 g. of sodium nitrite in 25 ml. of water was added with stirring during 5 minutes to a solution of 3.42 g. of 2-methoxymethyl-3-amino-4-methyl-5-aminomethylpyridine dihydrochloride. The temperature of the reaction mixture rose to 50°, and after an additional half-hour of stirring, the mixture was heated at 60–70° for 15 minutes. It was then concentrated to dryness under reduced pressure, and dried thoroughly. The residue was dissolved in absolute alcohol, and the salt removed by filtering. Addition of acetone precipitated 2-methoxymethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride in a yield of 1.37 g. (46%). One recrystallization followed by sublimation gave a product which melted at 177.5–178.5°.

Anal. Calcd. for $C_9H_{14}NO_3Cl$: C, 49.21; H, 6.42; N, 6.38. Found: C, 49.50; H, 6.22; N, 6.62.

2,5-Bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine Hydrochloride (VIII).—2-Methoxymethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride (3.7 g.) was hydrolyzed by means of 2.5 *N* hydrochloric acid in a sealed tube at 155° as described by Harris and Folkers.[4] Crystallization of the product from alcohol resulted in 1.5 g. (43%) of 2,5-bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine hydrochloride. After two recrystallizations from alcohol the product melted at 184–185°.

Anal. Calcd. for $C_8H_{12}NO_3Cl$: C, 46.72; H, 5.84; N, 6.81. Found: C, 46.63; H, 5.76; N, 6.95.

2,5-Bis-(hydroxymethyl)-3-hydroxy-4-methylpyridine.—A solution of the hydrochloride in water was neutralized with sodium bicarbonate. The insoluble material was collected on a filter and washed sparingly with alcohol and then with ether. After drying at 25° (1 mm.) for 3 hours, the material melted at 96–98° and contained one mole of water.

Anal. Calcd. for $C_8H_{11}NO_3 \cdot H_2O$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.24; H, 6.82; N, 7.59.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Condensation of Carboxylic Acid Hydrazides with Carbon Disulfide

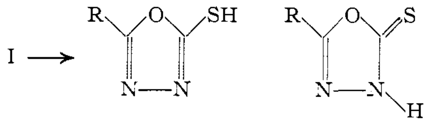
BY C. AINSWORTH

RECEIVED SEPTEMBER 30, 1955

The reaction of carboxylic acid hydrazides, carbon disulfide and alcoholic alkali to form 2-substituted-Δ^2-1,3,4-oxadiazoline-5-thiones has been found to be general for aliphatic, aromatic and heterocyclic carboxylic acid hydrazides and dihydrazides. An interesting thermal isomerization of 2-(3-(5)-pyrazolyl)-Δ^2-1,3,4-oxadiazoline-5-thione (VIII) to 7-mercaptopyrazolo[1,5-d]*as*-triazin-4(5H)-one (X) was observed.

The reaction of a carboxylic acid hydrazide with carbon disulfide was first reported by Busch and Starke,[1] who obtained potassium 3-benzoyldithiocarbazate (I, R = phenyl, R_1 = H) from benzoic acid hydrazide, carbon disulfide and alcoholic potassium hydroxide. Hoggarth[2] observed that compounds of type I when heated lost hydrogen sulfide and formed 2-substituted-1,3,4-oxadiazole-5-thiols (II). This observation was verified recently

$$RCONHNHR_1 + CS_2 + KOH \longrightarrow \underset{\text{I}}{RCONHNHR_1CS_2K} + H_2O$$

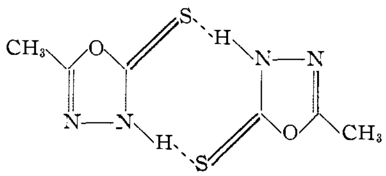


II III

by Young and Wood,[3] who also discussed the mechanism of the reaction.

A study of the reaction in this Laboratory was undertaken prior to Hoggarth's report and was prompted by our interest in azoles. The preparation of compounds of type I[4] has now been extended to heterocyclic (I, R = 4-pyridyl, R_1 = H) and N-substituted (I, R = methyl, R_1 = phenyl) acid hydrazides.

The ring-closed products, not reported previously, are contained in Table I. These compounds were prepared by heating a mixture of the appropriate carboxylic acid hydrazide, carbon disulfide and alcoholic alkali. Structure III, rather than II, was assigned to these products on the basis of the infrared findings.[5] The spectrum of 2-methyl-Δ^2-1,3,4-oxadiazoline-5-thione (III, R = CH_3) was used as a reference and is summarized in Table II. The assignment of the bands below 8 μ was assisted by a dilution study that indicated a monomer–dimer equilibrium. The structure of the dimer is presumed to be



The absorbance of the monomer NH band at 2.90 μ was determined for two different total concentrations (0.136 and 0.513 *M*) and was used to calculate a value of 0.088 for the dissociation constant in chloroform at 27°.

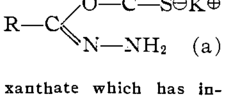
---

(1) M. Busch and M. Starke, *J. prakt. Chem.*, [2] **93**, 49 (1916).

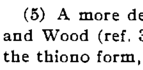
(2) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).

(3) R. W. Young and K. H. Wood, THIS JOURNAL, **77**, 400 (1955).

(4) Young and Wood (ref. 3) considered the possibility of the initial reaction of carbon disulfide taking place at the oxygen atom of the carboxylic acid hydrazide giving rise to a structure such as (a). We find that the infrared spectra of potassium 3-benzoyldithiocarbazate and its methyl ester are very similar to each other, but show none of the characteristic absorption of potassium ethyl xanthate which has intense bands between 8.5 and 10.0 μ attributed to the grouping



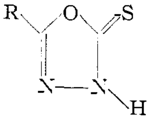
(a)



(5) A more detailed study will be published by H. Boaz. Young and Wood (ref. 3) mentioned the possibility of this system existing in the thiono form, at least in the solid state.

Table I

2-Substituted-Δ^2-1,3,4-oxadiazoline-5-thiones,



R	Yield, %	M.p., °C.	Formula	Analyses, %			
				Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found
C_2H_5	69[e]	44–45	$C_4H_6N_2OS$	36.91	36.70	4.65	4.85
n-C_3H_7	21[f]	47–48	$C_5H_8N_2OS$	41.64	41.73	5.59	5.83
p-$NO_2C_6H_4$	50[g]	207–209	$C_8H_5N_3O_3S$	43.04	43.11	2.26	2.39
$C_6H_5CH_2$	52[h]	130–131	$C_9H_8N_2OS$	56.23	56.23	4.20	4.13
p-$CH_3C_6H_4SO_2NHCH_2$[a]	77[h]	192–193	$C_{10}H_{11}N_3O_3S_2$	42.09	42.27	3.89	4.05
1-Naphthyl	45[i]	217–218	$C_{12}H_8N_2OS$	63.14	63.36	3.53	3.57
2-Pyridyl	88[i]	224–225	$C_7H_5N_3OS$	46.91	47.00	2.81	2.96
3-Pyridyl	72[i]	235–237	$C_7H_5N_3OS$	46.91	47.20	2.81	2.86
2-Indolyl[b]	90[j]	260–261	$C_{10}H_7N_3OS$	55.28	55.58	3.25	3.39
4(5)-Imidazolyl[c]	60[i]	270[k]	$C_5H_4N_4OS$	35.71	35.94	2.40	2.26
3α,7α,12α-Trihydroxy-23-norcholyl[d]	76[h]	260[k]	$C_{25}H_{40}N_2O_4S$	64.62	64.32	8.68	8.72

The starting carboxylic acid hydrazides were prepared according to the procedures reported by: [a] R. Schonheimer, *Z. physiol. Chem.*, **154**, 203 (1926); [b] A. Piccinini and L. Salmoni, *Gazz. chim. ital.*, **32**, [I] 252 (1902) [*Chem. Zentr.*, **73**, I, 1229 (1902)]; [c] I. E. Balaban, *J. Chem. Soc.*, **133**, 268 (1930); [d] S. Bondi and E. Muller, *Z. physiol. Chem.*, **47**, 499 (1906). [e] Obtained by distillation. Recrystallization solvent: [f] benzene–petroleum ether; [g] ethyl alcohol; [h] ethyl alcohol–water; [i] water; [j] acetic acid. [k] Melted with decomposition.

Table II[6]

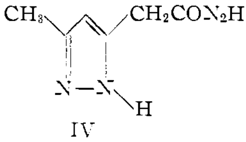
Summary of the Infrared Spectrum of 2-Methyl-Δ^2-1,3,4-Oxadiazoline-5-thione in Chloroform Solution

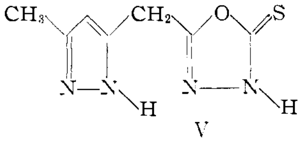
Wave length, μ	Assignment
2.90	NH, monomer
3.16	NH, dimer
3.30, 3.35	CH_3
6.12	C=N, stretching
6.66	C–NH, dimer
6.79	C–NH, monomer
7.20	CH_3, deformation
7.57	C=S, stretching, dimer
7.65	C=S, stretching, monomer

The compounds listed in Table I showed maxima that corresponded to those assigned to NH, C–NH and C=S in 2-methyl-Δ^2-1,3,4-oxadiazoline-5-thione. The bands in the spectra of 2-(pyridyl, indolyl and p-nitrophenyl)-Δ^2-1,3,4-oxadiazoline-5-thiones could not be so definitely assigned as in the simpler molecules. The compound obtained from p-tosylglycylhydrazide was assigned the general structure III.[7]

Formic acid hydrazide did not react like other acid hydrazides, but it yielded 2-mercapto-Δ^2-1,3,4-thiadiazoline-5-thione, a product that appears to be formed also from hydrazine and carbon disulfide in the presence of base.[8] Dicarboxylic acid hydrazides, however, reacted normally. Oxalic and terephthalic-acid dihydrazides formed, respectively, 2,2′-bi-(Δ^2-1,3,4-oxadiazoline-5-thione) and 2,2′-p-phenylenebis-(Δ^2-1,3,4-oxadiazoline-5-thione).

The product obtained from 2-hydroxy-6-methyl-4-pyrone and hydrazine hydrate,[9] namely, compound IV, was heated with carbon disulfide in alcoholic alkali and compound V was formed.


IV


V

The infrared spectrum of compound V exhibited maxima corresponding to those for the general structure III, and the ultraviolet absorption of compound V was very nearly identical with that of 2-methyl-Δ^2-1,3,4-oxadiazoline-5-thione.

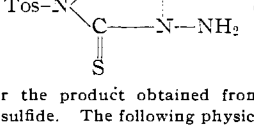
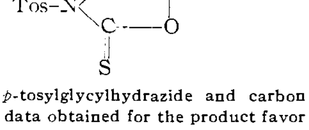
3(5)-Pyrazolecarboxylic acid hydrazide (VI) and carbon disulfide in alcoholic potassium hydroxide formed compound VII, which on heating lost hydrogen sulfide and gave compound VIII. The infrared spectrum of compound VIII was obtained as a mull and showed strong absorption at 3.2 (NH), 6.1 (C=N), 6.8 (C–NH) and 7.3, 7.4 μ (C=S). The formation of compound VIII indicated that the addition of carbon disulfide took place at the carboxylic acid hydrazide function rather than on the pyrazole nitrogen. When compound VIII was treated with Raney nickel, compound IX was formed.

An unexpected thermal isomerization took place when compound VIII was heated under reduced pressure. The product that was obtained from the attempted sublimation of compound VIII had the same elemental composition as the starting material, but had different physical properties. The melting point was about 20° lower. The in-

---

(6) A Beckman IR-2T infrared spectrophotometer was used.

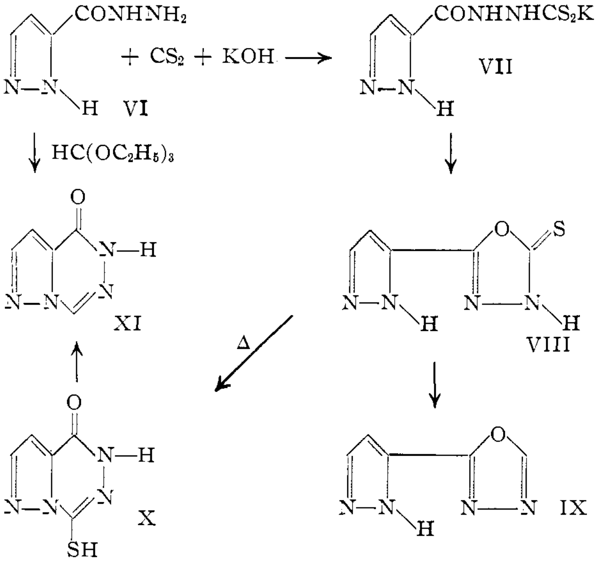
(7) A referee suggested the possibility of structures such as


or


for the product obtained from p-tosylglycylhydrazide and carbon disulfide. The following physical data obtained for the product favor the oxadiazoline-5-thione assignment. The pK'_a values in 66% dimethylformamide are 5.6 and 11.9 (initial pH 4.2). 2-Methyl-Δ^2-1,3,4-oxadiazoline-5-thione in the same solvent has a pK'_a of 6.0. The ultraviolet absorption spectrum in methanol has maxima at 228 and 264 mμ with log ε values of 4.18 and 4.16, respectively. Bands at 6.7 μ for C–NH and 7.5 μ for C=S occur in the infrared spectrum.

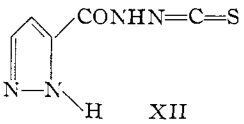
(8) M. Busch, *Ber.*, **27**, 2507 (1894).

(9) C. Ainsworth and R. G. Jones, This Journal, **76**, 3172 (1954).



frared and ultraviolet absorption spectra were greatly different from those of compound VIII, but corresponded to the data expected for compound X. The product was shown to be X by the fact that treatment of it with Raney nickel gave pyrazolo[1,5-*d*]*as*-triazin-4(5*H*)-one (XI), a material reported recently[10] from compound VI and ethyl orthoformate. The infrared spectrum of compound X was obtained as a mull and showed absorption at 3.2 (NH), 4.0 (narrow, medium intensity, SH) and 5.9 μ (C=O). The infrared absorption spectra of compounds X and XI were very similar to each other. Compound X was recovered unchanged after sublimation.

Models of compound VIII showed that the pyrazole NH and the thione-carrying carbon do not approach each other. Compound XII has been suggested as a possible intermediate[11] during the thermal isomerization of compound VIII to X. The NH of the pyrazole moiety of XII might be expected to add to the isothiocyanate grouping to form compound X.



XII

To further study this type of isomerization, 2-(2-indolyl)-Δ^2-1,3,4-oxadiazoline-5-thione and 2-(3-(5)-imidazolyl)-Δ^2-1,3,4-oxadiazoline-5-thione (see Table I) were heated under reduced pressure. Unfortunately, the compounds did not sublime smoothly but required temperatures near their decomposition points. The infrared data obtained on the small amount of sublimate indicated that the imidazole compound had undergone change, but the indole compound had not.

Acknowledgments.—The microanalyses were performed by W. L. Brown, H. L. Hunter, G. M. Maciak and G. Beckmann. The author is grateful to H. Boaz and J. W. Forbes for interpretations of the physical-chemical data.

Experimental[12]

2-Substituted-Δ^2-1,3,4-oxadiazoline-5-thiones. General Procedure.—A mixture of 0.1 mole of carboxylic acid hydrazide, 0.1 mole of potassium hydroxide, 20 ml. of carbon disulfide and 100 ml. of alcohol (ethyl or *n*-amyl) was heated under reflux until the evolution of hydrogen sulfide had nearly stopped (one to seven days). After removal of the solvent, the residue was dissolved in water and acidified with dilute hydrochloric acid. The resulting acid was collected, washed with water and air-dried. The compounds listed in Table I were prepared in this manner.

A mixture of 3.9 g. (0.02 mole) of terephthalic acid dihydrazide,[13] 2.4 g. (0.04 mole) of potassium hydroxide, 15 ml. of carbon disulfide and 100 ml. of *n*-amyl alcohol was heated under reflux for three days. The product was isolated according to the general procedure described above, and 2,2′-*p*-phenylenebis-(Δ^2-1,3,4-oxadiazoline-5-thione) was obtained from acetic acid as cubes, m.p. >300°; infrared maxima at 3.2, NH; 6.8, C-NH and 7.4 μ, C=S (mull). The yield was 3.5 g. (63%).

Anal. Calcd. for $C_{10}H_6N_4O_2S_2$: C, 43.15; H, 2.17; N, 20.13. Found: C, 43.38; H, 2.28; N, 20.10.

Similarly, oxalic acid dihydrazide,[14] carbon disulfide and alcoholic alkali yielded 2,2′-bis-(Δ^2-1,3,4-oxadiazoline-5-thione), obtained from water as prisms, m.p. >300°; infrared maxima at 3.1, NH; 6.9, 7.0, C-NH; and 7.7 μ, C=S (mull). The yield was 30%.

Anal. Calcd. for $C_4H_2N_4O_2S_2$: N, 27.71; S, 31.71. Found: N, 27.92; S, 31.72.

Formic acid hydrazide and carbon disulfide in alcoholic alkali was treated according to the general procedure given above. The 2-mercapto-Δ^2-1,3,4-thiadiazolidine-5-thione that resulted was recrystallized from ethyl acetate and obtained as prisms, m.p. 170° dec. (lit.[8] m.p. 168° dec.); infrared maxima at 3.27, NH; 4.10, SH; 6.65, C-NH and 7.90 μ, C=S. The yield was 15%.

Anal. Calcd. for $C_2H_2N_2S_3$: S, 64.03. Found: S, 64.30.

Potassium 3-Isonicotinyldithiocarbazate.—A mixture of 13.7 g. (0.1 mole) of isonicotinic acid hydrazide, 6 g. (0.1 mole) of potassium hydroxide, 10 ml. of carbon disulfide and 200 ml. of absolute ethyl alcohol was stirred at room temperature for three hours. About 200 ml. of dry ether was added and the product separated, in almost quantitative yield, as a yellow solid, m.p. >300°.

Anal. Calcd. for $C_7H_6KN_3OS_2$: S, 25.51. Found: S, 25.41.

Potassium 3-Acetyl-2-phenyldithiocarbazate.—A mixture of 4.5 g. (0.03 mole) of 1-acetyl-2-phenylhydrazine,[15] 1.8 g. (0.03 mole) of potassium hydroxide, 5 ml. of carbon disulfide and 100 ml. of absolute ethyl alcohol was stirred at room temperature for three hours. Ether was added, and the potassium 3-acetyl-2-phenyldithiocarbazate was obtained, in high yield, as a yellow solid, m.p. 185° dec.

Anal. Calcd. for $C_9H_9KN_2OS_2$: S, 24.26. Found: S, 23.86.

2-[(3(5)-Methyl-5(3)-pyrazolyl)-methyl]-Δ^2-1,3,4-oxadiazoline-5-thione (V).—A mixture of 1.5 g. (0.01 mole) of 3(5)-methyl-5(3)-pyrazoleacetic acid hydrazide,[9] 0.6 g. (0.01 mole) of potassium hydroxide, 5 ml. of carbon disulfide and 50 ml. of ethyl alcohol was heated under reflux overnight. After removal of the solvent, the residue was dissolved in water and treated with 1.6 ml. of 6 *N* hydrochloric acid. The solid that formed was collected, washed with water and recrystallized from 75 ml. of hot water. On cooling 0.5 g. (25% yield) of compound V separated as needles, m.p. 223–224° dec.; λ_{max} 262 mμ, log ε 4.26 (methanol); infrared maxima at 3.1, NH; 6.2, C=N, 6.5, C-NH and 7.3 μ, C=S (mull).

---

[10] C. Ainsworth, THIS JOURNAL, **77**, 1148 (1955). The spectrum of compound XI was obtained as a mull and showed absorption at 3.19, 3.25 (NH) and 5.87 μ (C=O).

[11] Discussion with C. C. Price.

[12] Melting points were determined with a Fisher–Johns assembly and are uncorrected.

[13] E. Davidis, *J. prakt. Chem.*, [2] **54**, 81 (1896).

[14] W. Borsche, W. Muller and C. A. Bodenstein, *Ann.*, **475**, 120 (1929).

[15] T. O. Jones, R. E. Halter and W. L. Myers, THIS JOURNAL, **75**, 6055 (1953).

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.84; H, 4.11. Found: C, 42.87; H, 4.25.

3(5)-Pyrazolecarboxylic Acid Hydrazide and Carbon Disulfide (a).—A mixture of 3.1 g. (0.025 mole) of 3(5)-pyrazolecarboxylic acid hydrazide,[16] 1.3 g. of potassium hydroxide and 5 ml. of carbon disulfide in 50 ml. of ethyl alcohol was stirred together at room temperature for 30 minutes. About 50 ml. of dry ether was added and the product separated in almost quantitative yield. Potassium 3-(3(5)-pyrazolecarbonyl)-dithiocarbazate (VII) melted with decomposition at about 210°, resolidified and melted again with dec. at 255–260°; $\lambda_{\max}$ 303 mμ, log ϵ 4.01 (methanol).

Anal. Calcd. for $C_5H_5KN_4OS_2$: C, 24.98; H, 2.10; N, 23.31; S, 26.68. Found: C, 25.37; H, 2.34; N, 23.60; S, 26.85.

A sample of potassium 3-(3(5)-pyrazolecarbonyl)-dithiocarbazate was heated at 230° for 15 minutes. The product was dissolved in water and acidified with dilute hydrochloric acid. The solid that formed was collected and recrystallized from water. It was shown by infrared data to be identical with compound VIII (see below).

(b).—A mixture of 6.3 g. (0.05 mole) of 3(5)-pyrazolecarboxylic acid hydrazide,[16] 2.8 g. (0.05 mole) of potassium hydroxide, 5 ml. of carbon disulfide and 200 ml. of ethyl alcohol was heated under reflux for three days. After removal of the alcohol the residue was dissolved in 100 ml. of water and acidified with dilute hydrochloric acid. The solid that separated was collected, washed well with water and air-dried. It melted between 200 and 205°. The product[17] was recrystallized from methanol–water mixture and 5.3 g. (63% yield) of 2-(3(5)-pyrazolyl)-Δ^2-1,3,4-oxadiazoline-5-thione (VIII) was obtained. A sample was recrystallized from methanol and obtained as a white solid, m.p. 220° dec.; $\lambda_{\max}$ 241 mμ, log ϵ 3.89; $\lambda_{\max}$ 286 mμ, log ϵ 4.24 (methanol); pK'_a 5.4 (66% dimethylformamide).

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.71; H, 2.40; N, 33.32. Found: C, 35.86; H, 2.60; N, 33.05.

A mixture of 2 g. of 2-(3(5)-pyrazolyl)-Δ^2-1,3,4-oxadiazoline-5-thione, 50 ml. of 95% ethyl alcohol and 5 g. of moist Raney nickel was heated under reflux for three hours. After removal of the nickel by filtration the filtrate was evaporated to dryness. The residue was recrystallized from hot water, and on cooling 200 mg. of 2-(3(5)-pyrazolyl)-1,3,-4-oxadiazole (IX) was deposited. It melted at 200–202°. A sample was obtained by sublimation, m.p. 204–205°; $\lambda_{\max}$ 236 mμ, log ϵ 4.06 (methanol).

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.13; H, 3.11; N, 41.20.

7-Mercaptopyrazolo[1,5-*d*]*as*-triazin-4(5*H*)-one (X).—A sample of 2-(3(5)-pyrazolyl)-Δ^2-1,3,4-oxadiazoline-5-thione was heated at 200° and 0.5 mm. of mercury pressure. The product that was obtained as the sublimate was 7-mercaptopyrazolo[1,5-*d*]*as*-triazin-4-(5*H*)-one, m.p. 201–202°; $\lambda_{\max}$ 234 mμ, log ϵ 3.81; $\lambda_{\max}$ 262 mμ, log ϵ 4.11; $\lambda_{\max}$ 297 mμ, log ϵ 4.09 (methanol); pK'_a 4.1 (66% dimethylformamide).

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.71; H, 2.40; S, 19.07. Found: C, 35.37; H, 2.52; S, 18.64.

A mixture of 1 g. of 7-mercaptopyrazolo[1,5-*d*]*as*-triazin-4(5*H*)-one, 50 ml. of 95% ethyl alcohol and 5 g. of moist Raney nickel was heated under reflux for six hours. After removal of the nickel by filtration, the filtrate was evaporated to dryness. The residue was dissolved in a small amount of 1 *N* sodium hydroxide and then acidified with acetic acid. The solid that separated was recrystallized from water and pyrazolo[1,5-*d*]*as*-triazin-4(5*H*)-one (XI) was obtained as needles, m.p. 265–267°; $\lambda_{\max}$ 264 mμ, log ϵ 3.86 (methanol). The melting point was not depressed when mixed with pyrazolo[1,5-*d*]*as*-triazin-4(5*H*)-one[10] prepared from 3(5)-pyrazolecarboxylic acid hydrazide and triethyl orthoformate.

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 43.95; H, 3.35; N, 41.17.

INDIANAPOLIS 6, INDIANA

---

[16] L. Knorr, *Ber.*, **37**, 3520 (1904).

[17] The first lot of this material was treated with Raney nickel and a small yield of compound XI was isolated, indicating that the product of this lot was a mixture of compounds VIII and X. Subsequent preparations did not appear to contain any of compound X.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Reaction of Phthaloylglycyl Chloride with 2-Methyl-2-thiazoline[1]

BY JOHN C. SHEEHAN, CURT W. BECK, KENNETH R. HENERY-LOGAN AND JAMES J. RYAN[2]

RECEIVED APRIL 3, 1956

As part of a program directed toward the synthesis of compounds structurally related to the penicillins, the reaction of phthaloylglycyl chloride (I) with 2-methyl-2-thiazoline (II) in the presence of triethylamine has been studied. Rather than yielding a β-lactam-thiazolidine structure, expected by analogy to the 2-phenyl-2-thiazoline case, the reaction leads to 2-methylene-3-phthaloylglycylthiazolidine (III) at low temperature and in the presence of one equivalent of base, and to 2-methyl-3-phthaloylglycyl-4-thiazoline (V) at higher temperatures and in the presence of excess base. The structures of compounds III and V were established by hydrogenation to 2-methyl-3-phthaloylglycylthiazolidine (VI). A mechanism for the reaction is proposed. Analogous products were obtained using phthaloyl-β-alanyl chloride (Ia) as the acylating agent.

The reaction of diacyl glycyl chlorides with 2-phenyl-2-thiazolines in the presence of triethylamine, yielding fused β-lactam-thiazolidine ring systems, has been a promising approach toward the synthesis of penicillin-type compounds.[3] In an investigation of the scope of this synthesis, we have studied the action of phthaloylglycyl chloride (I) and phthaloyl-β-alanyl chloride (Ia) on 2-methyl-2-thiazoline (II).

It was found that, depending on reaction conditions, either of two distinct types of products was formed. In the presence of one equivalent of triethylamine, I and II formed a "low temperature adduct" III, which precipitated together with triethylammonium chloride. The products were best separated by an aqueous wash, which converted III into a crystalline "hydrated adduct" IV with the addition of one equivalent of water. At 60°, and in the presence of excess triethylamine, a "high temperature adduct" V was obtained, which is isomeric with III, but which did not take up water on washing. Under conditions lying between these two extremes, products were formed which, after washing with water, analyzed for mixtures of compounds IV and V.

None of the products obtained possesses infrared absorption indicative of a β-lactam structure.

---

[1] This work was in part supported by grants from Swift and Co., Chicago, Illinois, and Bristol Laboratories, Syracuse, New York.

[2] Abstracted from parts of the Ph.D. Dissertations of J. J. Ryan, M.I.T., June 1949, and C. W. Beck, M.I.T., January 1955.

[3] J. C. Sheehan and G. D. Laubach, THIS JOURNAL, **73**, 4376 (1951).