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PREPARATION OF 5-SUBSTITUTED-1,3,4-OXADIAZOL-2(3*H*)ONES AND THEIR REACTIONS

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The recent disclosure by the authors (1) of the antitubercular activity of 5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)one (IIIa) and some of its derivatives has since been independently corroborated by Wilder Smith (2). The synthesis of this ring system and the study of methods of ring opening reported below are part of an investigation of syntheses of isonicotinic acid hydrazide and chemically related structures. Similar compounds have also been prepared by Yale, *et al.* (3) employing a different approach.

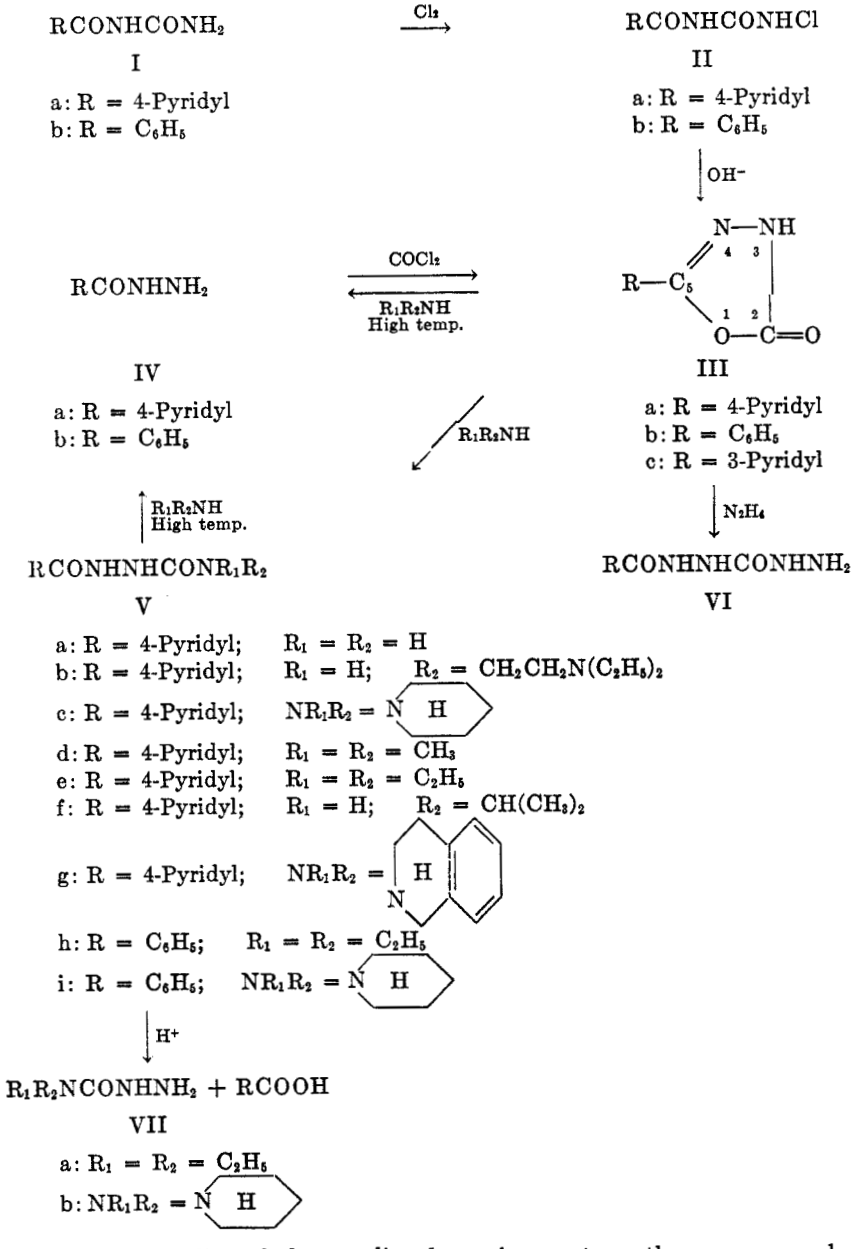
During a threatened shortage of hydrazine, this laboratory investigated syntheses of isonicotinic acid hydrazide that did not require this reagent. The conversion of benzoylurea (Ib) to benzoylhydrazide (IVb) by reaction with sodium hypochlorite was reported by Schestakoff (4). Benzoylchlorourea (IIb) was postulated as an intermediate which then underwent a Hofmann rearrangement to give the hydrazide. Diels and Okada (5) found that the chloroureide (IIb) when treated with alkali did not give the hydrazide but instead a cyclic compound later identified (6) as 5-phenyl-1,3,4-oxadiazol-2(3*H*)one (IIIb). On heating with aniline, benzoylhydrazide and diphenylurea were isolated.

In an analogous series of reactions, isonicotinylurea (Ia), to be used as a starting material in the synthesis of isonicotinic acid hydrazide, was prepared according to Jacobson (7) by the reaction of methyl isonicotinate with monosodium urea in acetone or preferably in liquid ammonia. We have also used this procedure to prepare nicotinylurea, 1-isonicotinyl-3-ethylurea, and 1-isonicotinyl-3-isopropylurea (Table I). In two instances this method proved to be inapplicable. When the sodium salt of symmetrical dimethylurea was reacted with methyl isonicotinate or ethyl nicotinate, only the corresponding pyridine carboxylic acids were isolated.

Although benzoylurea chlorinated readily in acetic acid solution (8), when this procedure was applied to isonicotinylurea, the starting material was recovered unchanged. However, when the chlorination was carried out in concentrated hydrochloric acid, a product (IIa) was obtained that liberated iodine from potassium iodide. Since the chloro derivative proved to be unstable, the crude product was dissolved in dilute alkali which caused rearrangement and cyclization to the oxadiazolone. On neutralization of the reaction mixture, a 45% yield of 5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)one was obtained calculated on isonicotinylurea.

Although the chlorination procedure worked well in the preceding case, it appeared to be sensitive to small changes and sometimes difficult to repeat. When 20% hydrochloric acid was used as the solvent for chlorination, the oxa-

diazolone obtained was difficult to purify. An attempt to chlorinate 1-isonicotinyl-3-ethylurea in concentrated hydrochloric acid was unsuccessful and the starting material was recovered unchanged.



For further studies of the oxadiazolone ring system, these compounds were more readily prepared from the hydrazides by reaction with phosgene following

TABLE I

UREIDES RCONHCONHR$_1$

R	R_1	Yield, %	Method	m.p., °C.	Empirical Formula	Analyses					
						Calc'd			Found		
						C	H	N	C	H	N
4-Pyridyl	H	41	A	240–241	$C_7H_7N_3O_2$	50.91	4.27	25.45	50.77	4.32	25.67
		68	B								
3-Pyridyl (11)	H	24	A	223–224	$C_7H_7N_3O_2$	50.91	4.27		50.74	4.45	
4-Pyridyl	C_2H_5	75	B	170–172	$C_9H_{11}N_3O_2$	55.95	5.74		56.04	5.64	
4-Pyridyl	$CH(CH_3)_2$	54	B	163–165	$C_{10}H_{13}N_3O_2$	57.96	6.32	20.28	58.20	6.29	20.33

the procedure of Dornow and Bruncken (9). This reaction took place readily in aqueous solution in the isonicotinyl series and yields were high (85%) when the hydrazide was unsubstituted. The presence of a substituent on the hydrazide, as in the cyclization of 1-isonicotinyl-2-isopropyl hydrazine under similar conditions, decreased the yield considerably (39%). A similar yield of 3-isopropyl-5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)one was obtained by Yale, *et al.* (3) by the reaction of the substituted hydrazine with dimethylcarbamyl chloride.

In animal experiments, Grunberg and Schnitzer (10) found 5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)one (IIIa) and the corresponding 3-isopropyl derivative active *in vivo* against *M. tuberculosis* while the compound derived from nicotinic acid (IIIc) was inactive. Although the intact oxadiazolones might possess this anti-tubercular activity, in the absence of studies of the metabolic fate of these drugs, it seems more likely that the activity is due to a split in the oxadiazolone ring to produce isonicotinic acid hydrazide. Chemically, Diels (5) converted IIIb to benzoylhydrazide in refluxing aniline. We have therefore studied the stability of the ring at various temperatures with ammonia and a series of amines.

The oxadiazolone ring (III) could be opened by amines to give two types of products, a hydrazide (IV) or a substituted semicarbazide (V) (Table II). The

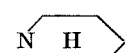
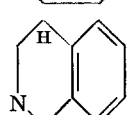
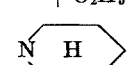
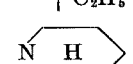
TABLE II

RING OPENING OF 5-(4-PYRIDYL)-1,3,4-OXADIAZOL-2(3H)ONE BY AMINES

Amine	Reaction Temp., °C.	Product
Ammonia	Rm. temp.	No reaction
Ammonia	70–80	Va
Isopropylamine	75–80	Vf
β-Diethylaminoethylamine	80	Vb
Piperidine	105	Vc
Diethylamine	120	Ve
Cyclohexylamine	134	IVa
Tetrahydroisoquinoline	135	Vg
β-Diethylaminoethylamine	145	IVa
2-Ethylhexylamine	169	IVa
Aniline	184	IVa

TABLE III

SUBSTITUTED SEMICARBAZIDES $RNHNHCONR_1R_2$

R	R_1	R_2	Reaction Temp., °C.	Reaction Time (hrs.)	Yield, %	m.p., °C.	Solvent	Empirical Formula	Analyses					
									Calc'd			Found		
									C	H	N	C	H	N
Isonicotinyl (12)	H	H	70–80	2	36	233	EtOH	[a]						
Isonicotinyl	$CH_2CH_2N(C_2H_5)_2$	H	80	2	82	181–182	CH_3CN	$C_{13}H_{21}N_5O_2$	55.90	7.58	25.07	56.44	7.41	24.95
Isonicotinyl	$CH(CH_3)_2$	H	75–80	2	77	206–207	CH_3CN	$C_{10}H_{14}N_4O_2$	54.05	6.34		54.32	6.06	
Isonicotinyl	$(CH_2)_3CH_3$	H	100	2	38	177–179	H_2O	$C_{11}H_{16}N_4O_2$	55.91	6.83		56.20	6.82	
Isonicotinyl	C_2H_5	C_2H_5	120	2.5	64	168–170	CH_3CN	$C_{11}H_{16}N_4O_2$	55.91	6.83		55.92	6.65	
Isonicotinyl			100	2	85	200–201	CH_3CN	$C_{12}H_{16}N_4O_2$	58.05	6.50	22.57	58.65 58.47	6.11 5.99	22.59
Isonicotinyl			135	2	63	157–159	EtOAc	$C_{16}H_{16}N_4O_2$	64.85	5.44		65.13	5.69	
Benzoyl	C_2H_5	C_2H_5	120	3	59	158–159	EtOAc	$C_{12}H_{17}N_3O_2$	61.26	7.28	17.86	61.05	7.26	18.29
Acetyl	C_2H_5	C_2H_5	90–95	2	71	120–122	C_6H_6-pet. ether	$C_7H_{15}N_3O_2$	48.54	8.73	24.26	48.65	8.18	24.85
Benzoyl			105	3	57	197–199	CH_3CN	$C_{13}H_{17}N_3O_2$	63.14	6.93		63.53	7.11	
H	C_2H_5	C_2H_5			49	110–112	*i*PrOH-Et_2O	$C_5H_{13}N_3O\cdot HCl$	35.82	8.42	25.07	35.62	8.23	25.00
H (13)					37	176–178[b]	EtOH-Et_2O	$C_6H_{13}N_3O\cdot HCl$	40.11	7.85	23.39	40.28	7.57	23.40

[a] Identified by mixture melting point with authentic sample prepared by reaction of isonicotinylhydrazide and potassium isocyanate, supplied by Dr. W. Wenner.[b] Lit. 185–186° (13).

course of the reaction appeared to be primarily a function of the temperature and the semicarbazide was an intermediate in the formation of the hydrazide. Although 5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)one (IIIa) did not react with liquid ammonia at room temperature, at 70–80° isonicotinyl semicarbazide (Va) was obtained. Other substituted semicarbazides prepared at temperatures up to 135° are listed in Table III. To prove that the semicarbazide was indeed an intermediate in the formation of the hydrazide, 1-isonicotinyl-4-diethylaminoethyl semicarbazide (Vb) was heated at 145° for 1 hour with β-diethylaminoethylamine to give a 56% yield of isonicotinic acid hydrazide. Similarly, heating Vb with piperidine at 150° for 2 hours gave a 26% yield of the hydrazide, and on refluxing Vc in β-diethylaminoethylamine for 1 hour, a 54% yield of isonicotinylhydrazide was obtained. It is of interest to note that Yale, *et al.* (3) converted 1-isonicotinyl-4,4-dimethylsemicarbazide (Vd) quantitatively to the oxadiazolone (IIIa) in refluxing pyridine.

While cyclohexylamine gave isonicotinic acid hydrazide at 134°, reaction with tetrahydroisoquinoline at 135° produced the semicarbazide. It would appear that although temperature is of prime importance in determining the reaction products, there are other factors, possibly base strength, that must also be considered. These factors were not studied further.

The oxadiazolones appear to be ideal starting materials for the preparation of substituted semicarbazides since substituents may be introduced readily at the 1 and 4 positions. On acid hydrolysis, 4-substituted semicarbazides are obtained. By this process we prepared 4,4-diethylsemicarbazide (VIIa) and piperidylcarbonylhydrazine (VIIb) from IIIb *via* Vh and Vi respectively.

The reaction of 5-phenyl-1,3,4-oxadiazol-2(3*H*)one with hydrazine was shown by Diels (5) to give benzoylcarbohydrazide. In an analogous reaction (IIIa) was opened with hydrazine to prepare 1-isonicotinylcarbohydrazide in high yield. This compound showed *in vivo* anti-tubercular activity. However, (IIIa) did not react when heated with phenylhydrazine in methanol under the same conditions.

EXPERIMENTAL[1]

Isonicotinylurea (*Method A*). To a stirred suspension of 10 g. of monosodium urea (7) in 15 cc. of acetone, 25 cc. of methyl isonicotinate was added. There was a rapid rise in temperature to about 40°. An additional 10 cc. of acetone then was added. The thick slurry was kept overnight at room temperature, filtered, and the filter cake was washed with acetone. The solid then was dissolved in 250 cc. of water. The solution (*p*H 11.5) was neutralized with acetic acid to *p*H 5.6 and isonicotinylurea then crystallized. Yield 8.4 g. (41%), m.p. 233–238° dec. Two crystallizations from water raised the melting point to 240–241° dec.

1-Isonicotinyl-3-ethylurea (*Method B*). To a well stirred solution of 31.7 g. of monoethylurea in 700 cc. of liquid ammonia, 6.3 g. of sodium was slowly added in small pieces. The reaction went rapidly and a finely divided white solid formed. When all the sodium had reacted, 60 cc. of methyl isonicotinate was added rapidly. A clear yellow solution resulted. The ammonia then was boiled off, and the residue was suspended in about 500 cc. of water and then neutralized to about *p*H 5 with acetic acid. After chilling, 52 g. (75%) of 1-iso-

[1] The authors are indebted to Dr. Al Steyermark and his staff for the analyses reported. All melting points are uncorrected.

nicotinyl-3-ethylurea, m.p. 168–171°, was filtered off. Recrystallization from water raised the melting point to 170–172°.

5-(4-Pyridyl)-1,3,4-oxadiazol-2(3H)one. A solution of 4 g. of isonicotinylurea in 110 cc. of concentrated hydrochloric acid was cooled in an ice-bath and a rapid stream of chlorine was passed through for 15 minutes. The solution then was diluted with 500 cc. of water, cooled, and neutralized with sodium carbonate. The product that separated was filtered and dried in a vacuum desiccator. An aqueous suspension of the material turned starch-iodide paper blue. A solution of 3.1 g. of the chloro compound in 50 cc. of 5% sodium hydroxide was neutralized, after several minutes at room temperature, with acetic acid. The solid that separated was filtered off and recrystallized from water to give 1.8 g. (45%) of 5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)one, m.p. 268–270°. Recrystallization from ethanol did not change the melting point.

Anal. Calc'd for $C_7H_5N_3O_2$: C, 51.55; H, 3.09; N, 25.77.

Found: C, 51.51; H, 2.86; N, 26.04.

A solution of 10 g. of isonicotinylhydrazide in 100 cc. of water was cooled in an ice-bath and a stream of phosgene was passed through for 15 minutes. The solution then was diluted, neutralized with sodium carbonate, and filtered. The crude oxadiazolone, 10.2 g. (85%) melting at 270–272°, was recrystallized from water or ethanol without significant change in melting point. A mixture melting point with the product prepared from isonicotinylurea showed no depression.

Conversion of 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)one (IIIa) *to isonicotinylhydrazide.* A mixture of 1 g. of IIIa and 4 cc. of aniline was heated to reflux for 3 to 4 minutes. After cooling, the reaction mixture was slurried in ether and extracted with water. On addition of levulinic acid to the aqueous layer, 1.0 g. of 4-(isonicotinylhydrazono)valeric acid (70%) crystallized, m.p. 208–209° (14).

Following the same procedure, cyclohexylamine gave an almost quantitative yield of hydrazide after 15 minutes at the reflux temperature, 2-ethylhexylamine gave a 70% yield after 2 hours at reflux, and β-diethylaminoethylamine a 44% yield after 1 hour at reflux.

1-Benzoyl-4,4-diethylsemicarbazide. A mixture of 5 g. of 5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (9) and 25 cc. of diethylamine was heated for 3 hours at 120° in a sealed tube. The product that crystallized on cooling was filtered, washed with ether, and recrystallized from ethyl acetate to give 4.3 g. (59%) of 1-benzoyl-4,4-diethylsemicarbazide, m.p. 158–159°. Further crystallization did not alter the melting point.

4,4-Diethylsemicarbazide hydrochloride. A solution of 10 g. of 1-benzoyl-4,4-diethylsemicarbazide in 100 cc. of 3 *N* hydrochloric acid was heated on a steam-bath for 1 hour. On cooling, benzoic acid crystallized. This was filtered off and the filtrate was concentrated to dryness *in vacuo*. The oily residue crystallized on scratching and was recrystallized from acetonitrile to give 3.5 g. (49%) of 4,4-diethylsemicarbazide hydrochloride, m.p. 108–111°. Recrystallization from isopropyl alcohol and ether raised the melting point to 110–112°.

Isonicotinylhydrazide from semicarbazides. (*a*) A solution of 2.0 g. of 1-isonicotinyl-4-(β-diethylaminoethyl)semicarbazide (Vb) in 20 cc. of β-diethylaminoethylamine was refluxed for 1 hour. Excess amine was removed by distillation *in vacuo*. On crystallization of the residue from acetonitrile, 550 mg. of isonicotinylhydrazide (56% yield) was isolated, m.p. 163–167°. The product was further identified by conversion to 4-(isonicotinylhydrazono)valeric acid, m.p. 210–211°.

(*b*) A solution of 2.0 g. of Vb in 25 cc. of piperidine was heated for 2 hours at 150° and worked up as above. A 26% yield of impure isonicotinylhydrazide, m.p. 159–164° was obtained. The product was treated with levulinic acid, and identified as 4-(isonicotinylhydrazono)valeric acid, m.p. 209–210°.

(*c*) The reaction of 1-isonicotinyl-2-piperidinocarbonylhydrazine (Vc) with β-diethylaminoethylamine carried out as in (*a*) gave a 54% yield of isonicotinylhydrazide, m.p. 161–165°.

1-Isonicotinylcarbohydrazide. A mixture of 3.0 g. of IIIa in 50 cc. of methanol containing 1.5 cc. of hydrazine was refluxed for 1 hour. The product crystallized from the hot solution

to give 2.8 g. (78%) of 1-isonicotinylcarbohydrazide, m.p. 215–216°. Recrystallization from water did not change the melting point.

Anal. Calc'd for $C_7H_9N_5O_2$: C, 43.30; H, 4.77; N, 35.88.
Found: C, 43.07; H, 4.65; N, 36.03.

SUMMARY

The synthesis of several substituted isonicotinylureas and the conversion of isonicotinylurea to 5-(4-pyridyl)-1,3,4-oxadiazol-2(3*H*)one has been described.

Methods of preparation of substituted semicarbazides, hydrazides, and carbohydrazides by the reaction of 5-substituted-oxadiazolones with amines are disclosed.

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