Physical Sciences Section

Pakistan J. Sci. Ind. Res., Vol. 30, No. 7, July 1987

SYNTHESIS OF SUBSTITUTED PYRIDINES

Part VIII. Formation of 1, 2-dihydro-4,-hydroxy-2-oxo-1-phenylpyridine-3-methylcarboxy-6-substituted carbamates and thiocarbamates*

M. A. Butt, Rasheeda Parveen, Rashid Kemal and Abdul Salam

PCSIR Laboratories, Off. University Road, Karachi-39

(Received December 30, 1986; revised April 22, 1987)

Alkyl-1, 2-dihydroxy-2-oxo-1-phenyl pyridine-3-carboxylates (I) react with N-substituted isocyanates and isothiocyanates in the presence of a base like triethylamine to yield their respective carbamate and thiocarbamate salts (II). U.V. and I.R. spectra of the new products have been recorded.

Key words: Isocyanate; Carbamate; Thiocarbamate.

INTRODUCTION

It has been demonstrated earlier [1] that the hydroxyl group at position 6 adjacent to the nitrogen in the dihydroxy pyridines (I) was relatively more reactive than the one at position 4, which followed from the fact that compounds of the type (I) on treatment with diazomethane, were methylated [2] invariably at position 6. In continuation of this work, studies on the formation of carbamates and thiocarbamates at position 6, are now reported. For example, it was found that when methyl 1,2-dihydro-4, 6-dihydroxy-2-oxo-1-phenylpyridine-3-carboxylate (I, R=Ph, R′ = CH_3) and phenylisothiocyanate were reacted together in the presence of triethylamine, it yielded an amine salt of the structure (II, R=Ph, R′ = CH_3, R″=Ph, R‴ = $N(C_2H_5)_3$, m.p. 156° (dec.), the latter on being hydrolysed with acidic ethanol (50 %) gave 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxycarbonyl-6-N-phenyl-thiocarbamate, (III, R=Ph, R′=CH_3) m.p. 200°C, while the OH group at position 4, remained unaffected. The presence of the latter was authenticated by formation of quarternary amine salts with ammonia, ethylamine, diethylamine and triethylamine of the formula (VII, R=R″=Ph, R′=CH_3) (V, R=R″=Ph, R′=CH3), VI, R=R″= Ph) and II, R=R″=Ph, R′=CH_3) respectively. The reactions of the formulation of carbamates and thiocarbamates are depicted in the following chart.

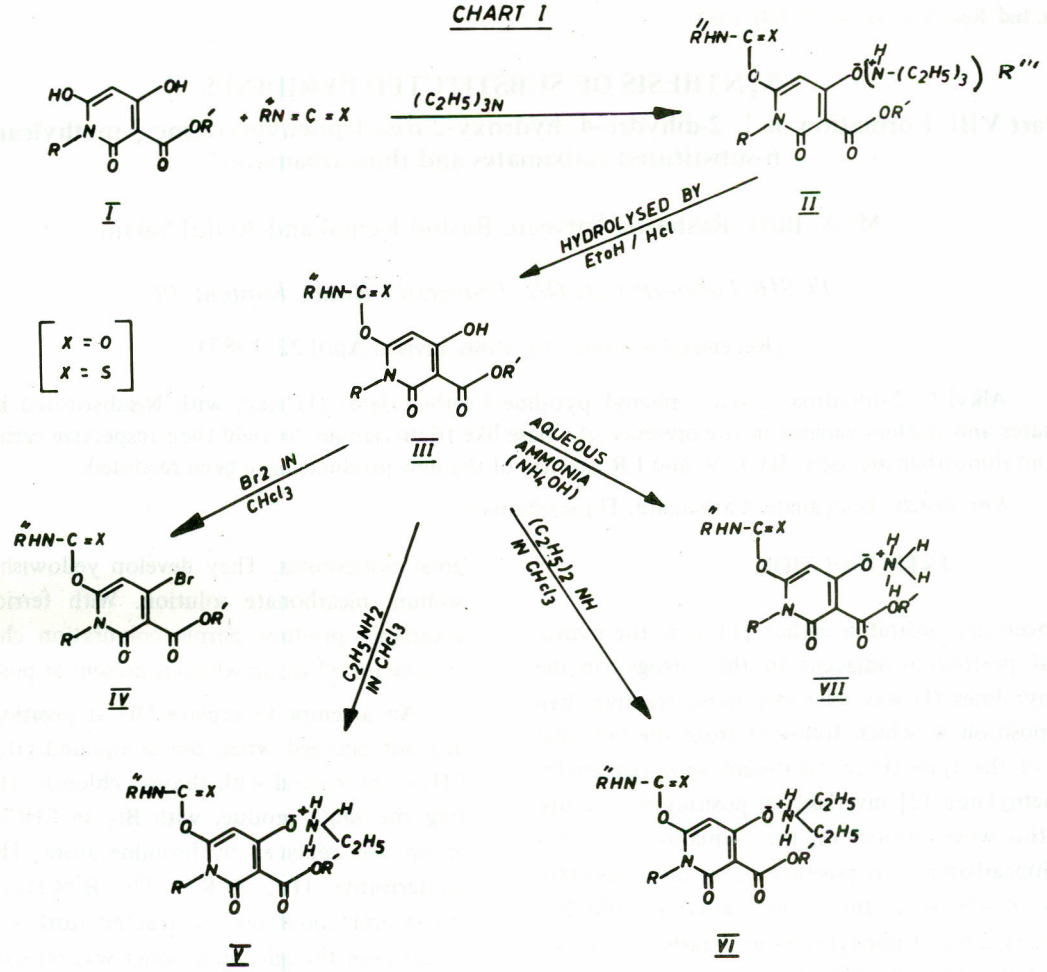
These carbamates (III, X=O) and thiocarbamates (III, X=S) are characterised by their insolubility in water and are soluble in dilute aquous alkalies like dil. sod. hydroxide solution. They are insoluble in dilute sulphuric acid but are easily dissolved in conc. sulphuric acid, re-precipitated on dilution with water giving back the original compounds. They develop yellowish colour with aq. sodium bicarbonate solution. With ferric chloride, they invariably produce purple colouration characteristic of a free hydroxyl group which is present at position 4.

An attempt to replace OH at position 4 by chlorine did not succeed when the compound (II, R=R″=Ph, R′=CH_3) was reacted with thionyl chloride. However, on reacting the same product with Br_2 in $CHCl_3$, the hydroxyl group was replaced by bromine atom. The resulting bromoderivative (IV, R=R″= Ph, R′=CH_3) was extremely stable and could not be reacted further with methoxide group even though the product was refluxed with sodium-methoxide in methanol for several hours. As demonstrated earlier, the OH at position 4, resisted formation of carbamate when reacted with several alkyl and aryl isocyanates and isothiocyanates. It preferably formed quarternary salts with secondary and tertiary amines, while no salt could be obtained with primary aromatic amine such as aniline etc.

The I.R. spectra of the carbamates and thiocarbamates (Table 1) and their amine salts (Table 2) have been studied. It was found that each of carbamates and thiocarbamates showed a single broad band between 1640 cm^{-1} and 1630 cm^{-1} attributable to pyridone carbonyl at position 2. While ester carbonyl at position 3 appeared at 1660 cm^{-1}. There were broad weak bands near the region 3310 cm^{-1} and 3410 cm^{-1} due to -NH at (6) and OH at (4). However, in case of amine salts (II) CO at position 2 absorbed between 1620 cm^{-1} and 1640 cm^{-1}, while ester CO at position 3 appeared invariably near 1600 cm^{-1} and 1710 cm^{-1}. While the absorption due to NH appeared characteristically at 2730 cm^{-1} and 2080 cm^{-1} which coincides with the findings recorded by Bellants *et. al* [2] for salts of triamines. These observations are in agreement with the

*Part VII. Published in Pakistan J. Sci. Ind. Res., 19, 103 (1976).

CHART I



structure assigned to these tables that the latter absorbed U.V. light in the 270-280 A^{O} region unlike the parent dihydroxy pridone (I) which have characteristic absorption [3] at 305^{O} irrespective of the substituent at position. This shift of 25 A^{O} units to the lower side seems due to the carbamate substituent at position 6.

Several carbamates and thiocarbamates and their amine salts prepared through this procedure are recorded in the following Tables I and 2 respectively along with their IR and UV spectroscopic data.

EXPERIMENTAL

Triethylamine salt of 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxy-carbonyl-6-N-phenylthiocarbamate (II, R=R''=Ph, R'''=N(C_2H_5)$_3$). Methyl-1, 2-dihydro-4, 6-dihydroxy-2-oxo-1-phenylpyridine-3-carboxylate (I, R=Ph, R'=OCH_3) (2.61 g, 0.01 mole) phenylisothiocyanate (1.35 g; 0.01 mole) and triethylamine (1.01 g; 0.01 mole) were heated on a water bath under anhydrous condition for 2 hrs. Excess of triethylamine was removed under vacuum and the residue was triturated with ether. White solid of triethyamine salt (II, R=R''=Ph, R'''=N(C_2H_5)$_3$)(4.47 g; 89.9 %) was obtained, which on recrystallisation from methanol-ether mixture, melted at 156-7^{O}C (dec.) Found : C,62.70; H, 6.20: N,8.3 : S, 6.30 % $C_{26}H_{31}N_3O_5S$ requires : C, 62.8; H, 6.20; N, 8.50; S, 6.4 %.

The salt (II, R=R''=Ph, R'=OCH_3, R'''=N(C_2H_5) 2.48 g was hydrolysed by the addition of an acidic soln. of ethanol (50 %) 20 ml. 1, 2-dihydro-4-hydroxy-2-oxo-phenylpyridine-3-methoxycarbonyl-6-N- phenylthiocarbamate (III, R=R''=Ph, R'=OCH_3), (1.8 g; 72 %) was filtered, washed with water, dried and recrystallised from methanol, m.p. 200^{O} (turns red and shrinks) Found : C,60.80; H, 3.50; N, 6.90; S, 8.30 % $C_{20}H_{16}N_2O_5S$ requires : C, 60.70; H, 4.00; N, 7.10; S, 8.10 %.

Triethylamine salt of 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxycarbonyl-6-(N-phenylcarbamate) (II, R=R''=Ph, R'=CH_3). Methyl-1, 2-dihydro-compound (I, R=R''=Ph, R'=CH_3) (2.61 g; 0.01 mole), phenylisocyanate (1.19 g; 0.01 mole) and triethylamine (1:01 g; 0.01 mole) were heated together under anhydrous conditions for 2 hrs. Excess of triethylamine was removed under vacuum and the residue triturated with ether. Trie-

thylamine salt of carbamate (II, R=R″=Ph, R′ = CH_3) was obtained as a white solid (3.61 g; 78.3 %), which was crystallised from methanol, had m.p. 160° (dec.) Found : C, 64.60; H, 6.30; N, 8.60; $C_{26}H_{31}O_6N_3$ requires C, 64.80; H, 6.40; N, 8.70. The amine salt (2.4 g) when hydrolysed by acidic ethanol sol. 20 ml; 50 % 1, 2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxycarbonyl-6-(N)-phenyl-carbamate (II, R=R″=Ph, R′=CH_3, R′′′=$(C_2H_5)_3N$) was obtained as a white solid (1.8 g; 75 %), which was washed dried and recrystallised from methanol. It melted at 215° Found : C, 63.50; H, 4.00; N, 7.40 % $C_{20}H_{16}N_2O_6$ requires: C, 63.10; H, 4.20; N, 7.30 %).

Triethylamine salts of carbamates and thiocarbamates (II) prepared similarly as described above, are recorded in Table 3 while the hydrolysed products (represented by formula (III) are listed in Table 4.

1, 2-Dihydro-4-bromo-2-oxo-1-phenylpyridine-3-methoxycarbonyl-6-N-phenylthiocarbamate (IV, R=R″=Ph). To the thiocarbamate (II, R=R″=Ph, R′=CH_3) (0.4 g, 0.001 mole) in chloroform (20 ml) was added bromine solution (Br_2 in $CHCl_3$; 5 %) until the colour of the latter persisted. The reaction mixture was allowed to rest at room temperature for thirty minutes. The solid was separated by filtration and washed with ether. 4-Bromo-derivative (IV) (0.2 g; 43.5 %) was obtained which on recrystallising from chloroform, showed m.p. 272° (dec.) λ_{max} 270 mμ, log ε 4.31. Found: C, 52.10; H, 3.10; N, 5.80; S, 6.50; Br, 16.8 % $C_{20}H_{15}BrN_2O_4S$ requires: C, 52.30, H, 3.30; N, 6.10; S, 7.0; Br, 17.4 %.

Diethylamine salt of 1, 2-dihyro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxycarbonyl-6-(N-phenyl) thiocarbamate (VI, R=R″=Ph, R′=CH_3): The thiocarbamate

Table 1. UV and IR spectra of 1,2-dihydro-4-hydroxy-2-oxo-1-phenyl pyridine 3-methoxy-6N-(alkyl and aryl substituted) carbamates and thiocarbamates (III, X=O, S).

S. No.	III		UV Light absorbtion in MeOH		IR Spectroscopic data in the region 3 – 6.7μ (KBr disc)			
	R″	X	λmax. mμ	logε	νmax. cm^{-1} C=O (2) and est. (3)	NC=X (6)	–NH(6) and OH(4)	
1.	*n*-Butyl-	O	267	4.19	1640s 1660sb	1565	2960s	3250s
2.	Phenyl-	O	280	4.20	1640s 1660s	1540	3050s	3360wb
3.	1-Naphthyl-	O	286	4.23	1630s 1660s	1565	2950s	3280s
4.	Acetyl-	S	280	4.06	1640sb 1660sb	1580	3310s(m)	3410m
5.	Methyl-	S	280	4.07	1640 1660	1530	3010bs	3110wb
6.	Ethyl-	S	280	4.24	1640s 1650	1520 1540	3000s(m)	3450wb
7.	Allyl-	S	280	4.03	1620s 1640s	1520	2960m 3080m	
8.	*n*-Propyl-	S	300	4.19	1660s 1680sb	1540 1560	2960s(m)	3260m
9.	*p*-Tolyl-	S	290	4.24	1640s 1660sb	1520b(m)	2920m	3020wb
10.	*p*-Bromophenyl-	S	290	4.13	1620s 1640s	1500b(w)	2960m	3400wb
11.	*m*-Methoxyphenyl-	S	280	4.18	1640s 1670s	1530	2920m	2960wb
12.	β-Phenylethyl-	S	280	4.18	1640s 1660s	1520	3020m	3400wb
13.	Phenyl-	S	288	4.13	1640s 1660s	1520b(m)	2900s(b)	

Table 2. UV and IR spectra of 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxy-6N-(alkyl and aryl substituted) carbamate, thiocarbamate, triethylamine salts II .

III			UV Light absorbtion 95 % Methanol		IR Spectroscopic data in the region 3 – 6.7μ (KBr disc)			
S.No.	R″	X	$\lambda_{max.}$ mμ	logε	$\nu_{max.}$ cm^{-1} C=O(2) and est. (3)		$\overset{+}{N}$H(6)	
1.	Acetyl-	S	267	4.29	1620s	1700s	2080,	2730w
2.	Methyl-	S	282	4.14	1620s	1705s	2240	2720m
3.	Ethyl-	S	282	3.96	1610s	1680s	2180	2700w
4.	Allyl-	S	282	4.17	1610s	1698s	2240	2670m
5.	*n*-Propyl-	S	282	4.15	1605s	1698s	2220,	2680w
6.	*p*-Tolyl-	S	288	4.24	1610s	1695s	2220m	2680b
7.	*p*-Bromophenyl-	S	289	4.30	1640s	1665s	2220,	2775m
8.	*m*-Methoxyphenyl-	S	288	4.23	1600sb	1690	2160	2680w
9.	β-Phenylethyl-	S	280	4.20	1600s	1705s	2320	2690m
10.	Phenyl-	S	288	4.13	1620s	1710s	2240m,	2720m

Table 3, 1,2-Dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxy-6N-alkyl and aryl substituted carbamates (III, X=O) and thiocarbamate triethylamine saltes (II, X=S).

S. No.	Alkyl, aryl isocyanate and Isolthiocyanates (0.01 mole)	1,2-Dihydro-2-oxo 1-phenylpyridine-6 N-Alkyl and Aryl substituted carbamates (III, X=O) and thiocarbamate triethylamine salts* (II, X=S) R″	% Yield	Solvent for crystalization	m.p. °C	Molecular formula	Analysis required % C	H	N	S	Analysis found % C	H	N	S
1.	C_6H_5NCO (1.19 g)	Phenyl-	95	MeOH	215°	$C_{20}H_{16}N_2O_6$	63.16	4.21	7.37	–	63.52	4.09	7.42	–
2.	n-C_4H_9NCO (0.99 g)	*n*-Butyl	92	MeOH	165-7°	$C_{20}H_{16}N_2O_6$	60.00	5.56	7.77	–	59.91	5.50	7.75	–
3.	1-$C_{10}H_7NCO$ (1.65 g)	*1*-Naphthyl	90	MeOH	274-5°	$C_{24}H_{9\,18}N_2O_6$	66.97	4.18	6.51	–	66.78	4.20	6.38	–
4.	CH_3-CO.NCS (0.01 g)	Acetyl-	80	Ether: Pet.ether	142°(d)	$C_{12}H_{29}N_3O_6S$	57.02	6.26	9.07	6.91	56.97	6.27	9.05	6.71
5.	CH_3.NCS (0.73 g)	Methyl-	85	MeOH: ether	179-80°(d)	$C_{21}H_{29}N_3O_5S$	57.93	6.66	9.65	7.35	58.18	6.52	9.63	7.65
6.	C_2H_5-NCS (0.87 g)	Ethyl-	90	Acetone: ether	148°(d)	$C_{22}H_{31}N_3O_5S$	58.79	6.90	9.35	7.12	58.74	6.94	9.27	7.26
7.	CH_2:CH.CH_2.NCS (0.99 g)	Allyl-	80	MEOH: ether	146°(d)	$C_{23}H_{31}N_3O_5S$	59.86	6.72	9.11	6.94	60.20	6.65	9.07	6.56
8.	CH_3-C_6H_4.NCS (1.01 g)	*m*-Tolyl-	85	Ether: Pet.ether	140°(d)	$C_{23}H_{23}N_3O_5S$	59.61	7.12	9.07	6.91	59.60	7.11	9.05	7.16
9.	*p*-CH_3.C_6H_4.NCS (1.49 g)	*p*-Tolyl-	90	Ether: Pet.ether	177°(d)	$C_{27}H_{33}N_3O_5S$	63.40	6.45	8.21	6.26	63.44	6.49	8.24	5.98
10.	*p*-Br.C_6H_4.NCS (2.14 g)	*p*-Bromophenyl-	90	Ether: Pet. ether	169°(d)	$C_{26}H_{30}BrN_3O_5S$	54.16	5.20	7.29	5.55 Br=13.88	54.46	5.24	7.01	4.90 Br=14.02
11.	*m*-CH_3O.C_6H_4.NCS (1.65 g)	*m*-Methoxyphenyl-	92	Ether: Pet. ether	129-30°(d)	$C_{27}H_{33}N_3O_6S$	61.48	6.26	7.96	6.07	61.50	6.25	7.93	6.25
12.	β-C_6H_5.CH_2.CH_2NCS (1.62 g)	β-Phenylethyl-	90	Ether: Pet. ether	166-68°	$C_{28}H_{24}O_5S$	64.12	6.48	8.01	6.10	64.07	6.64	7.80	6.29
13.	C_6H_5.NCS (1.35 g)	Phenyl	90	Ether: Pet. ether	156-7°(d)	$C_{26}H_{31}N_3O_5S$	62.77	6.23	8.45	6.43	62.71	6.23	8.29	6.25

(*) Carbamates and triethylamine salts of thiocarbamates were prepared by reacting 0.01 mole of methyl 1,2-dihydro-4, 6-dihydroxy-2-oxo-1 phenyl pyridine-3-carboxylate (I) with 0.01 mole of the isocyanate or isothiocyanate and 0.01 mole of triethylamine.

compound (III, R=R″-Ph, R′=CH_3) 1 g; .0025 mole) was suspended in chloroform and mixed with diethylamine liquid (0.1 ml; .005 mole) and the mixture was refluxed for 15 minutes. Excess of the liquid reactant along with chloroform was removed under vacuum. Diethylamine salt of thiocarbamate (VI, R=R″=Ph, R′=CH_3) was collected as a white solid (0.89 g; 67.8 %), which on recrystallisation from acetone, had m.p. 195°C (dec.), λ_{max} 280 mμ;

Table 4. 1,2-Dihydro-4-hydroxy-2-oxo-1-phenyl pyridine-3-methoxy 6N-alkyl and aryl substituted thiocarbamates III.

S. No.	Substituted alkyl, aryl thiocarbamate, triethylamine salts (II) R″	1,2-Dihydro-2-oxo-1-phenyl pyridine 6N-alkyl and Aryl thiocarbamates (III) R″	% Yield	m.P. °C	Molecular	Analysis required %				Analysis found %			
						C	H	N	S	C	H	N	s
1.	Aryl- (2.3 g)	CH_3-CO-	90	212°(d)	$C_{16}H_{14}N_2O_6S$	53.03	3.86	7.73	8.83	53.02	3.76	8.62	9.97
2.	Methyl- (2.1 g)	CH_3-	93	228°(d)	$C_{15}H_{14}N_2O_5S$	53.89	4.19	8.38	9.58	53.75	4.15	8.37	9.68
3.	Ethyl- (2.2 g)	C_2H_5-	94	180°	$C_{16}H_{16}N_2O_5S$	55.17	4.59	8.04	9.19	55.43	4.64	8.06	9.33
4.	Allyl- (2.3 g)	CH_2:CH.CH_2-	90	192°(d)	$C_{17}H_{16}N_2O_5S$	56.66	4.44	7.77	8.88	56.78	4.32	7.71	8.97
5.	*n*-Propyl- (2.3 g)	CH_3.$(CH_2)_2$-	94	176°	$C_{17}H_{18}N_2O_5S$	56.35	4.97	7.73	8.83	56.25	4.81	7.74	8.81
6.	*p*-Tolyl- (2.5 g)	*p*-$CH_3C_6H_4$-	94	210°(d)	$C_{21}H_{18}O_5S$	61.46	4.39	6.82	7.80	61.74	4.45	6.81	7.77
7.	*p*-Bromophenyl- (2.8 g)	*p*-$Br.C_6H_4$-	91	184°(d)	$C_{20}H_{15}BrN_2O_5S$	50.53	3.15	5.99	6.73	50.50	3.06	5.83	6.70
8.	*m*-Methoxyphenyl- (2.6 g)	*m*-$CH_3O.C_6H_4$-	95	220°(d)	$C_{21}H_{18}N_2O_6S$	59.18	4.22	6.57	7.51	59.18	4.21	6.56	7.49
9.	β-Phenylethyl- (2.6 g)	β-$C_6H_5.CH_2.CH_2$-	95	220°(d)	$C_{22}H_{19}N_2O_5S$	62.41	4.49	6.61	7.56	62.36	4.57	6.61	7.59

(*) All products were crystallised from methanol.

log ϵ=4.21. Found: C, 61.50; H, 8.90; S, 6.60 % $C_{24}H_{26}N_3O_5S$ requires : C, 61.50; H, 5.6; N, 9.00; S, 6.90 %.

The salt (VI, R=R″=Ph, R′=CH_3, R′ ′ ′=$(C_2H_5)_2NH$) when treated with acidic solution of ethanol (50 %) precipitated the original 4-hydroxythiocarbamate (III, R=R″=Ph, R′=CH_3), m.p. and mixed m.p. 200°. Found: C, 60.60; H, 3.90; N, 6.80; S, 7.90 % $C_{20}H_{16}N_2O_5S$ requires : C, 60.70; H, 4.00; N, 7.10; S, 8.10 %.

Ethylamine salt of 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxycarbonyl-6-N-phenylthiocarbamate (III, R′=R″=Ph, R′=CH_3). To the thiocarbamate (III, R=R″=Ph, R′=CH_3) 1 g; .0025 mole) suspended in chloroform (10 ml), was added ethylamine solution in $CHCl_3$ (20 ml; 2.5 %) and the mixture was refluxed on water bath for 15 mins. Excess of the solvent was removed under vacuum and the residue on triturating with ether, yielded ethylamine salt (V, R=R″=Ph, R′=CH_3) (0.8 g; 72 %) which on recrystallisation from acetone-ether mixture (1:1) melted at 167° (dec.), and showed no colouration with aq. $FeCl_3$ solution. It absorbed U.V. light in the region λ_{max} 280 mμ, log ϵ=4.2. Found: C, 64.10; H, 5.00; N, 9.40; S, 7.00 % $C_{22}H_{22}N_3O_5S$ requires: C, 64.4; H, 5.20; N, 9.50; S, 7.3 %.

The original thiocarbamate (II, R=R″=Ph, R′=CH_3) was regenerated when the salt (V, R=R″=Ph, R′=CH_3, R′ ′ ′=$C_2H_5NH_2$) in aq. ethanol (50 %) was acidified with dil. HCl(2H).

Ammonium salt of 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-methoxycarbonyl-6-N-phenylthiocarbamate (VII, R=R″=Ph, R′=CH_3). To the thiocarbamate (III, R=R″=Ph, R′=CH_3) (1 gm; 0.0025 mole) in 100 ml. flask was added slowly aqueous ammonia (25 %) while mixture was agitated constantly. The colour of the solution turned yellow. Ammonium salt (VII, R=R″=Ph, R′ ′ ′=NH_4) (0.8 g; 77 %) separated and on recrystallising from ethanol, melted 165° (dec.). It gave no colouration with aq. $FeCl_3$: It absorbed U.V. light in region λ_{max} 260 mμ, log ϵ=4.3. Found: C, 58.90; H, 4.30; N, 10.10; S, 7.5 % $C_{20}H_{19}N_3O_5S$ requires : C, 58.10; H, 4.60; N, 10.20; S, 7.4 %.

The ammonium salt on treatment with acidic ethanol regenerated the original thiocarbamate (III, R=R″=Ph, R′=CH_3), which was authenticated by taking a mixed melting point with the original sample.

Acknowledgement. The authors thank Dr. S.S. H. Rizvi, Director, PCSIR Laboratories, Karachi for his advice and help in this work and we also express our gratitude to Dr. A.S. Gilbert, The Wellcome Research Laboratories, England, for carrying out microanalysis of these compounds. We are also grateful to Mr. Mohammad Aleem Ahmed, Scientific Officer, PCSIR Laboratories, Karachi for his technical assistance.

REFERENCES

1. A. Butt, M. Hassan and Z. Mannawwar, Tetrahedron, **23**, 2461 (1967).
2. Bellants and Barcello, Anales Real Soc. Espon. fis. y. quin. Madrid, **52B**, 469 (1956).
3. H. Specker and H. Gawrasch, Ber, Dtsch, Chem. Des., **75**, 1338 (1942).