Chemistry of Heterocyclic Compounds, Vol. 34, No. 3, 1998

2-OXOOXAZOLOPYRIDINES.

2.* SYNTHESIS OF N′-ALKYL-N-(2-OXO-3-PYRIDYL)UREAS

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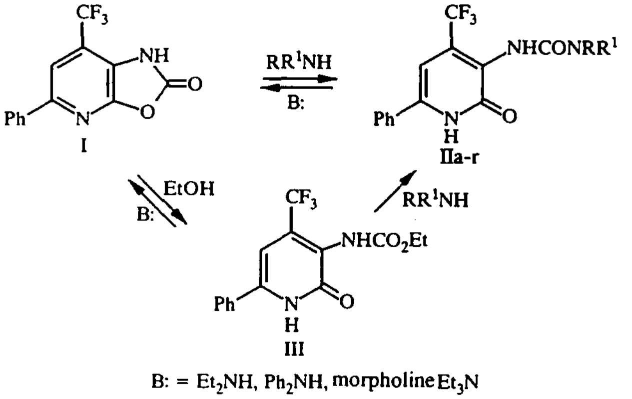
In reactions with amines 2-oxo-7-trifluoromethyl-5-phenyl-(1H)-oxazolo[5,4-b]pyridines and alkyl N-(2-oxo-3-pyridyl)carbamates are converted into N′-alkyl- and N,N′-dialkyl-N-(2-oxo-3-pyridyl)ureas respectively.

N′-Alkyl-N-(2-oxo-3-pyridyl)ureas and their properties and biological activity have been little studied [2-4]. 3-Pyridylureas are obtained in the reactions of pyridyl isocyanates [2, 5, 6], pyridyl azides [7], pyridylhydroxamic acids [8], and 2-oxooxazolo[5,4-*b*]pyridines [1, 9, 10] with amines.

It seemed to us expedient to study in greater detail the possibility of synthesizing 3-pyridylureas containing the CF_3 group in the molecule, for it extends the range of the biological activity of pyridine derivatives [11, 12]. While continuing the research in [1], we reacted 2-oxo-(1H)-oxazolo[5,4-*b*]pyridine (I) with ammonia, primary alkyl- and arylamines, aminoalcohols, and compounds containing a secondary amino group. In these reactions all the amino derivatives open the oxazolone ring with the formation of the corresponding 2-oxo-3-pyridylureas (IIa-r). Here, with the amines having the highest basicity (isobutylamine, allylamine, etc.) the reaction takes place even at room temperature, but the yields of the corresponding ureas do not exceed 36%. By heating it is possible to increase the yields to 93%. With weaker amines, such as *p*- or *m*-nitroanilines and 2,5-diaminopyridine, it was not possible to obtain the respective ureas, while with ammonia the reaction only took place under pressure.

The 3-pyridylureas (IId-g, i, k-n) were also obtained by heating 3-pyridyl carbamate (III) [13] with the respective amines.



B: = Et_2NH, Ph_2NH, morpholine Et_3N

1-Methyl-2-oxooxazolo[5,4-*b*]pyridine (IV) [13] and the carbamates (Va-c) [1] react with amines like the oxooxazole (I) and the carbamate (III). Thus, the same trisubstituted urea (VIa) was obtained when the oxooxazole (IV) and the 3-pyridyl carbamate (Va) [1] were heated with benzylamine.

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*For Communication 1, see [1].

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TABLE 1. Characteristics of Compounds (IIa-r)

Compound	R	R^1	Empirical formula	Solvent for recrystallization	Found % / Calculated %			mp, °C	PMR spectrum, δ, ppm, DMSO-d_6	IR spectrum, cm^{-1}	Yield, % (method)
					C	H	N				
1	2	3	4	5	6	7	8	9	10	11	12
IIa	H	H	$C_{13}H_{10}F_3N_3O_2 \cdot H_2O$	Ethanol	49,66 49,53	3,81 3,80	13,20 13,33	228...230	6,19 (2H, s, NH_2); 6,67 (1H, s, 5-H); 7,49 (3H, m, Ph); 7,64...7,96 (3H, m, Ph, NH); 12,42 (1H, NH)	3460, 3348, 3260, 2904, 1654, 1630, 1598, 1524	75,2
IIb	CH_3	H	$C_{14}H_{12}F_3N_3O_2$	DMFA – ethanol (3 : 10)	54,02 53,78	3,89 3,82	12,92 12,70	263...264	2,61 (3H, d, CH_3); 6,58 (2H, m, NH, 5-H); 7,47 (3H, m, Ph); 7,61...7,92 (3H, m, Ph, NH); 12,42 (1H, NH)	3324, 3280, 3200...2850, 1653, 1625, 1585	86,5 (A)
IIc	$CH(CH_3)_2$	H	$C_{16}H_{16}F_3N_3O_2$	DMFA	56,78 56,64	4,79 4,75	12,53 12,38	258...260	1,11 (6H, d, CH_3); 3,74 (1H, m, CH); 6,61 (2H, m, NH, 5-H); 7,51 (3H, m, Ph); 7,76 (3H, m, Ph, NH); 11,84 (1H, NH)	3298, 3200...2800, 1660, 1642, 1580	86,6 (A)
IId	$CH_2CH(CH_3)_2$	H	$C_{17}H_{18}F_3N_3O_2$	Ethanol	57,66 57,79	5,10 5,13	11,51 11,89	254...255	0,89 (6H, d, CH_3); 1,69 (1H, m, CH); 2,92 (2H, t, CH_2); 6,67...6,75 (2H, m, NH, 5-H); 7,50 (3H, m, Ph); 7,64...7,94 (3H, m, Ph, NH); 12,39 (NH)	3310, 3000...2800, 1660, 1634, 1578	36,0 (A*), 83,3 (B)
IIe	$(CH_2)_3CH_3$	H	$C_{17}H_{18}F_3N_3O_2$	DMFA – ethanol (3 : 10)	57,57 57,79	4,87 5,13	11,64 11,89	264...265	0,89 (3H, m, CH_3); 1,39 (4H, m, $2CH_2$); 3,08 (2H, m, CH_2); 6,50...6,89 (2H, m, NH, 5-H); 7,50 (3H, m, Ph); 7,64...7,94 (3H, m, Ph, NH); 12,40 (1H, NH)	3312, 3100...2860, 1642, 1630, 1578	59,3 (A), 81,3 (B)

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
IIf	$CH_2CH{=}CH_2$	H	$C_{16}H_{14}F_3N_3O_2$	DMFA	$\frac{56{,}87}{56{,}97}$	$\frac{4{,}16}{4{,}18}$	$\frac{12{,}43}{12{,}46}$	240...242	3,75 (2H, m, CH_2); 4,94...5,39 (2H, m, CH_2); 5,58...6,06 (1H, m, CH); 6,64 (1H, s, 5-H); 6,83 (1H, t, NH); 7,50 (3H, m, Ph); 7,64...8,01 (3H, m, Ph, NH); 11,68 (1H, NH)	3300, 3180...2860, 1661, 1653, 1579	93,3 (A), 34,0 (A*), 84,7 (B)
IIg	$(CH_2)_4CH_3$	H	$C_{18}H_{20}F_3N_3O_2$	DMFA	$\frac{58{,}54}{58{,}85}$	$\frac{5{,}41}{5{,}49}$	$\frac{11{,}24}{11{,}44}$	246...247	0,61...1,64 (9H, t, CH_3, m, $(CH_2)_3$); 2,97 (2H, m, CH_2); 6,50...6,89 (2H, m, NH, 5-H); 7,50 (3H, m, Ph); 7,64...7,94 (3H, m, Ph, NH); 12,44 (1H, NH)	3308, 2960, 2920, 1659, 1641, 1579	78,3 (B)
IIh	CH_2CH_2OH	H	$C_{15}H_{14}F_3N_3O_3$	DMFA	$\frac{52{,}48}{52{,}79}$	$\frac{4{,}06}{4{,}13}$	$\frac{12{,}23}{12{,}31}$	243...244	3,17 (2H, m, CH_2); 3,42 (2H, m, CH_2); 4,71 (1H, t, OH); 6,69 (1H, s, 5-H); 6,83 (1H, t, NH); 7,54 (3H, m, Ph); 7,81 (2H, m, Ph); 7,99 (1H, s, NH); 12,43 (1H, NH)	3302, 3180...2840, 1660, 1642, 1584	80,9 (A)
IIi	$CH_2CH(OH)CH_3$	H	$C_{16}H_{16}F_3N_3O_3$	Ethanol	$\frac{53{,}89}{54{,}09}$	$\frac{4{,}58}{4{,}54}$	$\frac{11{,}67}{11{,}83}$	235...236	1,06 (3H, d, CH_3); 3,03 (2H, m, CH_2); 3,67 (1H, m, CH); 4,69 (1H, d, OH); 6,50...6,97 (2H, m, NH, 5-H); 7,50 (3H, m, Ph); 7,78 (2H, m, Ph); 7,99 (1H, s, NH); 12,20 (1H, NH)	3312, 3180...2840, 1660, 1645, 1579	56,3 (A), 82,4 (B)
IIj	$C(CH_3)_2CH_2OH$	H	$C_{17}H_{18}F_3N_3O_3$	Dioxane	$\frac{55{,}25}{55{,}28}$	$\frac{5{,}24}{4{,}91}$	$\frac{11{,}45}{11{,}38}$	237...238	1,18 (6H, s, $2CH_3$); 3,55 (2H, s, CH_2); 4,84 (1H, OH); 6,68 (2H, 5-H, NH); 7,47 (3H, m, Ph); 7,76 (2H, m, Ph); 7,93 (1H, s, NH); 11,91 (1H, NH)	3326, 3274, 3026...2860, 1686, 1650, 1546	72,2 (A)

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
IIk	$(CH_2)_2CH(OH)CH_3$	H	$C_{17}H_{18}F_3N_3O_3$	Ethanol	55,01 55,28	4,91 4,91	11,16 11,38	227...229	1,08 (3H, d, CH_3); 1,50 (2H, q, CH_2); 3,14 (2H, q, CH_2); 3,69 (1H, m, CH); 4,47 (1H, d, OH); 6,53...6,86 (2H, m, NH, 5-H); 7,50 (3H, m, Ph); 7,64...8,11 (3H, m, Ph, NH); 12,47 (1H, NH)	3462, 3306, 3180...2800, 1657, 1643, 1678	74,8 (A), 80,9 (B)
II*l*	$CH_2CH(OH)Ph$	H	$C_{21}H_{18}F_3N_3O_3$	Dioxane	60,02 60,43	4,38 4,35	9,80 10,07	260...262	3,28 (2H, m, CH_2); 4,67 (1H, m, CH); 5,43 (1H, m, OH); 6,67 (1H, s, 5-H); 6,90 (1H, m, NH); 7,08...7,64 (5H, Ph; 3H, Ph); 7,78 (2H, Ph); 8,10 (1H, s, NH); 12,42 (1H, NH)	3552, 3304, 3100...2862, 1657, 1645, 1577	67,1 (A), 79,1 (B)
IIm	CH_2Ph	H	$C_{20}H_{16}F_3N_3O_2$	DMFA	61,69 62,01	4,03 4,16	10,60 10,85	255...257	4,31 (2H, d, CH_2); 6,67 (1H, s, 5-H); 7,06...7,64 (m, 1H, NH; 5H, Ph; 3H, Ph); 7,78 (2H, m, Ph); 7,92 (1H, s, NH); 12,17 (1H, NH)	3300, 3100...2800, 1655, 1641, 1557	74,3 (A), 62,5 (B)
IIn	Ph	H	$C_{19}H_{14}F_3N_3O_2$	DMFA	60,87 61,13	3,69 3,78	11,05 11,26	280...282	6,69 (1H, s, 5-H); 6,86...7,64 (m, 5H, Ph; 3H, Ph); 7,79 (2H, m, Ph); 8,01 (1H, s, NH); 9,14 (1H, s, NH); 12,58 (1H, NH)	3276, 3100...2960, 1667, 1643, 1622, 1557	64,3 (A), 90,38 (B)
IIo	1-Naphthyl	H	$C_{23}H_{16}F_3N_3O_2$	DMAA	64,92 65,25	3,93 3,81	9,59 9,92	290...291	6,78 (1H, s, 5-H); 7,14...8,36 (12H, m, Ph, naphthyl); 8,56 (1H, s, NH); 9,25 (1H, s, NH); 12,61 (1H, NH)	3270, 2926, 1668, 1642, 1560	45,4 (A)

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
IIp	2-Naphthyl	H	$C_{23}H_{16}F_3N_3O_2$	DMAA	$\frac{65{,}02}{65{,}25}$	$\frac{3{,}98}{3{,}81}$	$\frac{9{,}64}{9{,}92}$	288...289	6,72 (1H, s, 5-H); 7,22...7,94 (11H, m, Ph, naphthyl NH); 8,06 (2H, m, Ph); 9,33 (1H, s, NH); 12,56 (1H, NH)	3266, 3074, 2906, 1660, 1646, 1630, 1566	54,5 (A)
IIq	Et	Et	$C_{17}H_{18}F_3N_3O_2$	Ethanol	$\frac{57{,}53}{57{,}79}$	$\frac{5{,}29}{5{,}13}$	$\frac{11{,}67}{11{,}89}$	170...172	1,08 (6H, t, $2CH_3$); 3,31 (4H, q, $2CH_2$); 6,71 (1H, s, 5-H); 7,50 (4H, m, Ph, NH); 7,78 (2H, m, Ph); 12,00 (1H, NH)	3362, 3282, 3200...2800, 1692, 1678, 1630, 1580	75,4 (A)
IIr	$(CH_2CH_2)_2O$		$C_{17}H_{16}F_3N_3O_3$	Ethanol	$\frac{55{,}56}{55{,}87}$	$\frac{4{,}25}{4{,}39}$	$\frac{11{,}21}{11{,}44}$	209...211	3,00...4,83 (8H, m, $4CH_2$); 6,76 (1H, s, 5-H); 7,53 (3H, m, Ph); 7,87 (2H, m, Ph); 8,01 (1H, s, NH); 12,47 (1H, NH)	3186, 2926, 1674, 1614, 1578	90,2 (A)

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*The reaction was conducted at −20°C for 5 h.

TABLE 2. Characteristics of Compounds (VIa-c)

Com-pound	R^1	R	Empirical formula	Found % Calculated %			mp, °C	PMR spectrum, δ, ppm, deuterochloroform	IR spectrum, cm^{-1}	Yield, %
				C	H	N				
VIa*	CH_3	CH_2Ph	$C_{21}H_{18}F_3N_3O_2$	62,63 62,84	4,55 4,52	10,45 10,47	230...232	*3,00 (3H, s, CH_3); 4,22 (2H, d, CH_2); 6,85 (2H, 5-H, NH); 7,25 (5H, s, Ph); 7,53 (3H,m, Ph); 7,83 (2H, m, Ph); 12,55 (1H, NH)	3306, 3130...2800, 1646, 1618, 1532	64,7
VIb	CH_3	$(CH_2)_4CH_3$	$C_{19}H_{22}F_3N_3O_2$	59,65 59,84	5,73 5,81	11,10 11,02	205...207	0,64...1,78 (9H, t, CH_3; m, $(CH_2)_3$); 2,92...3,28 (5H, m, CH_2, CH_3); 4,31 (1H, NH); 6,78 (1H, s, 5-H); 7,44 (3H, m, Ph); 8,03 (2H, m, Ph); 13,14 (1H, NH)	3332, 3100...2800, 1662, 1646, 1534	80,4
VIc	CH_2Ph	CH_2Ph	$C_{27}H_{22}F_3N_3O_2$	67,94 67,92	4,71 4,64	8,60 8,80	130...132	4,20...4,69 (4H, m, $2CH_2$); 5,78 (1H, NH); 6,62 (1H, s, 5-H); 7,04...7,49 (m,10H, 2Ph; 3H, Ph); 7,64 (2H, m, Ph); 12,16 (1H, NH)	3328, 3090...2840, 1632, 1564, 1530	81,8

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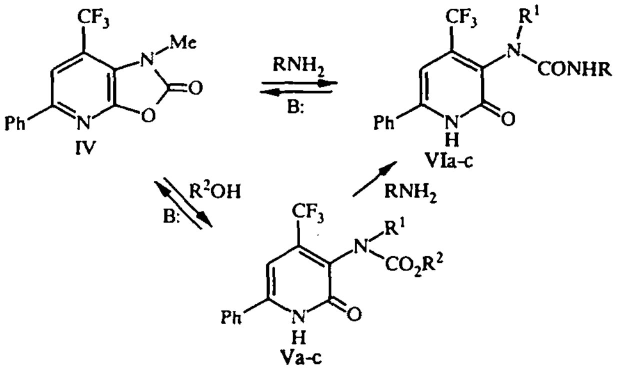
*The PMR spectrum of compound (VIa) was recorded in DMSO-d_6.



V a R^1 - Me, R^2 - Me, b R^1 - Me, R^2 - $(CH_2)_2CHMe_2$, c R^1 - CH_2Ph, R^2 -Et ;
VI a R^1 - Me, R - CH_2Ph, b R^1 - Me, R - $(CH_2)_4Me$, c R^1 - CH_2Ph, R - CH_2Ph

The reactions of the ureas (II, VI) and the carbamates (III, V) with amines are reversible. For example, the oxooxazoles (I, IV) respectively were obtained when the 3-pyridyl carbamates (III) [13] and (Va) [1] were heated with diethylamine, diphenylamine, or morpholine. The oxooxazole (I) was also obtained when the urea (IIb) was heated with triethylamine in dimethylacetamide (DMAA).

Thus, from the 2-oxooxazolopyridines (I, IV) and the carbamates (III, V) it was possible to obtain various ureas [derivatives of 4-trifluoromethyl-6-phenyl-2(1H)-pyridone] (Tables 1 and 2).

EXPERIMENTAL

The PMR spectra were recorded in DMSO-d_6 and deuterochloroform on a Bruker WH-90-DS spectrometer at 90 MHz with TMS as internal standard. The IR spectra were recorded on a Specord 71A instrument in paraffin oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}). The individuality of the compounds was checked by TLC on Silufol UV-254 plates. The yields, melting points, solvents for recrystallization, elemental analyses, and PMR and IR spectra of compounds (IIa-r, VIa) are given in Tables 1 and 2.

2-Oxo-4-trifluoromethyl-(6-phenyl-3-pyridyl)urea (IIa) ($C_{13}H_{10}F_3N_3O_2 \cdot H_2O$). A mixture of 0.14 g (0.50 mmole) of the oxooxazole (I) and 0.08 g (1.00 mmole) of ammonium carbonate was heated in an autoclave at 150°C for 2 h. The mixture was cooled, washed with water, and recrystallized from ethanol. We obtained 0.10 g (75.2%) of colorless crystals of compound (IIa).

N′-Substituted N-(2-Oxo-4-trifluoromethyl-6-phenyl-3-pyridyl)ureas (IIb-r). A. A solution of 0.20 g (0.72 mmole) of the oxooxazole (I) and 0.94 mmole of the respective amine in 20 ml of dioxane was heated at 95-100°C for 1.5 h for (IIb-e, h, *l*, o, p), 2 h for (IIf, i, m), 3 h for (IIk, n, r), 4 h for (IIj), and 6 h for (IIq). The ureas (IIb-r) were obtained. The ureas (IId, f) were also obtained with yields of 36 and 34% respectively by keeping the initial compounds at room temperature for 5 h in ethanol.

B. The pyridylureas (IId-g, m) were obtained by boiling 0.12 g (0.37 mmole) of the carbamate (III) and 5 ml of the respective amine [in the case of (IIf, m) 3 ml of DMAA was added] for 1 h for (IIm), 2 h for (IIg), and 3 h for (IId-f). The excess of the amine was distilled. The precipitate was recrystallized. The ureas (IIi-*l*, n) were also obtained by heating a solution of the carbamate (III) and 0.74 mmole of the respective amine in 5 ml of dioxane at 95-100°C for 1.5 h for (IIn), 3 h for (IIi, k, *l*), and 5 h for (IIj).

The compounds obtained by methods A and B did not give a melting point depression.

N′-Benzyl-N-methyl-N-(2-oxo-4-trifluoromethyl-6-phenyl-3-pyridyl)urea (VIa). A solution of 0.10 g (0.30 mmole) of the oxooxazolopyridine (IV) and 0.05 ml (0.40 mmole) of benzylamine in 10 ml of dioxane was heated at 95-100°C for 6 h. The precipitate was recrystallized from ethanol. We obtained 0.09 g (64.7%) of colorless crystals of compound (VIa).

N,N′-Dialkyl-N-(2-oxo-4-trifluoromethyl-6-phenyl-3-pyridyl)ureas (VIa-c). A solution of 0.20 g of the carbamate (Va-c) and 1 ml of the respective amine in 3 ml of DMAA was boiled. The mixture was cooled and diluted with water, and hydrochloric acid was added to pH 6-7. The precipitate was recrystallized from ethanol.

Reaction of the Carbamates (III, Va) and Urea (IIb) with Bases. A solution of 0.61 mmole of the carbamate (III) or (Va) and 0.72 mmole of triethylamine (diethylamine, diphenylamine, morpholine) in 5 ml of DMAA was boiled for 1 h.

The mixture was cooled, and dilute hydrochloric acid was added. The precipitate was recrystallized from ethanol. The yields of the oxooxazoles were 82.4-94.1% for (I) and 79.1-87.8% for (IV). Compound (I) was also obtained by heating the carbamate (III) and 0.72 mmole of diethylamine in 5 ml of dioxane at 95-100°C for 2 h. The yield was 87.4%. A solution of 0.64 mmole of the urea (IIb) and 0.77 mmole of triethylamine in 5 ml of DMAA was boiled for 3 h. The mixture was cooled, and dilute hydrochloric acid was added. The precipitate was recrystallized from ethanol. The yield of the oxooxazole (I) was 91.5%. The obtained compounds did not give a melting point depression with the authentic compounds [9, 13].

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