TABLE I

RATES OF ELIMINATION OF SALTS OF *cis*-2-HYDROSULFATOCYCLOPENTANESULFONIC ACID

Time, min.	Acid, ml.	Concn. of base	x	$k_2 \times 10^7$	$k_1 \times 10^3$
Barium salt, standard acid 0.02726 N, T = 75°					
0	18.90	0.02067	.....	..	..
30	18.38	.02011	0.00056	3.11	1.53
90	17.05	.01865	.00202	3.74	1.90
180	13.90	.01521	.00546	5.06	2.84
300	9.35	.01022	.01045	5.78	3.91
390	6.70	.00735	.01332	5.69	4.43
480	3.90	.00427	.01640	5.69	5.48
Barium salt, standard acid 0.03380 N, T = 85°					
0	15.05	0.02035	.....	..	
15	14.80	.02001	0.00034	3.78	
45	13.76	.01860	.00175	6.49	
105	11.28	.01525	.00510	8.09	
165	8.51	.01151	.00884	8.92	
230	6.10	.00825	.01210	8.76	
285	4.20	.00568	.01467	8.56	
Sodium salt, standard acid 0.02726 N, T = 75°					
0	19.22	0.02095			
61	18.95	.02066			
150	18.80	.02049			
320	18.70	.02039			
500	18.65				

0.04194 M in the salt and 100 ml. of 0.04194 N sodium hydroxide were thermostated and mixed. Twenty-five ml. aliquots taken at approximate time intervals were removed, cooled in an ice-bath and titrated with standard hydrochloric acid.

Rates of Elimination of Pyridine from 2-(1-Proto-1-pyridyl)-1-hexanesulfonate and 2-Phenyl-2-(1-proto-1-pyridyl)-1-ethanesulfonate.—Portions of 100 ml. each of a 0.04284 N sodium hydroxide solution and 0.04284 M aqueous solution of the dipolar ion, which had been equilibrated at 65.0° were mixed. Samples of 25.0 ml. of the reaction mixture were pipeted into an excess of 0.03380 N hydrochloric acid, and the solution back-titrated with the standard base solution using phenolphthalein indicator. This run gave k_2 = 1.31 × 10^{-3} l. sec.$^{-1}$ mole^{-1}. A similar run using a two molar quantity of base gave k_2 = 1.26 × 10^{-3}. An analogous experiment with equimolar concentrations of 2-phenyl-2-(1-proto-1-pyridyl)-1-ethanesulfonate (VII) and sodium hydroxide gave k_2 = 1.05 × 10^{-3} l. sec.$^{-1}$ mole^{-1}.

Rate of Elimination of Pyridine from *trans*-2-(1-Proto-1-pyridyl)-1-cyclopentanesulfonate (V).—In one experiment 10-ml. portions of a 0.04387 N solution of V were added from a buret to test-tubes each containing 10.0 ml. of 0.04387 N sodium hydroxide. The tubes were tightly stoppered with rubber stoppers, and were heated in an insulated vessel through which steam was passed. The temperature was maintained at 99.0 ± 0.5°. At appropriate time intervals, the samples were removed and added to an excess of 0.03229 N hydrochloric acid, and the acid was back-titrated with the standard base. The third-order constant calculated from these data, k_3 = 6.0 × 10^{-2} l. sec.$^{-1}$ mole^{-2}, had an average deviation in the constant of 5%. The values calculated for a second order "constant" × 10^4 were: 6.4, 5.6, 5.5, 4.6, 4.4, 3.8, 3.6.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

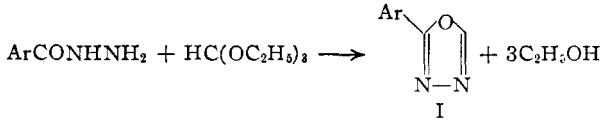
The Condensation of Aryl Carboxylic Acid Hydrazides with Orthoesters

BY C. AINSWORTH

RECEIVED SEPTEMBER 16, 1954

Nineteen 2-aryl-1,3,4-oxadiazoles, or 2-alkyl-5-aryl-1,3,4-oxadiazoles, were prepared by the condensation of aryl carboxylic acid hydrazides with orthoesters. In two examples the 1-acyl-2-ethoxymethylenehydrazine intermediate was isolated. Thiobenzoic acid hydrazide and ethyl orthoformate formed 2-phenyl-1,3,4-thiadiazole. 3-Pyrazolecarboxylic acid hydrazide and ethyl orthoformate gave pyrazolo[1,5-*d*]*as*-triazin-4(5*H*)-one rather than the oxadiazole.

Although 2,5-disubstituted-1,3,4-oxadiazoles have been prepared by dehydration of 1,2-diacylhydrazines,[1] no reference to 2-substituted-1,3,4-oxadiazoles of the type represented by I, appears in the literature. These latter compounds have now been made in good yield by the condensation of an aromatic carboxylic acid hydrazide with *excess* ethyl orthoformate. Extension of this reaction to higher orthoesters has led to the formation of 2-alkyl-5-aryl-1,3,4-oxadiazoles.



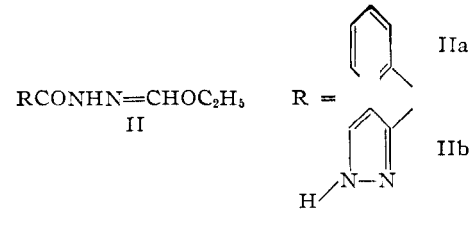
I

In carrying out this process experimentally, the reactants were heated under mild reflux after which the excess orthoester was removed and the oxadiazole purified by distillation or recrystallization. The compounds listed in Table I were prepared in this fashion. The starting aromatic carboxylic acid hydrazide may be carboxylic or heterocyclic.

(1) For a leading reference covering the older literature see R. Stolle, *J. prakt. Chem.*, [2] **68**, 130 (1903).

It is interesting to note that the dihydrazide of terephthalic acid reacts with ethyl orthoformate to give *p*-phenylene-bis-(1,3,4-oxadiazole-2).

In two examples, compounds of the type represented by II were isolated. Picolinic acid hydrazide with excess ethyl orthoformate, heated under re-

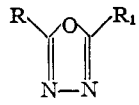


flux overnight, gave rise to 1-ethoxymethylene-2-picolinylhydrazine (IIa). Compound IIa lost ethanol when heated at 200° and formed 2-(2-pyridyl)-1,3,4-oxadiazole. This suggests that II is an intermediate in the formation of I, perhaps through its enol III.

Two products were obtained from 3-(or 5)-pyrazolecarboxylic acid hydrazide and ethyl orthoformate. The properties of one were in agreement

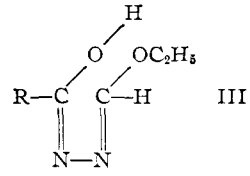
TABLE I

2-SUBSTITUTED OR 2,5-DISUBSTITUTED-1,3,4-OXADIAZOLES



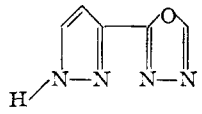
R	R_1	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl	H	70[a]	34–35	$C_8H_6N_2O$	65.75	65.95	4.14	3.98
o-Methoxyphenyl	H	79[b]	47–49	$C_9H_8N_2O_2$	61.36	61.61	4.58	4.78
p-Chlorophenyl	H	78[f]	134–135	$C_8H_5ClN_2O$	53.20	53.06	2.79	3.11
p-Nitrophenyl	H	79[f]	156–157	$C_8H_5N_3O_3$	50.26	50.53	2.64	2.75
α-Naphthyl	H	63[g]	65–66	$C_{12}H_8N_2O$	73.46	73.32	4.11	4.24
4-Pyridyl	H	82[h]	120–121	$C_7H_5N_3O$	57.14	56.97	3.43	3.56
3-Pyridyl	H	68[i]	75–76	$C_7H_5N_3O$	57.14	57.14	3.43	3.56
2-Quinolyl	H	70[f]	174–175	$C_{11}H_7N_3O$	67.00	66.92	3.58	3.71
Phenyl	CH_3	70	67–68[l]	$C_9H_8N_2O$	67.48	67.37	5.03	5.06
4-Pyridyl	CH_3	70[j]	150–151	$C_8H_7N_3O$	59.62	59.89	4.38	4.60
Phenyl	C_2H_5	80[c]	[m]	$C_{10}H_{10}N_2O$	68.95	68.82	5.79	5.86
o-Methoxyphenyl	C_2H_5	79[d]	[m]	$C_{11}H_{12}N_2O_2$	64.69	64.66	5.92	6.03
p-Chlorophenyl	C_2H_5	86[h]	93–94	$C_{10}H_9ClN_2O$	57.56	57.70	4.35	4.44
p-Nitrophenyl	C_2H_5	92[h]	133–134	$C_{10}H_9N_3O_3$	54.79	54.73	4.14	4.38
α-Naphthyl	C_2H_5	80[e]	[m]	$C_{14}H_{12}N_2O$	74.99	75.21	5.38	5.56
4-Pyridyl	C_2H_5	84[k]	57–58	$C_9H_9N_3O$	61.70	61.54	5.18	5.28

Purified by distillation: [a] b.p. 110° (0.5 mm.); [b] b.p. 125° (0.03 mm.); [c] b.p. 105° (0.1 mm.); [d] b.p. 135° (0.05 mm.); [e] b.p. 160° (0.1 mm.). Recrystallization solvent: [f] ethanol; [g] benzene–petroleum ether; [h] 95% ethanol; [i] ethyl acetate–petroleum ether; [j] benzene; [k] petroleum ether. [l] R. Stolle, *Ber.*, **45**, 273 (1912), reported 67°. [m] Liquid at room temperature.

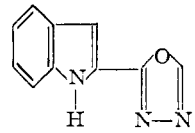


III

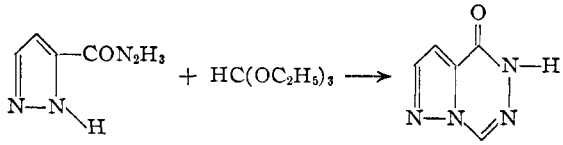
with the intermediate IIb. The other compound had the correct analysis for IV; however, it was soluble in dilute aqueous base and was reprecipitated by acid. These properties and infrared studies[2] were not in agreement with structure IV but suggested V or its tautomer. In this example the heterocyclic nitrogen was involved in ring closure rather than the oxygen.



IV

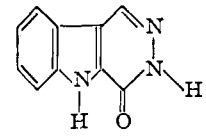


VI

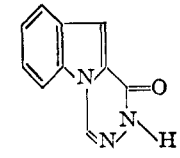


V

2-Indolecarboxylic acid hydrazide and ethyl orthoformate gave a single compound, $C_{10}H_7N_3O$. Considering the known activity of the 3-position of indole and by analogy with the reaction of 3-pyrazolecarboxylic acid hydrazide, structure VII or VIII might be expected. The compound, however, was different from VII, which was prepared by an unequivocal method,[3] and since it was not soluble in base, VIII also was eliminated. The starting acid hydrazide was obtained when the product was hydrolyzed under mild acidic conditions. These findings and infrared data[2] supported structure VI.



VII



VIII

The reaction of orthoesters with thiocarboxylic acid hydrazides appears to take place in the same way as carboxylic acid hydrazides. Thus, thiobenzoic acid hydrazide[4] with excess ethyl orthoformate formed 2-phenyl-1,3,4-thiadiazole.[5]

Acknowledgments.—The microanalyses were performed by W. L. Brown, H. L. Hunter, G. M. Maciak and Gloria Beckmann. The author is grateful also to Dr. Reuben G. Jones for helpful suggestions and to Dr. Harold E. Boaz for physical-chemical interpretations.

Experimental[6]

General Procedure.—A mixture of 20 g. of the carboxylic acid hydrazide and about 150 ml. of orthoester[7] was heated to boiling. Alcohol was evolved. After heating under mild reflux overnight, the excess orthoester was removed by evaporation under reduced pressure. The residue, if liquid, was distilled under diminished pressure or, if a solid, was recrystallized from an appropriate solvent. The compounds contained in Table I were prepared in this manner.

***p*-Phenylene Bis-(1,3,4-oxadiazole-2).**—A mixture of 3.9 g. of terephthalic acid dihydrazide[8] and 400 ml. of triethyl orthoformate was heated under reflux overnight. The

(2) To be reported by Dr. Harold E. Boaz.

(3) Unpublished findings of Dr. E. R. Shepard.

(4) B. Holmberg, *Arkiv Kemi, Mineral. Geol.*, **17A**, No. 23 (1944); [*Chem. Zent.*, [2] **115**, 210 (1944)].

(5) M. Ohta, R. Hagiwara and Y. Mizushima, *J. Pharm. Soc. Japan*, **73**, 701 (1953).

(6) Melting points were determined with a Fisher–Johns apparatus and are reported as read.

(7) Triethyl orthoformate, acetate and propionate were used.

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

excess orthoformate was removed, by heating under reduced pressure, and the residue was washed with cold ethanol. A sample was recrystallized from ethanol and obtained as plates, m.p. 275°. The yield was 3.9 g. (90%).

Anal. Calcd. for $C_{10}H_6N_4O_2$: C, 56.07; H, 2.82; N, 26.16. Found: C, 56.23; H, 2.64; N, 25.86.

2-(2-Indolyl)-1,3,4-oxadiazole (VI).—A mixture of 3.5 g. (0.02 mole) of 2-indolecarboxylic acid hydrazide[9] and 100 ml. of triethyl orthoformate was heated under reflux overnight. The excess orthoformate was removed, by heating under reduced pressure, and a solid remained. After washing with ethanol the product (1.8 g., 50% yield) was collected on a filter and air-dried. It melted over the range 196–200°. An analytical sample was obtained by sublimation at 180° (0.1 mm.), m.p. 207–208°.

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 65.03; H, 3.84; N, 22.74.

A one-gram sample dissolved in a solution formed from 10 ml. of ethanol and 10 ml. of 3 *N* hydrochloric acid was evaporated on the steam-bath. The residue was dissolved in about 75 ml. of water and 1 *N* sodium hydroxide was added to *p*H 10. The mixture was extracted with ethyl acetate. After removal of the ethyl acetate, by evaporation, the residue was recrystallized from ethanol and obtained as plates, m.p. 250°. The melting point was unchanged when mixed with authentic 2-indolecarboxylic acid hydrazide. In addition, the hydrolysis product and 2-indolecarboxylic acid hydrazide showed identical absorption in the infrared.

1-Ethoxymethylene-2-picolinylhydrazine (IIa).—A mixture of 27.4 g. (0.2 mole) of picolinic acid hydrazide and 100 ml. of triethyl orthoformate was heated under reflux overnight. After removal of the excess orthoformate, the product was distilled under reduced pressure, b.p. 140° (0.1 mm.). The yield was 35 g. (90%). A sample was recrystallized from ethyl acetate and obtained as cubes, m.p. 87–88°.

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.83; H, 5.76; N, 22.04.

(9) A. Piccinini and L. Salmoni, *Gazz. chim. ital.*, **32**, [I], 252 (1902); [*Chem. Zentr.*, [1] **73**, 1229 (1902)].

2-(2-Pyridyl)-1,3,4-oxadiazole.—A two-gram sample of 1-ethoxymethylene-2-picolinylhydrazine was heated for three hours at 210°. The solid which formed on cooling was recrystallized from ethanol and obtained as needles, m.p. 115°.

Anal. Calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.22; H, 3.60; N, 28.31.

3-Pyrazolecarboxylic Acid Hydrazide and Ethyl Orthoformate.—A mixture of 6.3 g. (0.05 mole) of 3-pyrazolecarboxylic acid hydrazide[10] and 100 ml. of triethyl orthoformate was heated under reflux for three days. After removal of the solvent, by heating under reduced pressure, the residue was extracted with 50 ml. of cold ethanol. The insoluble material (2.5 g.) was essentially pure pyrazolo-[1,5-*d*]-*as*-triazin-4(5*H*)-one (V), m.p. 265°. It was soluble in 1 *N* sodium hydroxide and was reprecipitated by acid. A sample was recrystallized from water and obtained as needles, m.p. 265°.

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.49; H, 2.91; N, 40.96.

The ethanol extract was concentrated to dryness. Addition of ether caused 1 g. of 1-ethoxymethylene-2-(pyrazole-3-carbonyl)-hydrazine (IIb) to separate. It was collected and recrystallized from ethanol–ether and then from methanol, m.p. 177°.

Anal. Calcd. for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.52; N, 30.76. Found: C, 45.72; H, 5.33; N, 31.07.

2-Phenyl-1,3,4-thiadiazole.—A solution of 1.5 g. (0.01 mole) of thiobenzoic acid hydrazide[4] and 20 ml. of triethyl orthoformate was heated under reflux for two days. After removal of the solvent, by heating on the steam-bath under reduced pressure, the residue was extracted with ether. The ether was evaporated and 1 g. of oil remained. This was identified as 2-phenyl-1,3,4-thiadiazole by comparison of the infrared spectrum with that of an authentic sample.[5]

(10) L. Knorr, *Ber.*, **37**, 3520 (1904).

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

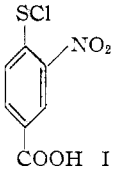
Derivatives of Sulfenic Acids. XIX. Synthesis and Characterization of 2-Nitro-4-carboxybenzenesulfenyl Chloride

BY ANTON J. HAVLIK[1] AND NORMAN KHARASCH

RECEIVED AUGUST 17, 1954

2-Nitro-4-carboxybenzenesulfenyl chloride, the first example of a compound of this type which contains both the carboxyl and sulfenyl chloride functions, has been synthesized and fully characterized. The possible utility of this compound for stereochemical studies is indicated and its stereospecific additions to the *cis*- and *trans*-2-butenes are reported.

The object of this work was to prepare and characterize 2-nitro-4-carboxybenzenesulfenyl chloride (I). In view of the known reactivities of aromatic



I

sulfenyl chlorides,[2] it was of interest to determine whether the carboxyl and sulfenyl chloride groups could coexist in a single molecule; but the main reason for seeking such a substance was in connection with eventual stereochemical studies, in which the carboxyl group could serve as a "handle" for resolution of racemic products formed *via* the sulfenyl chloride.[3]

While the *in situ* synthesis of 2-carboxybenzenesulfenyl chloride, by chlorination of 2-mercaptobenzoic acid, had been claimed in the patent literature, Price and Smiles[4] were unable to substantiate this report, and succeeded only in the preparation (in solution) of a dichloro compound, which they designated as II. They also obtained the same product by treatment of bis-(2-carboxyphenyl) disulfide with chlorine. The dichloro compound was not iso-

(1) Atomic Energy Commission Predoctoral Fellow, University of Southern California, 1951–1953. This paper was abstracted from a portion of the doctoral dissertation of A.J.H., University of Southern California, June, 1954.

(2) N. Kharasch, S. J. Potempa and H. L. Wehrmeister, *Chem. Revs.*, **39**, 269 (1946).

(3) The synthesis of possible amino-substituted aromatic sulfenyl chlorides—in which the amino group could serve for purposes of resolving optical isomers—also was considered. We suspect, however, that sulfenyl chlorides containing amino groups in them would generally be too reactive to exist as such.

(4) W. B. Price and S. Smiles, *J. Chem. Soc.*, 2858 (1928); *cf.* also German Patent 35,230.