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Synthesis of pyridine-2-sulphonhydrazide 1-oxide and α-(2-pyridylthio)acethydrazide and its 1-oxide*

A. M. COMRIE AND I. MIR

The title compounds and some of their alkylidene and acyl derivatives have been prepared. A preliminary examination of representative compounds revealed negligible antibacterial activity against selected Gram-positive and Gram-negative organisms.

THE introduction of isoniazid as a tuberculotherapeutic agent (Robitzek & Selikoff, 1952) originated from the observations that nicotinamide (Chorine, 1945), 3-aminoisonicotinic acid (Fox, 1952) and *p*-acetamidobenzaldehyde thiosemicarbazone (Domagk, Behnisch, Mietzsch & Schmidt, 1946) were tuberculostatic. Structural modification of the isoniazid molecule designed to discover new tuberculostatic drugs and to delimit its activity followed, leading subsequently to the discovery of 2-ethyl-isonicotinthioamide (ethionamide) (Rist, Grumbach, Libermann, Moyeux, Cals & Clavels, 1956).

Molecular modifications which have been explored include substitution of acyl, alkyl and alkylidene groups on the hydrazide moiety (Offe, Siefken & Domagk, 1952; Bernstein, Jambor, Lott, Pansy, Steinberg & Yale, 1953; Fox & Gibas, 1953), replacement of the carbonyl group by a sulphonyl group (Talik & Plazek, 1955; Comrie & Stenlake, 1958; Angulo & Municio, 1960), separation of the pyridine ring from the hydrazide group by a methylene or ethylene group (Katritzky, 1954) or by a thiomethylene group (Takahashi, Shibasaki & Uchibayashi, 1954), and modification of the ring nitrogen atom by quaternisation and *N*-oxidation (Bernstein & others, 1953). Examination of the isomeric picolinic acid hydrazide showed that it was active but too toxic for clinical use (Fox & Gibas, 1952) and that 1-oxide formation resulted in concomitant reduction of activity and toxicity (Bernstein & others, 1953). In the present work it was decided to examine the effect of (*a*) replacing the carbonyl group in picolinic acid hydrazide 1-oxide by a sulphonyl group and (*b*) separating the pyridine ring from the hydrazino-group in both picolinic acid hydrazide and its 1-oxide by a thiomethylene group.

2-Mercaptopyridine 1-oxide (Shaw, Bernstein, Losee & Lott, 1950) was converted by low temperature chlorination into pyridine-2-sulphonyl chloride 1-oxide which reacted with hydrazine to give the sulphonhydrazide (I; R = R′ = H) using a previously described method (Comrie & Stenlake, 1958). Arylidene derivatives (I; RR′ = ArCH:) were readily obtained from aromatic aldehydes in methanol.

Condensation of 2-mercaptopyridine 1-oxide and ethyl bromoacetate in ethanol gave the hydrobromide of the ester (II; X = OEt), which reacted

* For previous paper see Comrie & Stenlake (1961).

From the Department of Pharmacy, University of Strathclyde, Glasgow.

with either water, ammonia, hydroxylamine or hydrazine to give respectively the acid (II; X = OH), the amide (II; X = NH_2), the hydroxamic acid (II; X = NH·OH), and α-(2-pyridylthio)acethydrazide 1-oxide (II; X = $NH·NH_2$). The hydrazide reacted with aldehydes and ketones to give sparingly soluble crystalline alkylidene derivatives (Table 1) (II; X = NH·N:CRR′), with acid anhydrides to give acyl derivatives (II; X = NH·NH·CO·R), and with phenyl isocyanate to give the semicarbazide (II; X = NH·NH·CO·NH·Ph).

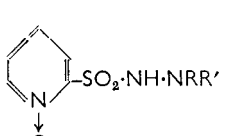
TABLE 1. *N′*-ALKYLIDENE-α-(2-PYRIDYLTHIO)ACETHYDRAZIDES (III; X = NH·N:CRR′)

Derivative (:CRR′)	M.p. °C	Yield %	Formula	Found %			Required %		
				C	H	N	C	H	N
Salicylidene	200–201 (decomp.)	70	$C_{14}H_{13}N_3O_2S$	58·25	4·5	14·6	58·5	4·6	14·6
Piperonylidene	167–170	60	$C_{15}H_{13}N_3O_3S$	57·4	4·3		57·1	4·2	
Veratrylidene	138–141	60	$C_{16}H_{17}N_3O_3S$	57·6	5·4		58·0	5·2	
p-Dimethylaminobenzylidene	186–188	92	$C_{16}H_{18}N_4OS$	60·9	5·7		61·1	5·8	
Cinnamylidene	135–136	54	$C_{16}H_{15}N_3OS$	64·2	4·9	14·7	64·6	5·1	14·1
Vanillylidene	165–167	40	$C_{15}H_{15}N_3O_3S$	57·3	5·2		56·8	4·8	
α-Phenylethylidene	142–144	74	$C_{15}H_{15}N_3OS$	63·1	5·55	15·0	63·15	5·3	14·7
Phenethylidene	152–153	70	$C_{15}H_{15}N_3OS$	62·9	5·4	15·4	63·15	5·3	14·7
Isopropylidene	128–130	86	$C_{10}H_{13}N_3OS$	53·5	5·8	19·0	53·8	5·9	18·8
Cyclohexylidene	112–114	72	$C_{13}H_{17}N_3OS$	59·35	6·6		59·3	6·5	
p-Methoxybenzylidene	136–138	33	$C_{15}H_{15}N_3O_2S$	59·5	5·1		59·8	5·0	
p-Hydroxybenzylidene	194 (decomp.)	52	$C_{14}H_{13}N_3O_2S$	56·7	4·7		56·3	4·7	
Hexahydro-2,4,6-trioxo-5-pyrimidinylidene*	290 (decomp.)	62	$C_{11}H_{11}N_5O_5S$	40·8	3·9	21·9	40·6	3·4	21·5

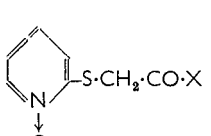
N′-ALKYLIDENE-α-(2-PYRIDYLTHIO)ACETHYDRAZIDE 1-OXIDES (II; X = NH·N:CRR′)

Salicylidene	230–232 (decomp.)	68	$C_{14}H_{13}N_3O_3S$	55·55	4·0	13·9	55·4	4·3	13·9
Piperonylidene	207–208	62	$C_{15}H_{13}N_3O_4S$	54·2	3·9	12·1	54·4	3·9	12·7
Veratrylidene	213–214 (decomp.)	61	$C_{16}H_{17}N_3O_4S$	54·8	5·1		55·3	4·9	
p-Dimethylaminobenzylidene	218–220 (decomp.)	56	$C_{16}H_{18}N_4O_2S$	58·6	5·45	16·2	58·2	5·5	17·0
Cinnamylidene	220–223 (decomp.)	66	$C_{16}H_{15}N_3O_2S$	61·55	4·9	13·3	61·3	4·8	13·4
Vanillylidene	198–200 (decomp.)	46	$C_{15}H_{15}N_3O_4S$	54·2	4·55	12·8	54·1	4·5	12·6
α-Phenylethylidene	201–203 (decomp.)	70	$C_{15}H_{15}N_3O_2S$	60·5	5·0	13·5	59·8	5·0	13·9
Phenethylidene	190–191	52	$C_{15}H_{15}N_3O_2S$	60·0	5·2		59·8	5·0	
Isopropylidene	210–211 decomp.)	83	$C_{10}H_{13}N_3O_2S$	50·3	5·3	17·7	50·2	5·5	17·6
2-Acetyl-1-methylethylidene (acetylisopropylidene)	175 (decomp.)	57	$C_{12}H_{15}N_3O_3S$	51·3	5·7	15·4	51·25	5·3	14·9
Furfurylidene	180–182	72	$C_{12}H_{11}N_3O_3S$	51·9	4·2	15·8	52·0	4·0	15·2
Hexahydro-2,4,6-trioxo-5-pyrimidinylidene*	183 (decomp.)	59	$C_{11}H_{11}N_5O_6S$	37·8	3·8	19·5	37·3	3·2	19·8

* Monohydrate.



(I)



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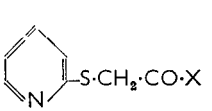

(III)

2-Mercaptopyridine reacted with ethyl bromoacetate giving the ester (III; X = OEt) hydrobromide, which was hygroscopic, and although it failed to give a satisfactory analysis the crude product reacted with hydrazine to give α-(2-pyridylthio)acethydrazide (III; X = NH·NH_2) in good yield (66%). The acethydrazide formed alkylidene derivatives (Table 1) (III; X = NH·N:CRR′), acyl derivatives (III; X = NH·NH·CO·R), and with allyl isothiocyanate gave the thiosemicarbazide (III; X = NH·NH·CS·NH·CH_2·CH:CH_2). In an excess of acetic anhydride it gave the diacetyl derivative (III; X = NH·NAc_2). With toluene-*p*-sulphonyl chloride, α-(2-pyridylthio)acethydrazide and its 1-oxide gave respectively the derivatives (III) and (II) (X = NH·NH·SO_2·C_6H_4·Me-*p*).

Attempts to prepare alkyl derivatives (III; X = NH·NRR′) were unsuccessful. Catalytic hydrogenation of alkylidene derivatives led to hydrogenolysis giving 2-mercaptopyridine, while chemical reduction in acid solution regenerated the acethydrazide and carbonyl compound. Condensation of ethyl α-(2-pyridylthio)acetate and *NN*-di-isopropylhydrazine, and the base-catalysed condensation of α-(2-pyridylthio)-acethydrazide and benzyl bromide gave grossly impure products which could not be purified for characterisation.

BACTERIOLOGICAL RESULTS

We thank Mr. Malcolm S. Parker, M.Sc., M.P.S. of this Department for the bacteriological examination of *N′*-benzylidene-*N*-(pyridine-2-sulphon)hydrazide 1-oxide and several representative alkylidene and acyl derivatives, and also the toluene-*p*-sulphonyl derivatives of α-(2-pyridylthio)acethydrazide and its 1-oxide. None of the compounds exhibited activity against *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, or *Bacillus subtilis*.

Experimental

Melting points are uncorrected.

Pyridine-2-sulphonhydrazide 1-oxide. Pyridine-2-sulphonyl chloride 1-oxide obtained by chlorination of 2-mercaptopyridine 1-oxide (1·27 g) at −5° and extracted into cold chloroform (120 ml) (Comrie & Stenlake, 1958) was added portionwise to hydrazine hydrate (1·0 g), and the mixture vigorously shaken after each addition and left at *ca.* 0° overnight. The precipitate was filtered off, suspended in ice-cold water (10 ml), filtered and dried *in vacuo*, giving the *sulphonhydrazide* as the monohydrate (0·3 g), m.p. 96–98° (decomp.) (from methanol). Found: C, 28·8; H, 3·9. $C_5H_9N_3O_4S$ requires C, 28·9; H, 4·3%.

*N′-Benzylidene-*N*-(pyridine-2-sulphon)hydrazide 1-oxide.* A solution of pyridine 2-sulphonhydrazide 1-oxide (0·189 g) and benzaldehyde (0·106 g) in methanol (10 ml) was vigorously shaken and the precipitate washed with a small volume of methanol and ether. The *benzylidene derivative* (0·16 g) was obtained as needles, m.p. 145–147° (decomp.) (from methanol). Found: C, 52·6; H, 4·1; N, 15·4. $C_{12}H_{11}N_3O_3S$ requires C, 52·0; H, 4·0; N, 15·2%.

N-(*Pyridine-2-sulphon*)*hydrazide*-N′-*veratrylidene* 1-*oxide*. Pyridine-2-sulphonhydrazide 1-oxide (0·189 g) and veratraldehyde (0·166 g) similarly gave the *veratrylidene derivative* (0·15 g), m.p. 146–148° (decomp.) (from ethanol). Found: C, 49·2; H, 4·1; N, 12·7. $C_{14}H_{15}N_3O_5S$ requires C, 49·85; H, 4·5; N, 12·5%.

Ethyl α-(2-*pyridylthio*)*acetate hydrobromide*. 2-Mercaptopyridine 1-oxide (3·8 g) and ethyl bromoacetate (5·0 g) in ethanol (50 ml) were refluxed for 1½ hr and the solvent removed under reduced pressure to give the *hydrobromide* (3·9 g), m.p. 120° (decomp.) (from ethanol-ether). Found: N, 5·2. $C_9H_{12}BrNO_3S$ requires N, 4·8%.

α-(2-*Pyridylthio*)*acethydrazide* 1-*oxide*. The crude product from the preceding experiment was dissolved in ethanol (40 ml), anhydrous hydrazine (0·9 g) added and the mixture refluxed for 5 hr. The solvent was removed under vacuum and the residue recrystallised from ethanol to give the *acethydrazide* 1-*oxide* (2·5 g), m.p. 200–201° (decomp.). Found: C, 42·2; H, 4·4; N, 20·5. $C_7H_9N_3O_2S$ requires C, 42·2; H, 4·6; N, 21·1%.

N′-*Benzylidene*-α-(2-*pyridylthio*)*acethydrazide* 1-*oxide*. α-(2-Pyridylthio)acethydrazide 1-oxide (0·398 g) and benzaldehyde (0·212 g) were shaken in methanol (10 ml) to effect solution, and then left at *ca.* 0° overnight. The precipitate was filtered off, washed with a small volume of methanol and ether to give the *benzylidene derivative* (0·4 g), m.p. 202–203° (decomp.) (from methanol). Found: C, 58·5; H, 4·55; N, 14·95. $C_{14}H_{13}N_3O_2S$ requires C, 58·5; H, 4·6; N, 14·6%.

Other *N*′-alkylidene derivatives (Table 1) (II; X = NH·N:CRR′) were similarly prepared.

α-(2-*Pyridylthio*)*acetic acid* 1-*oxide*. A solution of 2-mercaptopyridine 1-oxide (1·27 g) and ethyl bromoacetate (1·67 g) in ethanol (10 ml) was refluxed for 1½ hr and the solvent removed under reduced pressure. The residue was refluxed with water (10 ml) for 1½ hr and the solution evaporated to dryness. Recrystallisation from aqueous methanol gave α-(2-*pyridylthio*)*acetic acid* 1-*oxide* (1·0 g), m.p. 288° (decomp.). Found: C, 45·6; H, 4·0; N, 7·7. $C_7H_7NO_3S$ requires C, 45·4; H, 3·8; N, 7·6%.

α-(2-*Pyridylthio*)*acetamide* 1-*oxide*. 2-Mercaptopyridine 1-oxide (1·27 g) and ethyl bromoacetate (1·67 g) were refluxed in ethanol (10 ml) as above and the solvent removed. The residue was redissolved in ethanol (10 ml) and shaken with an excess of ammonia solution (d. 0·88) and the solution evaporated to dryness. The *amide* (1·0 g), m.p. 215°, was recrystallised from methanol. Found: C, 45·6; H, 4·3; N, 15·4. $C_7H_8N_2O_2S$ requires C, 45·65; H, 4·3; N, 15·2%.

α-(2-*Pyridylthio*)*acethydroxamic acid* 1-*oxide*. 2-Mercaptopyridine 1-oxide (1·27 g) and ethyl bromoacetate (1·67 g) in ethanol (10 ml) were refluxed as before and after removing the solvent the residue was added to hydroxylamine hydrochloride (1·1 g) in methanol (15 ml) containing sodium methoxide (1·1 g). The precipitate was filtered off and the filtrate concentrated at room temperature under reduced pressure. The *hydroxamic acid* (0·5 g) m.p. 195–197° (decomp.), slowly separated. Found: C, 41·9; H, 4·2. $C_7H_8N_2O_3S$ requires C, 42·0; H, 4·0%.

δ-Phenyl-α-[α-(2-pyridylthio)acetyl]-semicarbazide 1-oxide. α-(2-Pyridylthio)acethydrazide 1-oxide (0·398 g) and phenyl isocyanate (0·2 g) were shaken in acetonitrile (10 ml) for 1 hr and the solvent removed under reduced pressure. The residue was recrystallised from ethanol to give the *semicarbazide* (0·2 g), m.p. 194–195°. Found: C, 52·7; H, 4·2; N, 18·0. $C_{14}H_{14}N_4O_3S$ requires C, 52·8; H, 4·4; N, 17·6%.

N'N'-Diacetyl-N-[α-(2-pyridylthio)acetyl]hydrazine 1-oxide. α-(2-Pyridylthio)acethydrazide 1-oxide (0·398 g) was added in small portions to acetic anhydride (5 ml) and warmed to complete solution. The solid which separated on cooling was washed with ether, dried *in vacuo* and twice crystallised from methanol to give the *diacetyl derivative* (0·4 g), m.p. 135° (decomp.). Found: C, 46·5; H, 4·8; N, 14·9. $C_{11}H_{13}N_3O_4S$ requires C, 46·7; H, 4·6; N, 14·8%.

N'-(β-Carboxypropionyl)-N-[α-(2-pyridylthio)acetylhydrazine 1-oxide. α-(2-Pyridylthio)acethydrazide 1-oxide (0·398 g) was added to succinic anhydride (0·2 g) in methanol (10 ml). The precipitate was recrystallised from methanol to give the *product* (0·4 g), m.p. 200–201° (decomp.). Found: C, 44·4; H, 4·55; N, 14·85. $C_{11}H_{13}N_3O_5S$ requires C, 44·1; H, 4·4; N, 14·05%.

N'-(β-Carboxyacryloyl)-N-[α-(2-pyridylthio)acetyl]hydrazine 1-oxide. α-(2-Pyridylthio)acethydrazide 1-oxide (0·398 g) and maleic anhydride (0·2 g) reacted as described above to give the *product* (0·3 g), m.p. 110–113° (from methanol). Found: C, 44·8; H, 4·2; N, 14·8. $C_{11}H_{11}N_3O_5S$ requires C, 44·4; H, 3·7; N, 14·1%.

N-[α(2-Pyridylthio)acetyl]-N'-(toluene-p-sulphonyl)hydrazine 1-oxide. Toluene-*p*-sulphonyl chloride (0·38 g) was added to α-(2-pyridylthio)-acethydrazide 1-oxide (0·398 g) in dry pyridine (10 ml) and heated on a water-bath for 15 min. The solution was cooled, water added, and set aside for 3 hr. The precipitate was washed with a small volume of water and dried to give the *toluene-p-sulphonyl derivative* (0·29 g), m.p. 242° (decomp.) (from ethanol). Found: C, 47·4; H, 4·5. $C_{14}H_{15}N_3O_4S_2$ requires C, 47·6; H, 4·3%.

α-(2-Pyridylthio)acethydrazide. 2-Mercaptopyridine (1·11 g) was refluxed with ethyl bromoacetate (1·67 g) in dry ethanol (30 ml) for 2 hr and the solvent removed under reduced pressure, leaving a viscous oil which set to a hygroscopic solid (1·3 g). This was dissolved in dry ethanol (30 ml) and refluxed with anhydrous hydrazine (1·0 g) for 5–6 hr and again evaporated to dryness *in vacuo*. The solid residue was suspended in ice-cold water (10 ml), filtered and recrystallised from ethanol to give the *acethydrazide* (1·2 g), m.p. 90–92°. Found: C, 46·0; H, 4·9; N, 22·2. $C_7H_9N_3OS$ requires C, 45·9; H, 4·9; N, 22·9%.

N'-Benzylidene-α-(2-pyridylthio)acethydrazide. α-(2-Pyridylthio)acethydrazide (0·183 g) and benzaldehyde (0·106 g) were dissolved in methanol (10 ml). The solid separating was washed with a little methanol and ether, and recrystallised from methanol to give the *benzylidene derivative* (0·2 g), m.p. 191–192°. Found: C, 62·0; H, 4·7; N, 14·9. $C_{14}H_{13}N_3OS$ requires C, 62·0; H, 4·8; N, 15·5%.

Other *N'*-alkylidene derivatives (Table) (III; X = NH·N:CRR') were similarly prepared.

N'N'-*Diacetyl-α-(2-pyridylthio)acethydrazide.* α-(2-Pyridylthio)acethydrazide (0·183 g) was added in small amounts to freshly distilled acetic anhydride (5 ml). The mixture, which partially solidified, was dried at the pump, washed with ether and recrystallised from ethyl acetate to give the N'N'-*diacetyl derivative* (0·19 g), m.p. 141–143°. Found: C, 49·7; H, 4·9. $C_{11}H_{13}N_3O_3S$ requires C, 49·4; H, 4·9%.

N'-*Acetyl-α-(2-pyridylthio)acethydrazide.* α-(2-Pyridylthio)acethydrazide (0·183 g) and acetic anhydride (0·18 g) were dissolved in dry pyridine (5 ml) and the precipitate recrystallised from ethyl acetate to give the N'-*acetyl derivative* (0·1 g), m.p. 138–140°. Found: C, 48·0; H, 5·1; N, 18·1. $C_9H_{11}N_3O_2S$ requires C, 48·0; H, 4·9; N, 18·7%.

N'-(*β-Carboxypropionyl*)-N-[*α-(2-pyridylthio)acetyl*]*hydrazine.* α-(2-Pyridylthio)acethydrazide (0·183 g) and succinic anhydride (0·116 g) in methanol (10 ml) gave the *product* (0·2 g) m.p. 150–151° (from isopropanol). Found: C, 46·2; H, 4·6. $C_{11}H_{13}N_3O_4S$ requires C, 46·7; H, 4·7%.

N-[*α-(2-Pyridylthio)acetyl*]-N'-(*toluene*-p-*sulphonyl*)-*hydrazine.* Toluene-*p*-sulphonyl chloride (0·38 g) and α-(2-pyridylthio)acethydrazide (0·366 g) in dry pyridine (10 ml) were heated on a water-bath for 10 min and then cooled. The *toluene*-p-*sulphonyl derivative* (0·1 g) was isolated by adding water (50 ml) and on recrystallisation from ethanol had m.p. 165–167°. Found: C, 49·3; H, 4·6. $C_{14}H_{15}N_3O_3S_2$ requires C, 49·85; H, 4·5%.

δ-Allyl-α-[α-(2-pyridylthio)acetyl]-thiosemicarbazide. α-(2-Pyridylthio)-acethydrazide (0·366 g) and allyl isothiocyanate (0·2 g) in acetonitrile (5 ml) were heated on a water-bath for 10 min and then cooled to room temperature to give the *thiosemicarbazide* (0·32 g), m.p. 116–117° (from ethanol). Found: C, 46·3; H, 5·0. $C_{11}H_{14}N_4OS_2$ requires C, 46·8; H, 5·0%.

References

Angulo, J. & Municio, A. M. (1960). *Anales. real. Soc. espan. Fis. Quim.*, **56B**, 395–402.

Bernstein, J., Jambor, W. P., Lott, W. A., Pansy, F., Steinberg, B. A. & Yale, H. L. (1953). *Amer. Rev. Tuberc.*, **67**, 354–365.

Chorine, V. (1945). *C.R. Acad. Sci., Paris*, **220**, 150–151.

Comrie, A. M. & Stenlake, J. B. (1958). *J. chem. Soc.*, 3514–3518.

Comrie, A. M. & Stenlake, J. B. (1961). *J. Pharm. Pharmacol.*, **13**, 26–33.

Domagk, G., Behnisch, R., Mietzsch, F. & Schmidt, H. (1946). *Naturwiss.*, **33**, 315.

Fox, H. H. (1952). *J. org. Chem.*, **17**, 555–562.

Fox, H. H. & Gibas, J. T. (1952). *Ibid.*, **17**, 1653–1660.

Fox, H. H. & Gibas, J. T. (1953). *Ibid.*, **18**, 983–1002.

Katritzky, A. R. (1954). *J. chem. Soc.*, 4038–4039.

Offe, H. A., Siefken, N. & Domagk, G. (1952). *Z. Naturf.*, **7b**, 462–468.

Rist, N., Grumbach, F., Libermann, D., Moyeux, M., Cals, S. & Clavels, S. (1956). *C.R. Acad. Sci., Paris*, **242**, 2187–2189.

Robitzek, E. H. & Selikoff, I. J. (1952). *Amer. Rev. Tuberc.*, **65**, 402–428.

Shaw, E., Bernstein, J., Losee, K. & Lott, W. A. (1950). *J. Amer. chem. Soc.*, **72**, 4362–4364.

Takahashi, T., Shibasaki, J. & Uchibayashi, M. (1954). *Pharm. Bull., Japan*, **2**, 30–34.

Talik, Z. & Plazek, E. (1955). *Acta polon. pharm.*, **12**, 179–184.