Synthesis of 2,5-Disubstituted Oxazoles from Aldehydes and *N*-(Tosylmethyl)imino Synthons. Application to the Synthesis of Pimprinine Analogues

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A series of *N*-(tosylmethyl)imino compounds [$TosCH_2N{=}C(L)A$] has been applied to a new base-induced, one-operational synthesis of 2,5-disubstituted oxazoles from aromatic aldehydes. For substituent A of the imino compounds, which becomes the 2-substituent in the oxazoles, has been chosen methoxy, methyl and phenyl. The new method has been used also to synthesize seven pimprinine analogues, *i.e.*, 5-(-3)indolyl)oxazoles.

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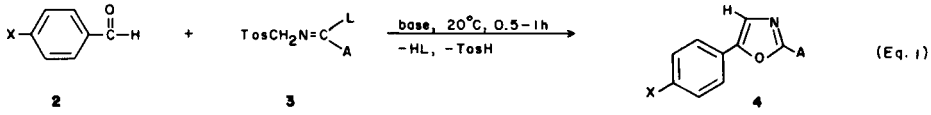
Pyrroles can be synthesized now by cycloaddition of a HC-N=C-A building block (**1**) to the C,C double bond of Michael acceptors. This work, together with the synthesis of *N*-(tosylmethyl)imino compounds [$TosCH_2N{=}C(L)A$], (**3**) from which the building blocks **1** are generated, is described in the foregoing paper (2). A similar cycloaddition of unit **1** to the C,O double bond of aldehydes would lead to oxazoles. In this paper we will show that such is indeed the case.

According to Equation 1 (Table I) a number of 2,5-disubstituted oxazoles is obtained in one operation by a base induced reaction between aromatic aldehydes and the newly developed synthons **3** (see Table I in the foregoing paper (3,4)). The overall result of Equation 1 is rationalized by a cycloaddition of the conjugate base of **3** (*i.e.*, the 2-azaallyl anion $TosC\bar{H}$-N=C(L)A, **5** to **2**, followed by elimination of the leaving group L and TosH (*cf.* reference 2). Thus the substituent A of **3** becomes the 2-substituent in the product oxazole **4**. The design of the imino compounds **3** is such that hetero as well as carbon substituents (A) can be introduced by this method (5). To prove this point we have chosen for A in **3** Me, Ph, MeO and MeS

Table I

Oxazoles **4** Synthesized from *N*-(Tosylmethyl)imino Compounds **3** and Aromatic Aldehydes



2 **3** **4**

Entry	Synthon (a)	L	A	X	Product	Yield (%)	Mp (°C)
1	**3f**	Cl	MeO	NO_2	**4a**	98	190-193
2	**3f**	Cl	MeO	C≡N	**4b**	60	140 and 145-146 (b)
3	**3f**	Cl	MeO	Cl	**4c**	–	*cf.* entry 8
4	**3a**	MeS	Ph	NO_2	**4d**	50	189.5-192 (Lit (26) 189.5-190.5)
5	**3a**	MeS	Ph	Cl	**4e**	14 (c)	98-102 (Lit (26) 96-96.5 and 102-103) (b)
6	**3d**	MeO	MeO	NO_2	**4a**	–	*cf.* entry 1
7	**3d**	MeO	MeO	C≡N	**4b**	–	*cf.* entry 2
8	**3d**	MeO	MeO	Cl	**4c**	61	66 and 79-81 (b)
9	**3d**	MeO	MeO	MeO	**4f**	92	101-102.5
10	**3d**	MeO	MeO	Me_2N	**4g**	74	101.5-103
11	**3b**	MeO	Me	H	**4h**	49	57-59 (Lit. (27) 58-59)
12	**3b**	MeO	Me	Cl	**4i**	63	74.5-75.5
13	**3c**	MeS	Me	Cl	**4i**	37	74.5-75.5
14	–	(d)	EtO	NO_2	**4j**	86	139-139.5
15	–	(d)	EtO	Me_2N	**4k**	60	74-75

(a) See references 3 and 4. (b) Dimorphous. (c) Obtained in two steps, *via* a 2-oxazoline intermediate (**7a**), see text. (d) Not prepared by Equation 1 but by direct displacement of 2-MeO in **4a** or **4g**, respectively, see text.

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(Table I in reference 2).

Although several good methods are available for the synthesis of oxazoles with 2- and 5-alkyl or aryl substituents (*i.a.* by the well known Robinson-Gabriel reaction), oxazoles with 2-RO or 2-RS substituents are less common (6). Their synthesis often requires more reaction steps. 2-Alkoxyoxazoles can be obtained, for example, from 4-oxazolin-2-ones, *via* 2-chlorooxazoles, followed by nucleophilic displacement of chloride (7). 2-Alkylthiooxazoles have been prepared by alkylation of 4-oxazoline-2-thiones (8). With this in mind we have concentrated our efforts mainly on the synthesis of 2-alkoxyoxazoles and their thio-analogues. The results are collected in Table I.

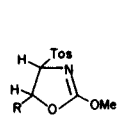
Results and Discussion.

Inspection of Table I shows that the results by reaction 1 are strongly dependent on the nature of the groups A, L and the substituent X in the aldehyde. The spread in yields is larger than with the pyrroles obtained previously from Michael acceptors and the same synthons **3** (2).

The best result was obtained with methyl *N*-(tosylmethyl)chloroformimidate (**3f**) and *p*-nitrobenzaldehyde with sodium hydride in 1,2-dimethoxyethane (DME), resulting in quantitative formation of **4a** (entry 1). Surprisingly, no oxazole was formed in the corresponding reaction with *p*-chlorobenzaldehyde (entry 3; note, however, that the desired oxazole **4c** is obtained in 61% yield using dimethyl *N*-(tosylmethyl)imino carbonate (**3d**) instead of **3f**, entry 8).

The dramatic differences in yield between entries 1, 2 and 3 are explained tentatively by the influence of strong electron-withdrawing substituents which would facilitate the β-elimination of TosH from the assumed intermediates **6a** (R = *p*-$O_2NC_6H_4$) and **6b** (R = *p*-N≡CC_6H_4), Scheme I, to give **4a** and **4b**, respectively. Unlike **6a** and **6b** the corresponding intermediate **6c** (R = *p*-ClC_6H_4) was shown by nmr to be present in the reaction mixture of entry 3. This is consistent with a slower elimination of TosH from **6c**, due to lower acidity of C(5)-H in **6c** relative to **6a** and **6b**. Thus, side-reactions taking place after the formation of **6c** may frustrate the synthesis of **4c** using **3f**. In such side-reactions the nature of substituent A at C(2) plays a crucial role as appears from a discussion of entries 4 and 5.

Scheme I



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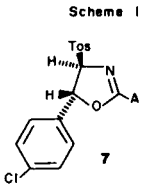

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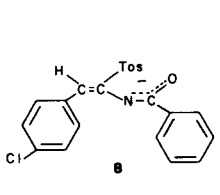

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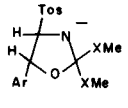

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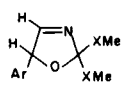

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Entries 4 and 5 show a similar trend for reactions of methyl *N*-(tosylmethyl)thiobenzimidate (**3a**), as compared with entries 1-3. Whereas **4d** was obtained in 50% in one step with potassium *t*-butoxide in 1,2-dimethoxyethane, reaction with *p*-chlorobenzaldehyde invariably gave complex mixtures, from which only 2-oxazoline **7a** (A = Ph, Scheme I) was isolated. In a separate step elimination of TosH from **7a** was effected in protic medium, methanol, with potassium carbonate (9) to give **4e** in 14% yield, in addition to TosH (83% yield) and products derived from ring opening of **7a**: benzamide (51% yield) and *p*-chlorophenylacetic acid (36% yield). The formation of these latter products can be visualized through an electrocyclic ring opening of **7a** after deprotonation at C(4) to give **8** (10), followed by loss of Tos^- and solvolysis of the resulting imene. Apparently, the ring opening of **7a** is facilitated by the stabilizing influence of a phenyl group at C(2) (A = Ph), because a similar reaction of **7b** (A = H) with potassium carbonate in methanol gives the expected 5-*p*-chlorophenyloxazole in 87% yield (9), without any ring opened products (see Experimental).

We have focussed our efforts mainly on cycloadditions of dimethyl *N*-(tosylmethyl)iminocarbonate (**3d**) and the dithio-analogue (**3c**) in order to obtain 2-MeO and 2-MeS substituted oxazoles, respectively. The best results with **3d** were obtained with excess of potassium *t*-butoxide in *t*-butyl alcohol-1,2-dimethoxyethane (entries 6-10). This reaction appears to be fairly generally applicable to aromatic aldehydes, with the exception of those with strongly electronegative substituents (entries 6 and 7). These exceptions are quite remarkable in comparison with entries 1-5, where, conversely, we got our best results with *p*-nitrobenzaldehyde. (Note also that the desired products of entries 6 and 7, *i.e.*, oxazoles **4a** and **4b**, are obtained in very high yields according to entries 1 and 2). The complex reaction mixtures obtained in entries 6 and 7 consisted mainly of water-soluble products, possibly due to a competing Cannizzaro reaction.

In principle, two ways are available to obtain 2-alkoxyoxazoles other than 2-methoxy: (i) By preparation of the diethoxy analogue of **3d**, etc, or: (ii) Simply by exchange of the 2-methoxy group in the oxazoles **4** by another alkoxy group. We have tested the second approach only. The 2-methoxy group is readily displaced for an ethoxy group to give **4j** (86% yield, entry 14, Table I) simply by refluxing **4a** for 75 minutes in ethanol with some solid potassium carbonate. Similarly, **4g** gives **4k** (entry 15), although stronger base and longer reaction times (16 hours) are then needed, reflecting the influence of X (nitro and *N,N*-dimethylamino, respectively). The reaction probably

involves an addition-elimination process. Unfortunately, especially in connection with the next paragraph, we have been unable to displace likewise the 2-MeO in **4a** for a RS-substituent (R = Et, *n*-Pr).

As an unpleasant surprise no 2-methylthiooxazoles (**4**, A = MeS) were obtained at all when dimethyl *N*-(tosylmethyl)dithiocarbonate (**3e**) was used (11). With the same aldehydes used with **3d**, employing potassium *t*-butoxide, sodium hydride, or potassium hydride in several solvents, only complex reaction mixtures were obtained with **3e**. There are some indications that in the reaction of **3d** to **4** a different path (different from reactions of **3a** and **3f**) is followed going through **9** and **10** (X = O, Scheme I), and that a similar sequence **10** → **4** (for X = S) is frustrated by addition of MeS^- to the C,N double bond in **10**. Anyway, 2-oxazolines of type **7** were not observed in any of the reactions carried out with **3b**, **3c**, or **3d**, not even when less than the calculated amount of base was used (12).

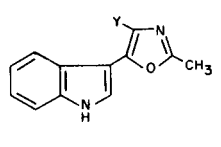
Structural proof of the oxazoles **4** (Table I) is based on correlation with authentic samples (in case of **4d,h**), on comparison of ^{1}H-nmr chemical shift data of C(4)-H with known oxazoles (13), and by ^{13}C-nmr for compounds **4a,c,g,i,j,k** (14).

From the above results it is clear that synthons **3** are useful in the synthesis of oxazoles too, although they are not always generally applicable. The widest scope was found for **3d** leading to 2-methoxyoxazoles. Our method using *N*-(tosylmethyl)imino compounds (**3**) certainly has a broader scope than the previous two step procedure of Cornforth using *N*-(ethoxycarbonylmethyl)imino derivatives, as exemplified by the formation of 2-methyl-4-ethoxycarbonyloxazole (**11**) (15).

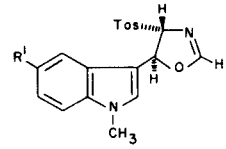
Synthesis of Pimprinine Analogues.

Pimprinine (5-(3-indolyl)-2-methyloxazole, **12a**) is one of the not so many naturally occurring oxazoles (6). It is a mold metabolite isolated in 1960 from *Streptomyces pimprina* (16), which shows considerable activity against hyperkinetical diseases (17), and of which further anticholinergic, antihistaminic and MAO-inhibiting activities have been reported (17,18). The structure of pimprinine has been confirmed by a 5-step synthesis starting with 3-acetylindole (19). The synthesis of 4-carbomethoxypimprinine (**12b**) has been reported without reference to biological acitivity (20).

Scheme II



12a Y = H
12b Y = $COOCH_3$



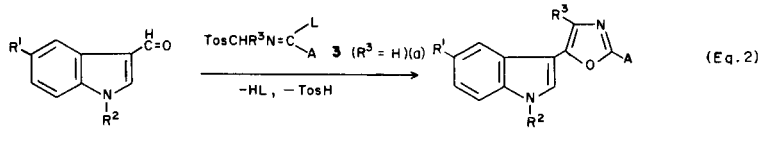
16a R' = H
16b R' = NO_2

Pimprinine (**12a**) is a 2,5-disubstituted oxazole derivative, with a 2-methyl substituent. It therefore seemed of interest to apply our new oxazole synthesis to the preparation of pimprinine and analogues, and to investigate their activity.

In principle pimprinine (**12a**, Scheme II) can be prepared in one step from indole-3-carboxyaldehyde (**13a**, $R^1 = R^2 = H$, Equation 2, Table II) and methyl *N*-(tosylmethyl)(thio)acetimidate (**3b** or **3c**), analogous to

Table II

Pimprinine Analogues **15** Synthesized with *N*-(Tosylmethyl)imino Compounds **3**



(Eq. 2)

13 **15**

Entry	R^1	R^2	R^3	L	A	Product	Yield (%)	Mp (°C)
1	H	Me	H	MeO	MeO	**15a**	61	82.5-83.5
2	MeO	Me	H	MeO	MeO	**15b**	45	92-93.5
3	NO_2	Me	H	MeO	MeO	**15c**	66	183-185 dec
4	H	$PhCH_2OCH_2$	H	MeO	MeO	**15d**	33	114.5-115.5
5	H	H (b)	Me	-	H (a)	**15e**	18 (c)	193-196
6	MeO	H (b)	Me	-	H (a)	**15f**	11 (c)	131-134.5
7	NO_2	H (b)	Me	-	H (a)	**15g**	22 (c)	263-266 dec

(a) The reactions of entries 5-7 are carried out with α-tosylethyl isocyanide **14** (= **3** with R^3 = Me; L and A are void) (23). (b) This hydrogen is protected during the reaction by an *N,N*-dimethylamido group. (c) Overall yields calculated on unprotected indolealdehyde.

Equation 1. However, under the conditions that were successful for the synthesis of oxazoles **4**, indolealdehyde **13a** remained unchanged. This failure was attributed to the acidic NH of **13a**, but even with *N*-methylindolealdehyde (**13b**, R^1 = H, R^2 = Me) and **3b** no conversion was obtained. Obviously, the vinylogous amide carbonyl of **13b** is not reactive enough to give reactions with the short-living anion of **3b**. This view is supported by the successful reaction of **13b** with dimethyl *N*-(tosylmethyl)iminocarbonate (**3d**) to give a 2-methoxy analogue of *N*-methylpimprinine (**15a**, Table II, entry 1). The anion of **3d** has a much longer half-life than **3b** (see foregoing paper (2)). Similar conversions were achieved with *N*-methyl protected 5-methoxy- and 5-nitroindolealdehydes and **3d** (entries 2 and 3).

In order to prepare pimprinine analogues with a free NH more readily replaceable protecting groups were introduced in **13** (R^1 = H): R^2 = *p*-$O_2NC_6H_4CO$ (**13c**), Me_2NCO (**13d**), *p*-$MeC_6H_4SO_2$ (**13e**). It was hoped that these electronegative protecting groups would also activate the aldehyde group by reversing the vinylogous amide resonance in **13** to some extent. Unfortunately, under the basic reaction conditions necessary in the oxazole synthesis the above protecting groups were not effective. From reactions of **13c-13e** and **3b** only **13a** (R^2 = H) was isolated, obviously formed by loss of the protecting group.

The benzyloxymethyl protecting group (21) is more stable under basic conditions, and indeed **13f** (R^1 = H, R^2 = $PhCH_2OCH_2$) was converted with **3d** to the pimprinine derivative **15d** (entry 4). Attempts to remove the benzyloxymethyl group, however, were unsuccessful (22).

Pimprinine analogues with a substituent at C(4) rather than C(2) were prepared successfully using α-tosylethyl isocyanide (**14**) (23) instead of **3** (entries 5-7). These reactions were carried out with dimethylamido *N*-protected indolealdehydes (**13d**, and the corresponding 5-derivatives), followed by removal of the protecting group. The analogous reaction of *N*-methylindolealdehydes and tosylmethyl isocyanide (TosMIC) with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) in 1,2-dimethoxyethane gave 2-oxazolines **16a** or **16b** (91% yield) from which the elimination of TosH to the corresponding 2,4-unsubstituted pimprinine analogues was unsuccessful (24).

Compounds **15a-c** showed *in vitro* only weak antihistaminic, and no anticholinergetic activity (25a). The antiepileptic or MAO-inhibiting activities of **15a-c** and **15f,g** were negative (25b).

EXPERIMENTAL

For general remarks, see reference 2. All experiments were carried out at room temperature unless stated otherwise.

2-Methoxy-5-*p*-nitrophenyloxazole (**4a**).

To a stirred solution of *p*-nitrobenzaldehyde (1.51 g, 10 mmoles) and methyl *N*-(tosylmethyl)chloroformimidate (**3f**) (1.31 g, 5 mmoles) in 1,2-dimethoxyethane (40 ml) was added sodium hydride (55% in mineral oil, 0.65 g, 15 mmoles). After 45 minutes the dark mixture was reduced to about 25% of its original volume and added to a saturated sodium chloride solution (200 ml). The yellow precipitate was collected, dissolved in dichloromethane and dried (magnesium sulfate). After removal of the solvent, the yellow solid was washed with 25 ml of diethyl ether-pentane (1:1) to give 1.07 g (98%) of **4a**, mp 189-192° slight dec. An analytically pure sample was obtained from acetone, mp 190-193° slight dec; ir (nujol): 1525 and 1345 cm^{-1} (NO_2); ^{1}H-nmr (deuteriochloroform) δ 4.12 (s, 3H), 7.20 (s, 1H), 7.57 and 8.17 (ABq, 4H); ^{13}C-nmr (DMSO-d_6) δ 162.8 (s, C(2)), 126.5 (d, $^1J_{[C-H]}$ = 197 Hz, C(4)), 144.0 (s, C(5)), 145.9 (s), 133.6 (s), 124.5 (d), 123.4 (d), 58.7 (q).

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 54.56; H, 3.66; N, 12.71. Found: C, 54.4; H, 3.6; N, 12.7.

5-*p*-Cyanophenyl-2-methoxyoxazole (**4b**).

To a stirred suspension of *p*-cyanobenzaldehyde (0.40 g, 3 mmoles) and **3f**, (0.65 g, 2.5 mmoles) in a mixture of 1,2-dimethoxyethane (7 ml) and *t*-butyl alcohol (3 ml) at −35° was added all at once potassium *t*-butoxide (0.80 g, 7 mmoles). After stirring for 10 minutes at −35 to 0° and 20 minutes at 0°, 50 ml of ice-water was added. The precipitate was collected, dissolved in dichloromethane, filtered over a layer of alumina (thickness of 5 cm) and concentrated to give 0.30 g (60%) of **4b**, mp 140 and 145-146°. An analytically pure sample was obtained by one crystallization from diethyl ether mp 140 and 145-146° (dimorphous); ir (nujol): 2225 cm^{-1} (C≡N); ^{1}H-nmr (deuteriochloroform) δ 4.11 (s, 3H), 7.12 (s, 1H), 7.57 (broad s, 4H).

Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 14.00. Found: C, 65.8; H, 4.0; N, 14.1.

5-*p*-Chlorophenyl-2-methoxyoxazole (**4c**).

A solution of *p*-chlorobenzaldehyde (0.70 g, 5.0 mmoles) and dimethyl *N*-(tosylmethyl)iminocarbonate (**3d**, 1.42 g, 5.5 mmoles) in 1,2-dimethoxyethane (30 ml) was added all at once to a stirred solution of potassium *t*-butoxide (3.42 g, 30 mmoles) in *t*-butyl alcohol (30 ml). After 45 minutes the mixture was added to saturated sodium chloride solution (~100 ml) and worked up as described for **4a**. The resulting viscous solid was crystallized from pentane to give 0.66 g (61%) of **4c**, melting at 66° and 77-81° (dimorphous). Another crystallization from pentane gave an analytically pure sample with the same melting behaviour; ^{1}H-nmr (deuteriochloroform): δ 4.12 (s, 3H), 7.05 (s, 1H), 7.42 (broad s, 4H); ^{13}C-nmr: see reference (14).

Anal. Calcd. for $C_{10}H_8ClNO_2$: C, 57.29; H, 3.85; Cl, 16.91; N, 6.68. Found: C, 57.0; H, 3.8; Cl, 16.8; N, 6.7.

5-*p*-Nitrophenyl-2-phenyloxazole (**4d**).

Solid potassium *t*-butoxide (0.13 g, 1.1 mmoles) was added to a stirred solution of methyl *N*-(tosylmethyl)thiobenzimidate (**3a**, 0.32 g, 1.0 mmole) in 1,2-dimethoxyethane (5 ml). After 3 minutes solid *p*-nitrobenzaldehyde (0.17 g, 1.1 mmoles) was added and stirring was continued for 20 minutes. Work-up as described for **4c**, followed by crystallization from ethanol gave 0.14 g (50%) of **4d**, mp 189.5-192° (lit (26) 189.5-190.5°). This material was identical by ir and mixture mp with a sample prepared by nitration of 2,5-diphenyloxazole (28).

5-*p*-Chlorophenyl-2-phenyloxazole (**4e**) and 5-*p*-Chlorophenyl-2-phenyl-4-tosyl-2-oxazoline (**7a**).

Analogous to the procedure described for **4d**, reaction of potassium *t*-butoxide (1.37 g, 12 mmoles), **3a** (3.82 g, 12 mmoles) and *p*-chlorobenzaldehyde (1.40 g, 10 mmoles) gave a yellow oil which was stirred for 2 hours with 70 ml of a mixture of diethyl ether-pentane (15:85). The resulting solid was crystallized from dichloromethane-diethyl ether-pentane to give 1.02 g (25%) of **7a**, mp 159-160.5°. Analytically pure **7a** was obtained by two more crystallizations from dichloromethane-pentane, mp 159.5-161°; ir (nujol) 1635 (C=N), 1315 and 1140 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform) δ 2.45 (s, 3H), 5.17 (d, 1H, J = 5.5 Hz), 6.20 (d, 1H, J = 5.5 Hz), 7.3-7.7 (m, 9H), 7.8-8.2 (m, 4H). The melting point and nmr were consistent with one stereoisomer for **7a**

only; the *trans* configuration is most likely the thermodynamically favoured one, *cf.* reference 29.

Anal. Calcd. for $C_{22}H_{18}ClNO_3S$: C, 64.15; H, 4.41; Cl, 8.61; N, 3.40; S, 7.78. Found: C, 64.0; H, 4.3; Cl, 8.7; N, 3.4; S, 7.7.

A solution of oxazoline **7a** (0.79 g, 1.9 mmoles) in methanol (30 ml) was refluxed for 1.5 hours with 1.4 g of solid potassium carbonate. After removal of the solvent the remaining solid was extracted with pentane (30 and 20 ml). The concentrated extracts gave a solid which was crystallized from hexane to give 0.070 g (14%) of **4e**, mp 98-102° (lit (26) 96-96.5° and 102-103°); ^{1}H-nmr (deuteriochloroform) δ 7.2-7.7 (m + q, 8H, J = 8.5 Hz), 7.8-8.2 (m, 2H).

The fraction not soluble in pentane was worked up as described for **4c** to give 0.12 g (51%) of benzamide, mp 127.5-131° (Handbook mp 132.5-133.5°), which was identified by ir and mixture mp. *p*-Toluenesulfinic acid (TosH) was identified in the water layer by reaction with sodium nitrite and hydrochloric acid to give Tos_2NOH (83% yield) (30). Next, the water layer was acidified to *p*H about 1 and extracted with dichloromethane from which 0.12 g (36%) of *p*-chlorophenylacetic acid was obtained, mp 101-103.5° (Handbook mp 103.5-104°). This material was identical with an authentic sample (ir and mixture mp).

2-Methoxy-5-*p*-methoxyphenyloxazole (**4f**).

This compound was prepared analogous to **4c** from *p*-methoxybenzaldehyde (0.68 g, 5.0 mmoles), dimethyl *N*-(tosylmethyl)iminocarbonate (**3d**, 1.29 g, 5.0 mmoles) and potassium *t*-butoxide (3.42 g, 30 mmoles) to give 0.94 g (92%) of **4f**, mp 97.5-100.5°, analytically pure material from diethyl ether-pentane, mp 101-102.5°; ^{1}H-nmr δ 3.73 (s, 3H), 4.05 (s, 3H), 6.86 (s, 1H), 6.85 and 7.41 (ABq, 4H, J = 8.5 Hz).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.39; H, 5.40; N, 6.82. Found: C, 64.5; H, 5.4; N, 6.9.

5-*p*-Dimethylaminophenyl-2-methoxyoxazole (**4g**).

This compound was prepared analogously to **4c** from *p*-dimethylaminobenzaldehyde (0.15 g, 1.0 mmole), **3d** (0.26 g, 1.0 mmole) and potassium *t*-butoxide (0.68 g, 6 mmoles). The crude product was chromatographed (aluminum oxide, Merck Act II-III, dichloromethane) to give 0.16 g (74%) of **4g**, mp 100-102°. Two crystallizations from diethyl ether-pentane gave analytically pure material, mp 101.5-103°; ^{1}H-nmr (deuteriochloroform): δ 3.09 (s, 6H), 4.16 (s, 3H), 6.68, 7.36 and 6.80 (ABq + s, 5H, J = 8.5 Hz).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.46; N, 12.84. Found: C, 66.1; H, 6.5; N, 12.7.

2-Methyl-5-phenyloxazole (**4h**).

To a cooled and stirred suspension (−5°) of sodium hydride (50% in oil, 1.58 g, 33 mmoles, freed from oil by washing with pentane) in a mixture of 1,2-dimethoxyethane (35 ml) and DMSO (8 ml) was added methyl *N*-(tosylmethyl)acetimidate fluorosulfonate (**3b**, 4.50 g, 13.2 mmoles) resulting in a rapid evolution of hydrogen. After *ca.* 3 minutes, benzaldehyde (1.48 g, 14 mmoles) as added. After stirring for 1.5 hours at room temperature, the mixture was added to saturated sodium chloride solution (500 ml). Extraction with pentane (2 × 180 ml), and crystallization from petroleum ether (40-60°) gave 0.98 g (49%) of **4h**, mp 57-59° (lit (27) 58-59°); ^{13}C-nmr (deuteriochloroform): δ 160.9 (s, C(2)), 117.1 (d, $^1J_{[C-H]}$ = 190 Hz, C(4)), 146.8 (s, $^2J_{[C-H]}$ = 15 Hz, C(5)), 149.3 (s), 123.8 (d), 115.7 (s), 111.6 (d), 57.1 (q), 39.5 (q). A sample prepared independently by a Robinson-Gabriel synthesis (27)from α-aminoacetophenone and acetic anhydride gave identical material (ir, mixture mp) in 40% yield.

5-*p*-Chlorophenyl-2-methyloxazole (**4i**).

This compound was prepared analogously to **4h** from *p*-chlorobenzaldehyde (4.50 g, 32 mmoles), **3b** (10.2 g, 30 mmoles) and sodium hydride (3.55 g, 50% in oil, 74 mmoles). From the pentane extract 3.56 g (63%) of solid **4i** was obtained, mp 70-73°. Crystallization (twice) from petroleum ether bp 40-60° gave an analytically pure sample, mp 74.5-75.5°; ^{1}H-nmr (deuteriochloroform): δ 2.51 (s, 3H), 7.21 (s, 1H), 7.35 and 7.57 (ABq, 4H, J = 9 Hz); ^{13}C-nmr; see reference 14.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.17; Cl, 18.30; N, 7.23. Found: C, 62.0; H, 4.2; Cl, 18.4; N, 7.2.

2-Ethoxy-5-*p*-nitrophenyloxazole (**4j**).

A solution of **4a** (88 mg, 0.40 mmole) in 8 ml of absolute ethanol was refluxed with potassium carbonate (56 mg, 0.40 mmole) for 75 minutes. After concentration and addition of water, the resulting yellow solid was washed (water, diethyl ether and pentane), dissolved in dichloromethane and dried (magnesium sulfate). Crystallization from dichloromethane-diethyl ether (*ca.* 1:20) gave 80 mg (86%) of **4j**, mp 139-139.5°; ir (nujol): 1610 (C=N) and 1510, 1345, 1330 cm^{-1} (NO_2); ^{1}H-nmr (deuteriochloroform): δ 1.50 (t, 3H), 4.52 (q, 2H), 7.21 (s, 1H); ^{13}C-nmr (DMSO-d_6): δ 162.1 (s, C(2)), 126.5 (d, $^1J_{[C-H]}$ = 197 Hz, C(4)), 143.6 (s, C(5)), 145.8 (s), 133.6 (s), 124.5 (d), 123.3 (d), 68.0 (t), 14.1 (q).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.1; H, 4.4; N, 11.9.

5-*p*-Dimethylaminophenyl-2-ethoxyoxazole (**4k**).

A solution of **4g** (0.44 g, 2.0 mmoles) and potassium *t*-butoxide (0.28 g, 2.4 mmoles) were refluxed for 16 hours in 50 ml of absolute ethanol under nitrogen. Work-up similar to **4j** gave 0.28 g (60%) of **4k**, mp 74-75° (from diethyl ether-pentane, 1:5); ^{1}H-nmr (deuteriochloroform): δ 1.35 (t, 3H), 2.86 (s, 6H), 4.36 (q, 2H), 6.64 (s, 1H), 6.56 and 7.24 (ABq, 4H); ^{13}C-nmr (deuteriochloroform): δ 160.6 (s, C(2)), 117.4 (d, $^1J_{[C-H]}$ = 190 Hz, C(4)), 146.7 (s, C(5)), 149.7 (s), 124.3 (d), 116.4 (s), 112.1 (d), 66.9 (t), 40.1 (q), 14.2 (q).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.0; H, 6.9; N, 12.0.

5-*p*-Chlorophenyl-4-tosyl-2-oxazoline (**7b**) and 5-*p*-Chlorophenyloxazole.

A solution of tosylmethyl isocyanide (1.95 g, 10 mmoles, (9)) and *p*-chlorobenzaldehyde (1.54 g, 11 mmoles) in 1,2-dimethoxyethane (15 ml) was stirred for 45 minutes with diazabicyclo[4.3.0]non-5-ene (DBN, 0.12 g, 1.0 mmole). The concentration to about 30% of its original volume, addition of diethyl ether and cooling gave 3.11 g (93%) of **7b**, mp 163° dec. Two crystallizations from acetone furnished an analytically pure sample, mp 157° dec; ir (nujol): 1615 (C=N), 1310 and 1140 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): δ 2.47 (s, 3H), 4.97 (d of d, 1H, J = 6 and 1.5 Hz), 6.02 (d, 1H, J = 6 Hz), 7.20 (d, 1H, J = 1.5 Hz), 7.3-7.9 (q + broad s, 8H). The *trans* configuration was assigned on the same arguments used with **7a** (see above).

Anal. Calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.23; H, 4.20; Cl, 10.56; N, 4.17; S, 9.55. Found: C, 57.2; H, 4.2; Cl, 10.8, N, 4.1; S, 9.5.

Reaction of **7b** (0.64 g, 1.9 mmoles) and potassium carbonate (1.40 g) analogously to **4e** gave 0.30 g (87%) of 5-*p*-chlorophenyloxazole, mp 66.5-68° (lit (9) 66-67°).

2-Methoxy-5-(1-methyl-3-indolyl)oxazole (**15a**).

This compound was prepared analogously to **4c** from 1-methylindole-3-carboxaldehyde (31) (**13b**, mp 69-70°, 0.31 g, 2.0 mmoles) (lit (32) mp 67°) and **3d** (0.50 g, 2.1 mmoles). The resulting yellow oil was crystallized from diethyl ether-pentane (charcoal) to give 0.28 g (61%) of **15a**, mp 82-83.5°. After two more crystallizations analytically pure material was obtained, mp 82.5-83.5° ^{1}H-nmr (deuteriochloroform): δ 3.61 (s, 3H), 4.01 (s, 3H), 6.70 (s, 1H), 6.9-7.1 (m, 4H), 7.4-7.6 (m, 1H).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.30; N, 12.27. Found: C, 68.2; H, 5.4; N, 12.1.

2-Methoxy-5-(5-methoxy-1-methyl-3-indolyl)oxazole (**15b**).

This compound was prepared analogously to **4c** from 5-methoxy-1-methylindole-3-carboxaldehyde (31) (mp 137-139°, 1.89 g, 10 mmoles) (lit (33) mp 134-135°) and **3d** (2.83 g, 11 mmoles). The resulting brown oil was chromatographed (aluminum oxide, Act. II-III; dichloromethane-pentane, 1:1), followed by crystallization from diethyl ether to give 1.13 g (45%) of **15b**, mp 90-92°. An analytically pure sample was obtained after two more crystallizations, mp 92-93.5°; ^{1}H-nmr (deuteriochloroform): δ 3.69 (s, 3H), 3.87 (s, 3H), 4.10 (s, 3H), 6.8-7.3 (m, 5H).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.7; H, 5.5; N, 10.9.

2-Methoxy-5-(1-methyl-5-nitro-3-indolyl)oxazole (**15c**).

This compound was prepared analogous to **4c** from 1-methyl-5-nitroindole-3-carboxaldehyde (31) (mp 204-206°, 0.20 g, 1.0 mmole) (lit (34) mp 198-200°) and **3d** (0.26 g, 1.0 mmole). Chromatography as described for **15b** (with acetone-diethyl ether, 1:1) and crystallization from acetone-diethyl ether gave 0.18 g (66%) of **15c**, mp 183-185° (slight dec). Attempts to obtain analytically pure material were unsuccessful; ^{1}H-nmr (DMSO-d_6): δ 3.87 (s, 3H), 4.11 (s, 3H), 7.19 (s, 1H), 7.82 (s, 1H), 7.5-8.1 (q + d, 2H), 8.52 (d, 1H, J = 2 Hz); exact mass calcd. for $C_{13}H_{11}N_3O_4$: m/e 273.075; found: m/e 273.077.

5-(1-Benzyloxymethyl-3-indolyl)-2-methoxyoxazole (**15d**) and 1-(Benzyloxymethyl)indole-3-carboxaldehyde (**13f**, (35)).

To a solution of indole-3-carboxaldehyde (7.25 g, 50 mmoles) in 1,2-dimethoxyethane (200 ml) was added sodium hydride (50% in mineral oil, 2.90 g, 60 mmoles). When the evolution of hydrogen had almost stopped (*ca.* 15 minutes) benzyloxymethyl chloride (8.61 g, 55 mmoles) in 1,2-dimethoxyethane (10 ml) was added in *ca.* 3 minutes. After 1 hour the mixture was added to a saturated sodium chloride solution (0.81), and the precipitate was crystallized from diethyl ether-pentane to give 8.30 g (63%) of **13f**, mp 64.5-66.5°. After two more crystallizations from dichloromethane-diethyl ether-pentane an analytically pure sample was obtained, mp 70-72°; ir (nujol): 1645 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 4.45 (s, 2H), 5.53 (s, 2H), 7.1-7.7 (m, 8H), 7.71 (s, 1H), 8.0-8.3 (m, 1H), 9.86 (s, 1H).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.8; H, 5.7; N, 5.2.

Compound **15d** was prepared analogously to **4c** from **13f** (see above, 0.53 g, 2.0 mmoles) and **3d** (0.51 g, 2.0 mmoles) in a yield of 0.22 g (33%), mp 109-111.5° (from diethyl ether). Two more crystallizations gave analytically pure **15d**, mp 114.5-115.5°; ^{1}H-nmr (deuteriochloroform): δ 4.13 (s, 3H), 4.46 (s, 2H), 5.56 (s, 2H), 7.04 (s, 1H), 7.2-7.6 (m, 9H), 7.7-8.0 (m, 1H).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.83; H, 5.43; N, 8.38. Found: C, 71.9; H, 5.3; N, 8.4.

5-(3-Indolyl)-4-methoxyloxazole (**15e**).

Acetonitrile (25 ml) was added to sodium hydride (50% in mineral oil, 0.52 g, 12 mmoles, oil removed by washing with pentane) followed by indole-3-carboxaldehyde (1.45 g, 10 mmoles). When the evolution of hydrogen had stopped (*ca.* 10 minutes) dimethylcarbamoyl chloride (1.51 g, 14 mmoles) was added dropwise. Work-up as described for **4c** gave 1.50 g crude 1-dimethylcarbamoylindole-3-carboxaldehyde (**13d**), mp 98-101.5° (pure **13d** mp 103.5-105° (35)).

To a solution of α-tosylethyl isocyanide (36) (1.35 g, 6.5 mmoles) in DMSO (25 ml) was added 1.22 g (*ca.* 5.6 mmoles) of crude **13d** (above), followed by sodium hydride (55% in mineral oil, 0.49 g, 11.3 mmoles). After stirring for 1.5 hours and work-up as described for **4c** a viscous oil was obtained. This oil was hydrolyzed in a mixture of ethanol (35 ml), 1,2-dimethoxyethane (25 ml) and water (25 ml) with sodium hydroxide (3 g) by stirring for 10 hours. After concentration of the mixture to about 30% of its original volume and work-up as described for **4c** the crude product was chromatographed over aluminum oxide (Act. II-III, dichloromethane) followed by crystallization from dichloromethane-diethyl ether (1:10) to give 0.30 g (18% calculated on indole-3-carboxaldehyde) of **15e** as a yellow-green solid, mp 193-196°. Recrystallization from dichloromethane-diethyl ether (10:1) and from ethanol gave an analytically pure sample with the same mp; ir (nujol): 3200 (NH), 1635-1615 cm^{-1} (C=N); ^{1}H-nmr (acetone, d_6) δ 2.36 (s, 3H), 7.1-8.2 (m, 7H).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.5; H, 5.0; N, 14.2.

5-(5-Methoxy-3-indolyl)-4-methyloxazole (**15f**).

Following the procedure described for **15e**, 5-methoxyindole-3-carboxaldehyde (5.25 g, 20 mmoles) was converted to 1-dimethylcarbamoyl-5-methoxyindole-3-carboxaldehyde as a semi-solid (6.5 g) of which 0.59 g (*ca.* 2.4 mmoles) was reacted with α-tosylethyl isocyanide (0.53 g, 2.4 mmoles) in DMSO (5 ml). Chromatography of the hydrolyzed mixture gave a pale-brown oil, which was crystallized from diethyl ether-pentane, then from dichloromethane-diethyl ether-pentane yielding 0.069 g (11% overall) of **15f** as a pale yellow solid, mp 127-130.5°. Three more crystallizations gave an analytically pure sample, mp 131-134.5°, ir (nujol): 3200 (broad NH), 1640-1615 cm^{-1} (C=N); ^{1}H-nmr (deuteriochloroform): δ 2.38 (s, 3H), 3.90 (s, 3H), 6.95 (d of d, 1H, J = 9 and 2.5 Hz), 7.2-7.5 (m, 3H), 7.96 (s, 1H), 9.0-9.5 (m, 1H).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.26. Found: C, 68.1; H, 5.3; N, 12.3.

4-Methyl-5-(5-nitro-3-indolyl)oxazole (**15g**).

Following the procedure described for **15e** 5-nitroindole-3-carboxaldehyde (5.76 g, 30 mmoles) was converted to 1-dimethylcarbamoyl-5-nitroindole-3-carboxaldehyde 6.88 g crude product) of which 1.03 g (*ca.* 3.9 mmoles) was reacted with α-tosylethyl isocyanide (0.86 g, 3.9 mmoles) in DMSO (7 ml). Hydrolysis (2.5 hours) finally lead to a dark red solid, which was washed with dichloromethane, crystallized from acetone-diethyl ether to give 0.24 g (22% overall) of **15g**, mp 260-263° slight dec. Two more crystallizations gave an analytically pure sample, mp 263-266° slight dec; ir (nujol): 3150 (NH), 1640-1620 (C=N), 1520 and 1330 cm^{-1} (NO_2); ^{1}H-nmr (DMSO-d_6) δ 2.41 (s, 3H), 7.73 (d, 1H, J = 9 Hz), 8.0-8.3 (m + s, 2H), 8.45 (s, 1H), 8.85 (d, 1H, J = 2.5 Hz).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.2; H, 3.8; N, 17.2.

5-(1-Methyl-5-nitro-3-indolyl)-4-tosyl-2-oxazoline (**16b**).

To a stirred suspension of tosylmethyl isocyanide (0.39 g, 2.0 mmoles) and 1-methyl-5-nitroindole-3-carboxaldehyde (0.41 g, 2.0 mmoles) in a mixture of 1,2-dimethoxyethane (10 ml) and diethyl ether (5 ml) was added dropwise DBN (0.50 g, 4.0 mmoles). The precipitate was collected after 1.5 hours, washed twice with diethyl ether-pentane (1:1) and twice with diethyl ether, to give 0.73 g (91%) of **16b**, decomposing at about 180°. Attempts to purify the compound by crystallization were unsuccessful; ir (nujol): 1610 (C=N), 1530 and 1335 (NO_2), 1320 and 1140 cm^{-1} (SO_2); ^{1}H-nmr (DMSO-d_6): δ 2.48 (s, 3H), 3.92 (s, 3H), 5.79 (d of d, 1H, J = 6 and 2 Hz), 6.42 (d, 1H, J = 6 Hz), 7.4-8.3 (m, 8H), 8.47 (d, 1H, J = 2 Hz).

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(3) The synthesis of the *N*-(tosylmethyl)imino compounds **3** is described in reference 2. To avoid confusion the same numbers **3** are used for these compounds in both papers.

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