

SYNTHESIS OF HETEROBICYCLIC COMPOUNDS

Part V. Formation of 4,5-dioxopyridino-(3,4-e)(1,3)-oxazines*

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Abstract. 1-Substituted -1,2-dihydropyridinodioxines (1) with one molecule of alkylamine (2) yield in general 3-substituted derivatives of 2,2-dimethyl-4,5-dioxo-2,3,5,6-tetrahydropyridino-(3,4-e)(1,3)-oxazine system (3) quantitatively. The products (3A) are very stable to acidic and basic reagents but methoxide in methanol degraded (3) R=Ph; R'=Et) diagnostically first to an amide (4) and then to the pyridone ester (5). The latter was prepared authentically from a known route. IR and UV spectra have also been recorded in support of structure 3A.

Earlier attempts to form pyridinooxazines from amino-pyranooxazine were unsuccessful [1]. Another route to form pyridinooxazine from pyridinoanilides (14,15) and phosgene in alkaline media precipitated only the starting material. While these attempts were underway, Crum and Frankes [2], reported one of the four possible pyridinooxazines 2H-pyrido - (4,3-e)-1,3-oxazine-2,4-(3H)-dione (12) and also mentioned another [3] analogue, 2-H-pyrido- (2,3-e) - 1,3-oxazine-2,4 (2H) - dione (13).

A new general route to the synthesis of derivatives of the system 4,5-dioxo-pyridino (3,4-e)-(1,3)-oxazine (3A) is now reported.

It was found that on treatment of 7-methoxy-2,2-dimethyl-4,5-dioxo-6-phenylpyridino-(1,3)-dioxine [4] (1, R=Ph) with one mole of methylamine yielded a product with a formula $C_{17}H_{18}NO_4$, mp 236° (3A, R=Ph, R=Me)

evidently formed by the replacement of one oxygen atom by nitrogen as depicted in Chart 1.

There are two possible formulas that the new product 3 could be assigned, i.e. structures 3A and 3B. The latter is rejected on the following basis:

(1) The dioxin ring in product 1 and α -pyrones, both have anhydride structure and the latter is converted easily into pyridones [5]. It is more likely therefore that an amino group replaces oxygen at position 3 than at 1. This favours formula A.

(2) The evidence in favour of structure 3A is strengthened by formation of first an amide, $C_{15}H_{15}N_2O_4$ (4, R=Ph, R'=Et), mp 148° , and then a pyridone ester (5, R=Ph) whose structure itself was confirmed by forming it from a known compound (6, R=Ph). The formation

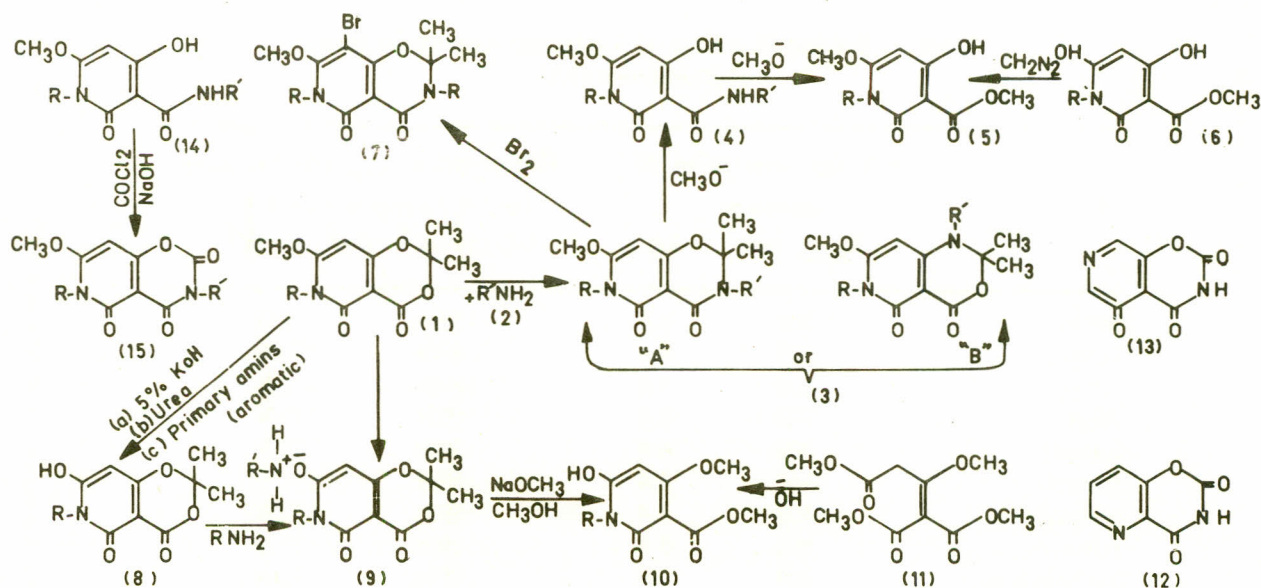


Chart I

*Part IV. Pakistan J. Sci. Ind. Res., 15, 243 (1972).

of these two products is possible only, if the product (3) has the structure A.

Compounds 3A are rather stable being unchanged either on attempted hydrolysis of methoxy at position (7) with 2N HCl and with alcoholic alkali, or on reaction with s- amines. The product (3A, R=Ph, R' = Et), however, on bromination formed a bromoderivative (7, R = Ph, R' = Et), mp 198°C, λ_{\max} 309, log ϵ 4.4. Aromatic amines did not react with compounds 1 to form products 3A, but instead they hydrolysed the 7-methoxy group to form an hydroxy product 8. Attempts to react the latter compound (8, R=Ph) with primary and secondary amines were also not achieved because adducts were formed which stabilised the compound against further attack. However, the adduct (9, R=Ph, R'=Et) with methoxide in methanol gave a previously known [6] product.

Studies IR and UV spectra supported structure (3A) for the new products. The stretching frequencies due to pyridone carbonyl at position 5 and oxazine carbonyl at position 4 are not affected notably by various substituents at position 3. Thus the amide carbonyl at the 4 position absorbed typically at ν 1701-1723 cm^{-1} and at 5-position it absorbed at ν 1685-1699 cm^{-1} . This compares favourably well with carbonyl frequencies data for such type of compounds found by Crum and Frankes [2].

The IR spectrum for product 4, (R=Ph, R'=Et) has also been found to correspond to the structure assigned to it, for instance, there are two broad bands in the region 2660 cm^{-1} and 3080 cm^{-1} , mainly due to bonded OH and NH. The amide carbonyl 3 absorbed at

1669 cm^{-1} while the pyridone carbonyl at position 2, absorbed at λ 1645 cm^{-1} .

The UV spectra of compounds 3A in methanol contained a characteristic absorption maximum in the region 307-309nm (Table 1) while the parent dioxin[4] system (1) absorbed at 311-316nm. This showed that replacement of oxygen by nitrogen in compounds represented by formula 1 does not affect the absorption considerably i.e. only to the extent of (4-7 nm). A similar situation is observed on converting α -pyrones to α -pyridones. The UV absorption for the product (4, R=Ph, R'=Et) was in the region λ_{\max} , 305 nm, log ϵ 4.2), characteristic for pyridones [6].

EXPERIMENTAL

2,2-Dimethyl-4,5-dioxo-7-methoxy-3-methyl-6-phenyl-2,3,5,6-tetrahydropyrido-(3,4,e)-(1,3)-oxazine (3A, R=Ph, R'=CH₃).

To the 7-(methoxy)-dioxine (1, R=Ph) (0.5g) suspended in dry acetone (70 ml), was passed methylamine gas (2 min). The solution was dried under reduced pressure and the solid residue crystallised from dry acetone to give prismatic rods of the pyridooxazine (3A, R=CH₃, R'=Ph) (0.3 g) m.p. 235° (decomp).

Found: C, 65.0; H, 5.9; N, 8.9. C₁₇H₁₈N₂O₄ requires: C, 64.6; H, 5.7; N, 9.0%.

Several other pyridinooxazines prepared as above are listed in Table 2.

Table 1. UV and IR spectra of 3-substituted pyridino-(3,4-e)-(1,3)-oxazines (3A).

R	UV light absorption 95% methanol			IR absorption λ_{\max} (cm^{-1}) mainly for 3-6.7 μ region (KBr)	
	λ_{\max}	$\mu\mu$	log ϵ	C-O (5) cm^{-1}	C-O (4) cm^{-1}
Methyl-	309		4.4	1690s	1701s
Ethyl-	308		4.4	1690s	1708s
n-Propyl-	309		4.4	1690s	1712s
Allyl-	307		4.4	1685s	1719s
n-Butyl-	309		4.4	1698s	1712s
Benzyl-	307		4.4	1695s	1705s
n-Hexyl-	309		4.4	1693s	1723s
n-Nonyl-	309		4.4	1692s	1712s
β -Phenylethyl-	309		4.4	1699s	1720s

Table 2. Formation of 3-Substituted 2,2-Dimethyl-4,5-dioxo-7-methoxy-6-phenyl-2,3,4,6-tetrahydropyridin (3,4-e) (1-3)oxazines (solvent for crystallisation: acetone-petroleum ether).

Alkylamines	Quantity (ml)	Reactions (min)	Product (yield)	mp (°C)
Ethylamine	5ml (70%) aq. soln	20	3-Ethyl- 92%	190
n-Propyl- amine	0.5	20	3-Tropyl- 96%	137
Allylamine	0.5	20	3-Allyl- 90%	160
n-Butlamine	0.5	20	3-Butyl 95%	180
Cyclohexyl- amine	0.5	20	3-Cyclohexyl 90%	182
Nonylamine	0.5	20	3-Nonyl 92%	94
Benzylamine	0.5	20	3-Benzyl 91%	176
β -Phenyl- ethylamine	0.5	20	3-Phenyl- ethyl 90%	110

Molecular formula	Analysis required %			Analysis found %		
	C	H	N	C	H	N
$C_{18}H_{20}N_2O_4$	65.9	6.1	8.5	65.6	5.9	8.7
$C_{19}H_{22}N_2O_4$	66.7	6.4	8.2	66.2	6.3	8.4
$C_{19}H_{20}N_2O_4$	67.1	5.9	8.2	66.7	5.7	8.5
$C_{20}H_{24}N_2O_4$	76.4	6.7	7.9	67.0	6.6	8.1
$C_{22}H_{26}N_2O_4$	69.1	6.8	7.3	68.7	6.7	7.6
$C_{25}H_{34}N_2O_4$	70.4	8.0	6.6	70.3	8.0	7.0
$C_{23}H_{22}N_2O_4$	70.8	5.6	7.2	70.4	5.5	7.5
$C_{24}H_{24}N_2O_4$	71.3	5.9	7.0	5.8	5.8	7.0

1,2-Dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-carboxy-N-ethylamide (4, R=Ph, R'=Et).

Product 3A (R=Ph, R'=Et) (200 mg) was poured into methanol (5 ml) containing sodium methoxide from sodium (60 mg). The mixture was heated under reflux for 30 min and freed from solvent under reduced pressure. The residue was diluted with water (25 ml) and acidified with 2N HCl. The solid was filtered and dried. It crystallised from acetone-petroleum ether in prismatic needles, m.p. 149°.

Found: C, 62.8; H, 5.8; N, 9.5. $C_{12}H_{16}N_2O_4$ requires: C, 62.5; H, 5.6; N, 9.7%.

Methyl -1,2-dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-carboxylate (5) from *1,2-Dihydro-4-hydroxy-6-methoxy-1-phenylpyridine-3-N-ethylcarboxamide* (4).

To a solution of methanol containing sodium methoxide, from sodium (0.28 g/10 ml) was added the pyridone-N-ethylamide (4) (0.2 g). The solution was refluxed for 40 min and the solvent removed. The residue was diluted with water and acidified (2N HCl). The solid thus obtained was filtered, washed, dried and weighed (0.10 g). It was crystallised from aqueous alcohol and it melted at 218° (decomp); there was no depression in admixture with the sample prepared as below. It gave reddish brown colour with aqueous ferric chloride and dissolved in aqueous sodium bicarbonate solution.

Found: C, 61.2; H, 4.7; N, 4.9. $C_{14}H_{13}NO_5$ requires C, 61.1; H, 4.7; N, 5.1%.

Methyl-1,2-dihydro-4-hydroxy-6-methoxy-1-phenylpyridine-3-carboxylate (5) from *methyl-1,2-dihydro-4-dihydroxy-1-phenylpyridine-3-carboxylate*.

4,6-dihydroxypyridine (6) (2.5 g) was dissolved in alcohol - chloroform mixture (500 ml, 1:1) and to it was added diazomethane solution in ether until the yellow colour persisted. The contents were allowed to rest for 2 hr and the solvent was removed under reduced pressure. On triturating the residue with acetone the solid pyridone (5, R=Ph) weighed (2.15 g) after being recrystallised from ethanol, it melted at 218° (decomp). It gave a reddish brown red colour with aqueous ferric chloride solution and dissolved in aqueous solution.

Found: C, 61.1; H, 4.7; N, 4.9. $C_{14}H_{13}NO_5$ requires: C, 61.1; H, 4.7; N, 5.1%.

Ethylamino salt of 2,2'-dimethyl-4,5-dioxo-7-hydroxy-6-phenylpyridino-(3,4-e)-(1,3)-dioxine (9, R=Ph, R'=Et).

7-Hydroxy compound 7 (0.5 g) in chloroform (10 ml) was treated with ethylamine (5 ml, 70% aq soln) and the mixture was refluxed for 15 min. The excess of liquid was removed under vacuum and the solid weighed (0.5 g). It melted at 182° (decomp) on recrystallisation from acetone-petroleum ether mixture. The compound gave coloration with aq ferric chloride and dissolved in aq sodium bicarbonate.

Found: C, 61.7; H, 5.8; N, 8.2. $C_{17}H_{13}N_2O_5$ requires: C, 61.8; H, 5.5; N, 8.5%.

Formation of methyl-6-hydroxy-4-methoxy-1-2-dihydro-1-phenyl-pyridine-3-carboxylate (10).

Ethylamino salt (9, R=Ph, R'=Et) (0.5 g) was added to methanol (20 ml) containing sodium methoxide from sodium (0.3 g), and the mixture refluxed for 30 min. The excess of the solvent was removed under reduced pressure and the residue diluted with water and acidified with HCl (2N). The white solid (0.4 g) was recrystallised from methanol and then had m.p. 253° (decomp). It gave a reddish brown colour with ferric chloride and was soluble in aq sodium bicarbonate. The product showed no depression in mp when admixed with an authentic [6] sample.

Found: C, 61.20; H, 4.2; N, 5.10. $C_{14}H_{13}NO_5$ requires: C, 61.10, H, 4.7, N, 5.10%.

Reaction of ethylamino salt (9, R=Ph, R'=Et) *with dilute HCl.*

Compound 9 (R=Ph, R'=Et) (0.5 g) was dissolved in water (10 ml) and the solution acidified with dilute HCl (2N). The precipitate was filtered and dried (0.4 g). It recrystallised from acetone and had mp 214° (decomp), identical in all respects with 2,2'-dimethyl-4,5-dioxo-7-hydroxy-6-phenylpyridino (4,3-e)-(1,3)-dioxin (IR and UV identical).

Found: C, 62.70; H, 4.50; N, 4.7. $C_{15}H_{13}NO_{15}$ requires: C, 62.70, H, 4.50; N, 4.9%.

Action of aqueous potassium hydroxide on 2,2'-dimethyl-4,

5-dioxo-7-methoxy-6-phenylpyridino (3,4-e)-(1,3)-dioxin (1, R=Ph).

Compound 1 (R=Ph) (0.5g) was treated with aq KOH (15%). The mixture was warmed on a water bath until the solid dissolved. This solution was acidified and the solid filtered off, dried and weighed (0.4 g). It reddened at 160° and melted at 214° (decomp). It was recrystallized from acetone. It gave no depression in mp with an authentic sample of 2,2-dimethyl-4,5-dioxo-7-hydroxy-6-phenylpyridino(3,4-e (1,3)-dioxin. It also gave aq ferric chloride test and dissolved in aq sodium bicarbonate.

Found : C, 62.9; H, 4.6; N, 5.0. $C_{15}H_{13}NO_5$ requires C, 62.7; H, 4.5; N, 4.9%.

Action of Aniline on the 7-methoxy compound (1, R=Ph)

7-Methoxy compound (1, R=Ph) (0.5 g) and aniline (0.5 ml), were warmed under anhydrous condition until the solid dissolved. Addition of petroleum ether precipitated the solid (0.4 g) which after being crystallised twice from acetone-chloroform, reddened at 160° and melted at 214° (decomp). It showed no depression in mp when admixed with an authentic sample of 7-hydroxy product (7, R=Ph).

Found: C, 62.8; H, 4.8; N, 4.6. $C_{15}H_{13}NO_5$ requires: C, 62.7; H, 4.5; N, 4.9%.

8-Bromo-3,4-dihydro-4,5-dioxo-2,2-dimethyl-3-ethyl-7-methoxy-6-phenylpyrido (3,4-e)-(1,3)-oxazine (7, R=Ph, R'=Et).

Ethyl oxazine 3A (R=Ph, R'=Et)(200 mg) was suspended in carbon tetrachloride (50 ml) and a dilute solution of bromine in carbon tetrachloride was added dropwise till a persistent yellow coloured solution was obtained. Solvent was removed under reduced pressure. The residue was crystallised from boiling carbon tetrachloride. The bromo derivative (0.18 mg) had mp 198°. It absorbed UV light at λ_{max} 319, $\log \epsilon$ 4.4.

Found : N, 7.0; Br, 20.3. $C_{20}H_{19}N_2O_4$ requires: N, 6.9; Br, 19.7%.

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