109. *Acylation of* 1,4-*Dihydro*-4-*thiopyridine.*

By A. M. Comrie.

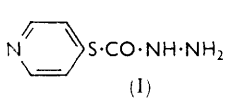
Condensation of 1,4-dihydro-4-thiopyridine and chloroformic esters in ethanol gives 4-alkoxycarbonylthiopyridinium chlorides and, in aqueous sodium hydrogen carbonate, alkyl 1,4-dihydro-4-thiopyridine-1-carboxylates. The bases liberated from the hydrochlorides isomerize to the thiopyridones which are unstable to heat and light, giving 4-alkylthiopyridines and/or di-4-pyridyl sulphide. A mechanism is proposed for the photolysis of the 1-ester to di-4-pyridyl sulphide.

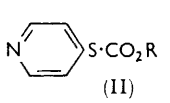
Interest in the acylation of 1,4-dihydro-4-thiopyridine (4-thiopyridone) arose as a result of an attempt to prepare 4-pyridylthioformhydrazide (I), which was required for comparison with isonicotinhydrazide as an antituberculosis agent. Analogues of the latter, in which the pyridine nucleus is separated from the hydrazide group by a methylene or thiomethylene group, are devoid of antituberculosis activity,[1,2] but it was considered that the required compound could not be dismissed *a priori*.[3]

Addition of ethyl chloroformate to 1,4-dihydro-4-thiopyridine in cold ethanol gave a

[1] Katritzky, *J.*, 1954, 4038.
[2] Takahashi, Shibasaki, and Uchibayashi, *Pharm. Bull.* (*Japan*), 1954, **2**, 30.
[3] Fox and Gibas, *J. Org. Chem.*, 1952, **17**, 1653.

red solution, which became yellow and yielded the hydrochloride of ethyl (4-pyridylthio)-formate (II; R = Et). The base was liberated from the hydrochloride as a pale yellow oil, which reacted with hydrazine hydrate in ethanol, regenerating 1,4-dihydro-4-thiopyridine instead of giving the required compound (I). When kept under a vacuum, the oil slowly became red and solidified. Recrystallization from light petroleum gave an orange solid with a satisfactory analysis for the expected base (II; R = Et), but its


(I)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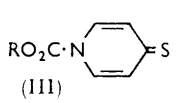
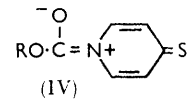

(III)


(IV)

ultraviolet absorption spectrum was similar to that of 1,4-dihydro-4-thiopyridine,[4] although the peaks shown by the latter at 230 and 340 mμ had shifted to 245 and 370 mμ, respectively. It was, therefore, assigned the thione structure (III; R = Et), the bathochromic shift probably being due to some contribution from the " quinonoid " structure (IV). Basic character would not be expected for structure (III; R = Et), and indeed the compound was readily extracted into ether from dilute hydrochloric acid.

The red solution obtained on initial mixing of the reactants showed absorption at 370 mμ, indicating ethoxycarbonylation at the nitrogen atom. The yellow solution finally obtained showed no absorption in this region, nor did the yellow oil obtained when the hydrochloride was basified. The base (II; R = Et) appears to be unstable in the absence of acid and reverts to the isomeric thione (III; R = Et). A similar $S \longrightarrow N$-acyl shift has been reported for 2-ethoxycarbonylthio-4-methylimidazole.[5]

The ester (III; R = Et) is more conveniently prepared in good yield by condensing 1,4-dihydro-4-thiopyridine and ethyl chloroformate in cold aqueous sodium hydrogen carbonate.

When kept at room temperature for several days, the thione (III; R = Et) lost its orange colour and gave, unexpectedly, di-4-pyridyl sulphide in 90% yield. The same product was obtained on exposing an ethanolic solution of the thione to sunlight or ultraviolet light, or by heating it under reflux, and the reaction could be followed by observing the change in the ultraviolet absorption spectrum. No diethoxycarbonyl sulphide could be detected.

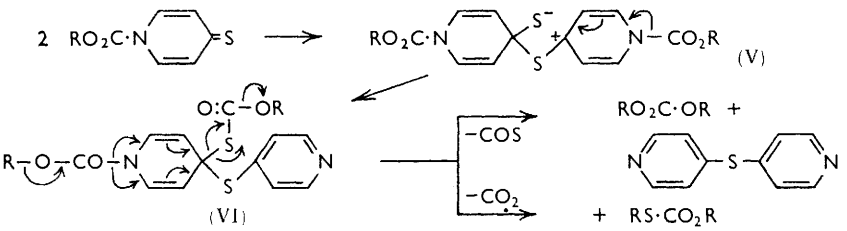
To shed further light on the formation of di-4-pyridyl sulphide, the solid thione was exposed to ultraviolet light until the spectrum showed no absorption at 370 mμ. Fractional distillation of the resulting oil gave ethyl carbonate and ethyl thiocarbonate, which were identified by comparison of their infrared absorption spectra with authentic material.[6] The non-volatile fraction proved to be di-4-pyridyl sulphide.

Substances containing a $>C{:}S$ group are known to dimerise on being heated[7] or on ultraviolet irradiation,[8] and from the disappearance of the peak at 370 mμ it seemed likely that the thione group was involved, probably with formation of an intermediate (V). Migration of an ethoxycarbonyl group from nitrogen to sulphur, giving structure (VI) followed by decarboxylation and alkyl migration, would account for di-4-pyridyl sulphide and ethyl thiocarbonate. Carbon dioxide was detected by placing the thione in the centre chamber and lime-water in the outer chamber of a Conway cell. The formation of ethyl carbonate probably takes place by an alternative pathway involving elimination of carbonyl sulphide, which was detected by palladous chloride solution.[9]

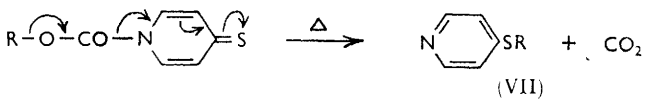
The thione also lost carbon dioxide when heated above its m. p. and distillation of the resulting liquid gave an oil and a small residue of di-4-pyridyl sulphide. The oil showed

[4] Ross, *J.*, 1951, 1374; Jones and Katritzky, *J.*, 1958, 3610; Albert and Barlin, *J.*, 1959, 2384.
[5] Lawson and Morley, *J.*, 1956, 1103.
[6] Felumb, *Bull. Soc. chim. France*, 1957, 890.
[7] Schönberg, Vargha, and Kaltschmitt, *Ber.*, 1931, **64**, 2582.
[8] Schönberg, *Trans. Faraday Soc.*, 1936, **32**, 517.
[9] Dede, *Chem.-Ztg.*, 1914, **38**, 1073 (from *Chem. Abs.*, 1915, **9**, 424).

no ultraviolet absorption above 300 mμ and, on oxidation, gave the known 4-ethylsulphonylpyridine,[10] which could not be obtained as a solid but formed a crystalline picrate. Decarboxylation and alkyl migration probably takes place as shown. Ethyl 2-mercapto-4-methylimidazole-1-carboxylate undergoes an analogous transformation into



2-ethylthio-4-methylimidazole.[5] Decarboxylation of the methyl, benzyl, or allyl ester (III) took place spontaneously at room temperature or on heating, giving the respective sulphides (VII); the first two were identified by comparison with authentic material;[11,12]



the allyl compound was characterized by analysis and comparison with the product obtained by condensation of allyl bromide and 1,4-dihydro-4-thiopyridine. The ester (III; R = $Cl{\cdot}CH_2{\cdot}CH_2$) decomposed slowly at room temperature and rapidly when heated, to give di-4-pyridyl sulphide; no 4-2′-chloroethylthiopyridine was detected.

Exposure of an ethanolic solution of each thione to sunlight gave di-4-pyridyl sulphide, identified as its dipicrate, and decomposition of the solid gave carbon dioxide and carbonyl sulphide.

Benzoylation of 1,4-dihydro-4-thiopyridine in alkali gave a product which showed no absorption above 300 mμ, formed a picrate, and was, therefore, 4-benzoylthiopyridine. Acetylation in acetic anhydride gave 1-acetyl-1,4-dihydro-4-thiopyridine, which showed typical peaks *ca.* 250 and 370 mμ; it was readily hydrolyzed in air and unstable in ethanol, but distilled under reduced pressure without appreciable decomposition.

Experimental

The author thanks Mr. W. MacCorkindale and Mr. D. Caldwell for the microanalysis. Ultraviolet absorption spectra were determined for ethanol solution.

4-*Alkoxycarbonylthiopyridinium Chlorides* (Table 1).—The chloroformic ester (0·011 mole) in ethanol (5 ml.) was added slowly to a well-cooled solution of 1,4-dihydro-4-thiopyridine (0·01 mole) in ethanol (30 ml.), and the resulting red solution kept overnight at 0°. The solvent was removed under reduced pressure at room temperature and the pale yellow residue washed with ether. Recrystallization from ethanol–ether gave the *product.*

Alkyl 1,4-*Dihydro*-4-*thiopyridine*-1-*carboxylates* (Table 2).—(*a*) The 4-alkoxycarbonylthiopyridinium chloride in water (10 ml.) was neutralized with aqueous ammonia and extracted with ether (2 × 25 ml.). The ether solution was dried (Na_2SO_4) and evaporation at room temperature left a pale yellow oil which became red and slowly solidified in a vacuum. Recrystallization from ether or light petroleum (b. p. 40—60°) gave the *product* as golden-brown needles or plates, in 15—35% yield.

(*b*) The chloroformic ester (0·011 mole) was added dropwise to an ice-cold solution of 1,4-dihydro-4-thiopyridine (0·01 mole) in water (30 ml.) containing sodium hydrogen carbonate (1 g.) and vigorously shaken till no more carbon dioxide was released and only a faint smell of

[10] Burton and Davy, *J.*, 1947, 52.
[11] King and Ware, *J.*, 1939, 873.
[12] Stevenson, Cranham, Cummings, and Brooks, B.P. 758,658/1956.

TABLE 1.

4-Alkoxycarbonylthiopyridinium chlorides.

R	M. p.	Formula	Yield (%)	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Methyl	194—196°	$C_7H_8ClNO_2S$ *	82	41·0	3·4	40·9	3·9
Ethyl	210—212	$C_8H_{10}ClNO_2S$ †	86	43·9	4·6	43·7	4·6
2-Chloroethyl	233—235	$C_8H_9Cl_2NO_2S$	58	37·4	4·0	37·8	3·6
Allyl	222—224	$C_9H_{12}ClNO_2S$ ‡	51	43·0	4·5	43·4	4·8
Benzyl	228—230	$C_{13}H_{14}ClNO_2S$ ‡	42	52·6	4·5	52·1	4·7

* Found: N, 7·15. Reqd.: N, 6·8%. † Found: N, 6·5. Reqd.: N, 6·4%. ‡ Monohydrate.

TABLE 2.

Alkyl 1,4-dihydro-4-thiopyridine-1-carboxylates (III).

R	M. p.	Formula	$\lambda_{max.}$† (mμ)	$\lambda_{max.}$† ε	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Methyl	68—69°	$C_7H_7NO_2S$	244, 370	2900, 26,500	49·9	4·0	8·3	49·7	4·2	8·3
Ethyl	90	$C_8H_9NO_2S$ *	245, 370	3600, 31,000	52·8	4·9	7·8	52·5	5·0	7·65
2-Chloroethyl	92	$C_8H_8ClNO_2S$	244, 369	3300, 26,000	44·5	3·6	6·5	44·1	3·7	6·4
Allyl	65	$C_9H_9NO_2S$	245, 370	3500, 30,000	55·4	4·1	7·3	55·4	4·6	7·2
Benzyl	68	$C_{13}H_{11}NO_2S$	245, 370	3500, 33,000	63·8	4·9	6·0	63·6	4·5	5·7

* Found: S, 17·5. Reqd.: S, 17·5%. † In ethanol.

the chloroformic ester remained. Then the mixture was set aside at 0° for ~1 hr. and the solid was filtered off, washed with a small volume of ice-cold water, and dried at the water-pump. A solution of this material in ether or light petroleum (b. p. 40—60°) was filtered, dried (Na_2SO_4), and concentrated, to give the *product* in 75—80% yield.

Decomposition. (*a*) The thione (III) (0·92 g.) was exposed to ultraviolet light until the product failed to show an absorption peak at 370 mμ. Fractional distillation of the resulting brown oil under reduced pressure gave ethyl carbonate (0·12 g.), b. p. 52°/20 mm., and ethyl thiocarbonate (90 mg.), b. p. 65°/20 mm. The residue, recrystallized from light petroleum (b. p. 40—60°) (charcoal), gave di-4-pyridyl sulphide [11] (0·20 g.), m. p. 72°, $\lambda_{max.}$ 230 (ε 8500) 254 (ε 12,000), and 290 mμ (ε 7600) (dipicrate,[11] m. p. 229°).

(*b*) Exposure of an ethanolic solution of the thione (0·92 g.) to sunlight until there was no absorption at 370 mμ gave di-4-pyridyl sulphide (0·42 g., 90%), m. p. 72°. The change was accelerated by heat and, in the presence of hydrogen chloride, *di-4-pyridyl sulphide dihydrochloride monohydrate*, m. p. 246°, separated in rods (Found: C, 42·9; H, 4·4; N, 10·0. $C_{10}H_{12}Cl_2N_2OS$ requires C, 43·0; H, 4·3; N, 10·0%).

(*c*) The thione (0·92 g.) was heated on a boiling-water bath till effervescence ceased (½ hr.). Distillation of the residue under reduced pressure gave *4-ethylthiopyridine* (0·41 g.), b. p. 104—105°/18—20 mm., n_D^{18} 1·5713, $\lambda_{max.}$ 268 mμ (ε 12,600) (Found: C, 59·85; H, 6·2; N, 10·2. C_7H_9NS requires C, 60·4; H, 6·5; N, 10·1%) [*picrate*, orange needles, m. p. 146° (from ethanol) (Found: C, 42·4; H, 3·0; N, 15·3. $C_{13}H_{12}N_4O_7S$ requires C, 42·45; H, 3·3; N, 15·2%)]. The residue after distillation of the 4-ethylthiopyridine gave di-4-pyridyl sulphide [11] (68 mg.), m. p 72° [from light petroleum (b. p. 40—60°)].

4-Ethylsulphonylpyridine.—4-Ethylthiopyridine (0·7 g.) was oxidized with potassium permanganate,[10] giving the product as a colourless oil (0·34 g.), n_D^{18} 1·5340, $\lambda_{max.}$ 266 mμ (ε 3400), which failed to crystallize at room temperature (Found: N, 8·3. Calc. for $C_7H_9NO_2S$: N, 8·2%) (lit.,[10] m. p. 29°) [*picrate*, plates, m. p. 166° (from methanol) (Found: C, 38·7; H, 3·05; N, 14·0. $C_{13}H_{12}N_4O_9S$ requires C, 39·0; H, 3·0; N, 14·0%)].

4-Methylthiopyridine.—The thione (III; R = Me) (0·85 g.) was heated on a water-bath till effervescence ceased. The residue, which solidified on cooling, recrystallized from light petroleum (b. p. 40—60°) (charcoal), to give the product (0·28 g.), m. p. 46° (Found: C, 57·3; H, 6·3; N, 11·15. Calc. for C_6H_7NS: C, 57·6; H, 5·65; N, 11·2%) [picrate, m. p. 170—171° (from methanol) (Found: C, 40·5; H, 2·6; N, 15·4. Calc. for $C_{12}H_{10}N_4O_7S$: C, 40·7; H, 2·85; N, 15·8%)] (lit.,[11] base, m. p. 46°; picrate, m. p. 245°). The base from the condensation of methyl iodide and 1,4-dihydro-4-thiopyridine formed a picrate, m. p. 170—171°.

4-Allylthiopyridine.—The thione (III; R = allyl) (0·98 g.) was heated on a boiling-water

bath till effervescence ceased and the resulting oil distilled under reduced pressure, to give 4-*allylthiopyridine*, b. p. 145°/18—20 mm., n_D^{18} 1·5872, $\lambda_{max.}$ 265 mμ (ε 12,300) (Found: C, 63·1; H, 5·9; N, 9·2. C_8H_9NS requires C, 63·6; H, 6·0; N, 9·3%) [*picrate*, m. p. 147° (from methanol) (Found: C, 44·1; H, 3·0; N, 14·8. $C_{14}H_{12}N_4O_7S$ requires C, 44·2; H, 3·2; N, 14·7%)].

4-*Allylthiopyridine Hydrobromide*.—1,4-Dihydro-4-thiopyridine (1·11 g.) in ethanol (20 ml.) was refluxed with allyl bromide (1·31 g.) for 5 min. On cooling, the *hydrobromide* (1·9 g.), m. p. 188—189°, separated as pale yellow needles (Found: C, 41·6; H, 4·2; N, 6·2. $C_8H_{10}BrNS$ requires C, 41·4; H, 4·3; N, 6·0%). Basifying an aqueous solution and extracting with ether gave 4-allylthiopyridine, n_D^{18} 1·5875, which formed a picrate, m. p. 147°.

4-*Benzylthiopyridine*.—The thione (III; R = CH_2Ph) (0·61 g.), when heated on a boiling-water bath, gave the product (0·24 g.), m. p. 70° [from light petroleum [b. p. 40—60°) (charcoal)], $\lambda_{max.}$ 265 mμ (ε 12,500) (picrate, m. p. 170°) (lit.,[12,13] base, m. p. 70—71°; picrate, m. p. 170°).

Di-4-pyridyl Sulphide.—The thione (III; R = $Cl{\cdot}CH_2{\cdot}CH_2$) (0·54 g.), heated as in the previous experiment, gave the product [11] (0·2 g.), m. p. and mixed m. p. 72° (authentic ultraviolet spectrum).

4-*Benzoylthiopyridine*.—1,4-Dihydro-4-thiopyridine (1·11 g.), sodium hydrogen carbonate (1 g.), and benzoy lchloride (1·4 g.) gave the 4-*benzoylthiopyridine* (0·63 g.) as plates, m. p. 76° [from light petroleum (b. p. 40—60°)], $\lambda_{max.}$ 243 (ε 11,100), 268 mμ (ε 12,600), under the conditions described for the esters (III) (Found: C, 66·45; H, 4·2; N, 6·4. $C_{12}H_9NOS$ requires C, 67·0; H, 4·2; N, 6·5%). This product gave a *picrate*, needles, m. p. 164° (from methanol) (Found: C, 48·9; H, 2·7; N, 12·15. $C_{18}H_{12}N_4O_8S$ requires C, 48·65; H, 2·7; N, 12·6%).

1-*Acetyl*-1,4-*dihydro*-4-*thiopyridine*.—1,4-Dihydro-4-thiopyridine (1·11 g.) was dissolved in warm acetic anhydride (2 ml.), and the solvent was removed under reduced pressure on a water-bath. The residue which crystallized on cooling gave the *acetyl derivative* (0·61 g.), m. p. 89°, as crimson prisms from benzene–light petroleum (b. p. 40—60°), $\lambda_{max.}$ 252, 378 mμ (Found: C, 55·0; H, 4·7; N, 9·1. C_7H_7NOS requires C, 54·9; H, 4·6; N, 9·15%).

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[13] Comrie and Stenlake, *J. Pharm. Pharmacol.*, 1961, **13**, 26.