Tetrahedron. Vol. 26, pp. 3185 to 3193. Pergamon Press 1970. Printed in Great Britain

MESOIONIC 3-AMINO-5-IMINO OXAZOLINE DERIVATIVES

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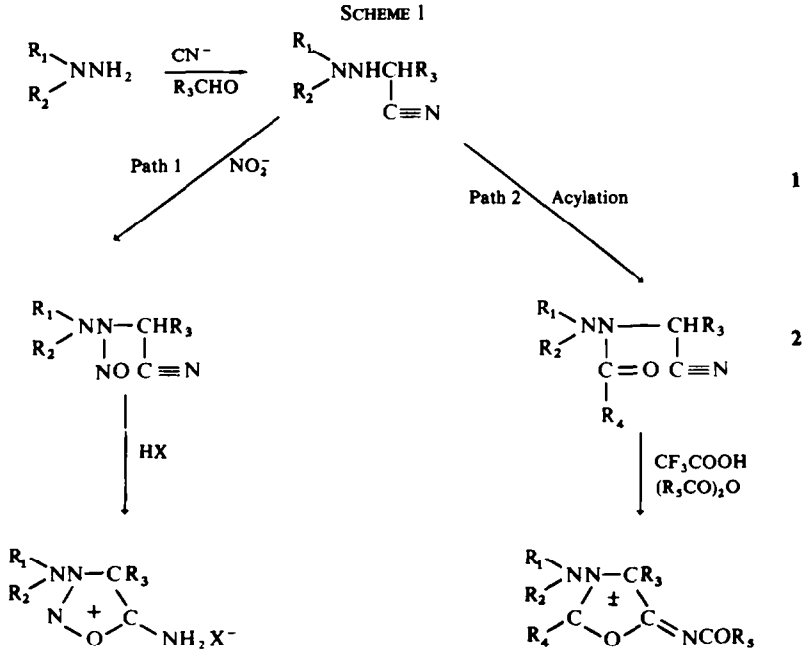
(*Received in USA* 16 *December* 1969; *Received in the UK for publication* 24 *February* 1970)

Abstract—Condensation of aldehydes, unsymmetrical disubstituted hydrazines and cyanide resulted in the formation of Mannich bases which, after acylation, formed 6-acylated 3-amino-5-imino oxazolines on acid/acid anhydride treatment. Structure 3 was assigned to these mesoionic compounds on spectral evidence.

HUISGEN and his school coined the name münchnone[1] for the mesoionic oxazolones, previously discovered in their laboratory.[2] We would like to report on the synthesis of a related mesoionic system, the 3-amino-5-iminooxazolines. The condensation of aldehydes, cyanide and 1,1-disubstituted hydrazines resulted in the formation of Mannich bases (1) useful in the synthesis of 3-aminosydnone imines[3] (Scheme 1, path 1). The same Mannich bases were acylated by common methods and the acyl derivatives (2) ring closed with the help of trifluoroacetic acid. This step was generally performed in the presence of acid anhydride, which yields the acylated 3-amino-5-iminooxazolines (3)(Scheme 1, path 2).

SCHEME 1



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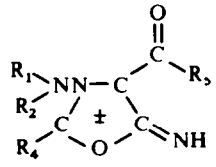
Acylated 3-amino-5-iminooxazolines are rather unstable compounds, in contrast to the stable acylated 3-aminosydnone imines.[3] Recrystallization from hydroxylic solvents is frequently accompanied by considerable decomposition. The N^6-trihaloacetyl derivatives do not form hydrochlorides, stressing the non-basic character of the exocyclic nitrogen in position 3.

The compounds obtained and their spectral data are listed in Table 1. The spectral properties are in agreement with the assigned structures. All substances exhibit pronounced UV maxima, even the simplest alkyl substituted representatives (**3a**) and (**3b**). IR and NMR spectra show close similarities to those of the sydnone imines.[3,4] The hydrogen in the 4-position has a characteristic IR stretching frequency near 3145 cm^{-1} and appears in the NMR spectrum as a singlet at 7·59–7·87 ppm, not exchangeable with deuterated water. The latter finding excludes the alternative structure (**4**), the Dakin–West reaction product, for compounds (**3a**), (**3b**) and **3c**). Furthermore, the N-H would exchange with ease in deuterated water and salt formation of (**4**) should be expected.



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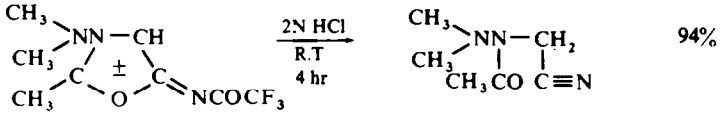
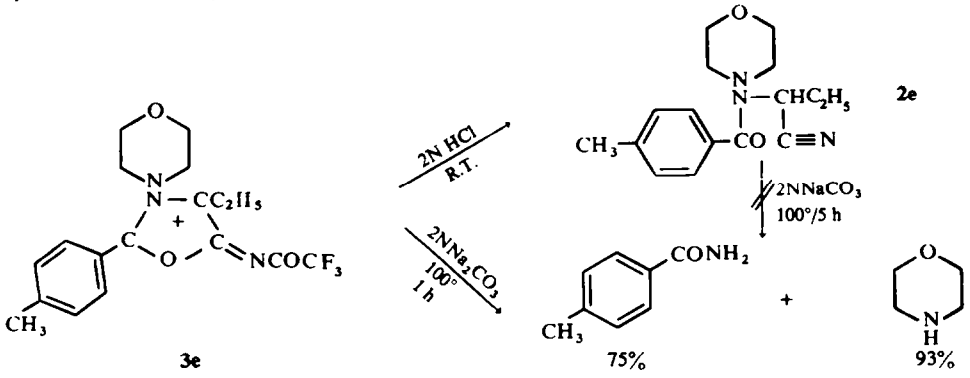
Structure (**3**) was further confirmed by degradation of (**3a**) under mildly acidic conditions. The ring closure was reversed and the acylated nitrile (**2a**) was recovered. The loss of the trifluoromethylketo group of structure (**4**) would not be expected to take place under the conditions employed. Acid hydrolysis of (**3e**) proceeded in analogous fashion.



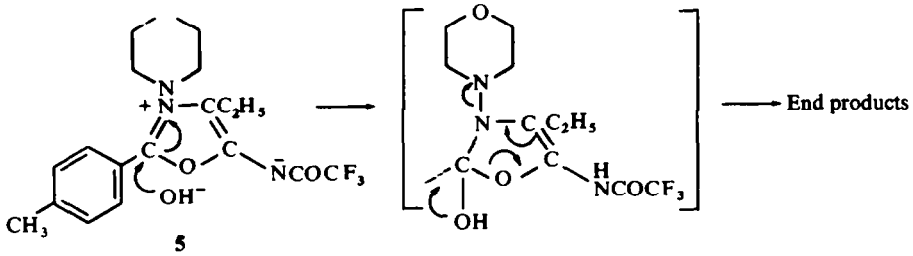
3a **2a**

In contrast to the simple reversal of ring formation in aqueous acid, stands the more complex degradation of (**3e**) in hot 2N Na_2CO_3 solution. *p*-Toluoylamide and morpholine were the products isolated.



3e

The basic degradation involves the cleavage of an N—N bond with formation of morpholine under non-reductive conditions. The cleavage presumably takes place via direct attack of the mesoionic ring by base, since the nitrile (**2e**) is stable under identical conditions. The inability of the nitrogen, in position 3, to protonate in trifluoroacetic acid, and the unusually low carbonyl absorption in the IR spectrum of (**3e**), indicates that (**5**) is a major contributor to the possible mesomeric structures of (**3e**). The degradation could, therefore, be envisaged as addition of hydroxyl to the zwitterionic structure (**5**).



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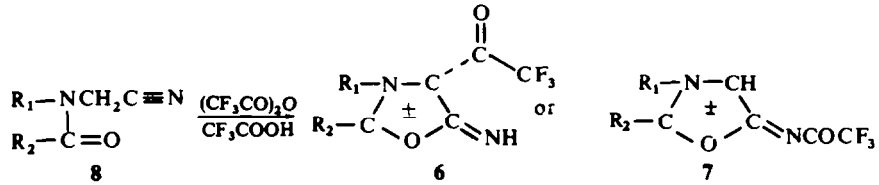
Further hydrolytic products, representing carbon 4 and 5 of the mesoionic ring, could not be isolated.

With the structure of the acylated 3-amino-5-iminooxazolines established as (**3**), it became of interest to re-examine the 3-aryl-5-iminooxazolines reported[5] to be Dakin–West reaction products (**6**). If the ring formation proceeds, analogous to **2** → **3**, compounds (**7**) would be expected.

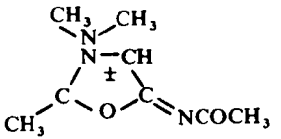
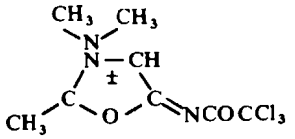
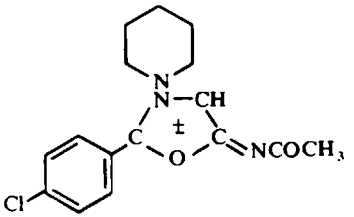


8 **6** **7**

Starting with (**8a**) (R_1 = *p*-chlorophenyl; R_2 = phenyl) the ring closure was performed under the conditions described[5] and a product with physical properties, similar to those expected, was obtained. It was impossible to distinguish between **6a** and **7a** from the NMR spectrum, since the hydrogen in question was obscured by the complex aromatic region. The presence of the typical IR stretching frequency at 3165 cm^{-1} indicated, however, that the product formed had structure (**7a**).

To prove the attachment of the acyl group to the exocyclic nitrogen, a 2,3-dialkylmünchnone imine, **7b** (R_1 = R_2 = CH_3) was prepared. This compound shows the expected spectral properties (Table 2). The 7·05 ppm peak cannot be abolished on exchange with deuterated water, excluding the Dakin–West product (**6b**). **7b** was independently prepared by ring closure of **7a** to **9**, followed by acylation.

TABLE 1

		IR (KBr) cm^{-1}	UV (ethanol) λ_{max}, (mμ) ε		NMR ppm	Solvent
3a		3145 1630 1612 1595	282	17600	2 C—CH_3 :2·68 s 3 N—CH_3 :2·90 s 4 C—H :7·87 s	DMSO
3b		3125 1610 1575	293	14800	2 C—CH_3 :2·60 s 3 N—CH_3 :2·82 s 4 C—H :7·59 s	DMSO
3c		3145 1605	250 365	12600 13800	4 C—H :7·77 s 6 $COCH_3$:2·22 s	$CDCl_3$

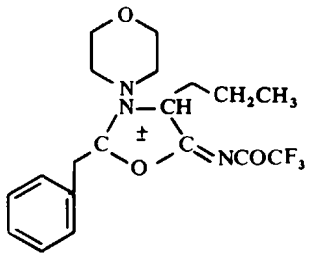
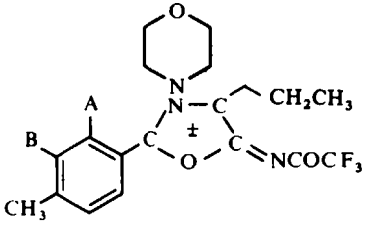
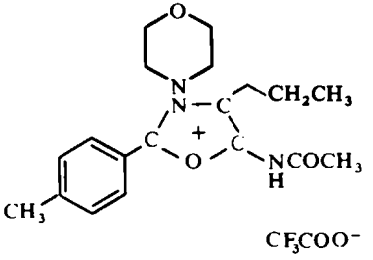
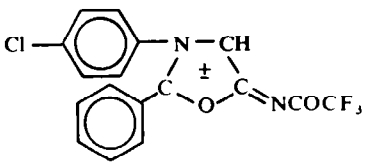
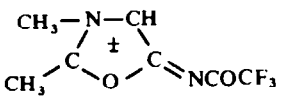
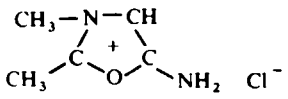
3d		1650 1630 1615	249 285	8600 8300	4 CH_2CH_3 :1·10 t $J_{7·5}$ 4 CH_2CH_3 :2·88 q	
3e		1635 1620 1005	253 343	20800 15000	2 C—H_A :8·15 d $J_{9·0}$ 2 C—H_B :7·52 d $J_{9·0}$ 4 $CH_2\underline{CH_3}$:1·22 t $J_{8·0}$ 4 $\underline{CH_2}CH_3$:3·10 q $J_{8·0}$	$CDCl_3$
3f		1715 1675	240 297	10600 12300	4 $CH_2\underline{CH_3}$:1·37 t $J_{8·0}$ 4 $\underline{CH_2}CH_3$:3·02 q $J_{8·0}$ 6 $\overline{COCH_3}$:2·30 s	

TABLE 2

		IR (KBr) cm^{-1}	UV (ethanol) λ_{max}, mμ ε		NMR ppm	Solvent
7a		3165 1630 1595 1580 1570 1545	246 346	15200 16700	arom 7·45 7·9	$CDCl_3$
7b		3125 1625 1580	282	16600	2 C—CH_3 :2·68 3 N—CH_3 :3·78 4 C—H :7·05	DMSO
9		3085 1680 1615 1598 sh.	280	5950		

EXPERIMENTAL

The NMR spectra were determined on a Varian A-60, UV spectra recorded on a Bausch and Lomb 505, IR spectra on a Perkin–Elmer Infracord 237 B.

N',N'-Dimethylhydrazinoacetonitrile (**1a**). To a stirred soln of 12 g (0·2 mole) of 1,1-dimethylhydrazine, 30 ml of water and 15 ml of conc HCl, 13 g, (0·2 mole) of KCN dissolved in 26 ml of water and 15 ml (0·2 mole) of 40% HCHO soln were added. The mixture was kept at room temp overnight, basified with excess 2N NaOH soln and repeatedly extracted with ether. The combined and dried ether extracts were evaporated *in vacuo*, the remaining light yellow oil (17·2 g) showed on TLC, besides the expected compd, only minor impurities. The material was sufficiently pure for the next step. A sample was dissolved in MeOH, acidified with HCl, and crystallized on addition of ether. Recrystallized from methanol/ether. m.p. 133–134°; IR (KBr): 2250 cm^{-1} (C≡N); Analysis: (Found: N, 30·72. Calc. for C_4HgN_3·HCl. N, 30·99%).

N-Acetyl-N',N'-dimethylhydrazinoacetonitrile (**2a**) 9·9 g (0·1 mole) of **1a** were dissolved in 25 ml of acetic anhydride and warmed on the water bath for 30 min. Excess acetic anhydride was removed *in vacuo* and the residue crystallized from ether/light petroleum. 10 g (71%); m.p. 65–67°; IR (KBr): 2240 cm^{-1} (C≡N), 1650 cm^{-1} (C=O); Analysis: (Found: C, 50·85; H, 7·87; N, 29·57. Calc for $C_6H_{11}N_3O$: C, 51·04; H, 7·85; N, 29·77%).

3-Dimethylamino-2-methyl-5-trifluoroacetylimino-ψ-oxazole (**3a**). 14·1 g (0·1 mole) of **2a** were dissolved in 40 ml of trifluoroacetic anhydride and 25 ml CF_3COOH and kept for 1 h at room temp. The soln was concentrated *in vacuo*, the residue treated with ether and the precipitate crystallized from EtOH/ether. 19·7 g (83%); m.p. 194–196° (dec); Analysis: (Found: C, 40·97; H, 4·51; N, 17·60. Calc for $C_8H_{10}F_3N_3O_2$: C, 40·50; H, 4·25; N, 17·32%).

3-Dimethylamino-2-methyl-5-trichloroacetylimino-ψ-oxazole (**3b**). 14·1 g (0·1 mole) **2a** dissolved in 30 ml trichloroacetic anhydride and 20 ml of CCl_3COOH were heated to 60° for 1 h. On addition of ether, crystals separated which were recrystallized from acetonitrile/ether. 15·2 g (53%); m.p. 164–165°; Analysis: Found: C, 33·45; H, 4·00; Cl, 37·18; N, 14·65. Calc for $C_8H_{10}Cl_3N_3O_2$: C, 33·52; H, 3·52; Cl, 37·12; N, 14·66%).

N-(1-Piperidino) aminoacetonitrile (**1c**). The compd was prepared according to **1a** from 100 g (1 mole) N-aminopiperidine. The crude oil was distilled *in vacuo*, the fraction collected at 78°–80°/0·1 mm proved homogeneous on TLC. 68 g (49%).

N-(p-Chlorobenzoyl)-N-(1-piperidino) aminoacetonitrile (**2c**). To 41·7 g (0·3 mole) of **1c**, dissolved in 200 ml of pyridine, 61·2 g (0·35 mole) *p*-chlorobenzoyl chloride were added. After 12 h, at room temp, the mixture was poured on ice and repeatedly extracted with $CHCl_3$. The washed and dried $CHCl_3$ extracts were evaporated *in vacuo*, and the residue crystallized from ether/light petroleum. 54·5 g (65%); m.p. 118–119°; IR (KBr): 2240 cm^{-1} (C≡N), 1650 cm^{-1} (C=O); Analysis: (Found: C, 60·38; H, 6·18; Cl, 12·72; N, 15·24. Calc for $C_{14}H_{16}ClN_3O$: C, 60·53; H, 5·83; Cl, 12·76; N, 15·12%).

5-Acetylimino-2-p-chlorophenyl-3-(1-piperidino)-ψ-oxazole (**3c**). 27·8 g (0·1 mole) of **2c** dissolved in 40 ml CF_3COOH and 75 ml of acetic anhydride were kept at room temp for 1 h, followed by evaporation *in vacuo*. The residue was crystallized from acetonitrile/ether to afford 31·6 g (73%) of yellow crystals, m.p. 191–192°, (dec); Analysis: (Found: C, 49·59; H, 4·77; Cl, 8·03; N, 9·71. Calc for $C_{16}H_{18}ClN_3O_2CF_3COOH$ C, 49·83; H, 4·41; Cl, 8·17; N, 9·71%).

4·3 g (0·01 mole) of the above salt dissolved in 100 ml $CHCl_3$, was twice washed with ice cold soln of satd $NaHCO_3$. The $CHCl_3$ layer was dried, evaporated to dryness *in vacuo* and the residue was crystallized from acetonitrile/ether to afford 1·64 g (51%), m.p. 134–135° (dec); Analysis: (Found: C, 60·06: H, 5·94; Cl, 10·96; N, 13·11. Calc for $C_{16}H_{18}ClN_3O_2$: C, 60·08; H, 5·67; Cl, 11·08; N, 13·14%).

N-(4-Morpholino)-2-aminobutyronitrile **1d**). The compd, prepared according to **1a** from 102 g (1 mole) of N-aminomorpholine and 58 g (1 mole) of propionaldehyde, yielded an oil, showing only a minor impurity on TLC, sufficiently pure for the next step. 128 g (76%).

N-Dihydrocinnamoyl-N-(4-morpholino-2-aminobutyronitrile (**2d**). Procedure **2c** was used starting with 84·5 g (0·5 mole) of **1d** and 101 g (0·6 mole) of dihydrocinnamoyl chloride. The substance was crystallized from ether after chromatography on silicic acid. 58·5 g (39%); m.p. 75°–76°; IR (KBr): 2220 cm^{-1} (C≡N), 1670 cm^{-1} (C=O); Analysis: (Found: N, 13·81. Calc for $C_{17}H_{23}N_3O_2$: N, 13·94%).

4-Ethyl-3(4-morpholino)-2-phenethyl-5-trifluoroacetylimino-ψ-oxazole (**3d**). 15 g (0·05 mole) of **2d** dissolved in 30 ml trifluoroacetic anhydride, and 60 ml CF_3COOH were kept at room temp for 1 h, concentrated *in vacuo* and the residue, dissolved in $CHCl_3$, was repeatedly extracted with cold satd $NaHCO_3$

soln. The dried $CHCl_3$ extract was evaporated and the resin crystallized from $CHCl_3$/ether. 10·1 g (51%); m.p. 133–134° (dec); Analysis: (Found: C, 57·89; H, 5·34; N, 10·48. Calc for $C_{19}H_{22}F_3N_3O_3$: C, 57·42; H, 5·57; N, 10·57%).

N-(4-Morpholino)-N-p-toluoyl-2-aminobutyronitrile (**2e**). Procedure **2c** was used starting with 169 g (1 mole) of **1d** and 185·3 g (1·2 mole) of *p*-toluoylchloride. The substance was crystallized from acetonitrile/ether. 161 g (56%); m.p. 129–131°; IR(KBr): 2225 cm^{-1} (C≡N), 1650 cm^{-1} (C=O); Analysis: (Found: C, 66·68; H, 7·21; N, 14·71. Calc for $C_{16}H_{21}N_3O_2$; C, 66·87; H, 7·37; N, 14·62%).

4-Ethyl-3-(4-morpholino)-2-p-toluoyl-5-trifluoroacetylimino-ψ-oxazole (**3e**). The same procedure as **3d** was employed, starting with 7·1 g (0·25 mole) of **2e**. Crystallized from $CHCl_3$/ether. 54·5 g (59%) of yellow crystals; m.p. 199° (dec); Analysis: (Found: C, 56·11; H, 5·25; N, 10·97. Calc for $C_{18}H_{20}F_3N_3O_3$: C, 56·39; H, 5·25; N, 10·96%).

5-Acetylimino-4-ethyl-3-(4-morpholino)-2-p-toluoyl-ψ-oxazole (**3f**). Procedure **3c** was used starting with 28·7 g (0·1 mole) of **2e**. Crystallized from $CHCl_3$/ether. 16·5 g (37%); m.p. 144–146° (dec); Analysis: (Found: C, 54·29; H, 5·75; N, 9·51. Calc for $C_{18}H_{23}N_3O_3 \cdot CF_3COOH$: C, 54·17; H, 5·45; N, 9·47%).

Acid hydrolysis of **3a**. 2·37 g (0·01 mole) of **3a** dissolved in 50 ml 2N HCl remained for 4 h at room temp and was then repeatedly extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried, evaporated to dryness *in vacuo* and the residue crystallized from ether/light petroleum, followed by distillation at 20μ/80° bath temp. 1·33 g (94%); m.p. 64–66°; IR (KBr): 2240 cm^{-1} (C≡N); 1650 cm^{-1} (C=O); Analysis: (Found: C, 50·79; H, 7·46; N, 29·50. Calc for $C_6H_{11}N_3O$: C, 51·04; H, 7·85; N, 29·77%).

Acid hydrolysis of **3e**. 3·83 g (0·01 mole) of **3e** were dissolved in 100 ml of 2N HCl. The yellow colour immediately disappeared. After a few mins the soln became cloudy, finally crystals separated out, which were collected after one h. at room temp and recrystallized from acetonitrile/light petroleum. 2·75 g (96%); m.p. 129–130°; IR (KBr): 2225 cm^{-1} (C≡N), 1650 cm^{-1} (C=O); Analysis: (Found: C, 66·80; H, 7·41; N, 14·59. Calc for $C_{16}H_{21}N_3O_2$: C, 66·87; H, 7·37; N, 14·62%).

This compound showed IR, UV and NMR spectra, identical with **2e**. The mixed melting point did not show any depression.

Base hydrolysis of **3e**. 7·67 g (0·02 mole) of **3e** were suspended in 100 ml 2N Na_2CO_3 soln and refluxed for 1 h. The resulting clear soln was cooled, the separated crystals A were collected and repeatedly washed with water. The filtrate B was worked up separately.

A. Recrystallized from $CHCl_3$/light petroleum 2·01 g (74·5%); m.p. 159–161°. The substance is identical by IR, m.p. and m.m.p., with an authentic sample of *p*-toluoylamide.

B. The aqueous phase was continuously extracted with ether for 24 h. The dried ether extract was acidified with etheric HCl and evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of EtOH. On addition of ether, crystals separated. 1·62 g (93%); m.p. 176–179°.

The substance is identical by IR, m.p. and m.m.p., with morpholine hydrochloride.

N-Benzoyl-p-chloroanilinoacetonitrile (**8a**). *p*-Chloroanilinoacetonitrile was prepared according to lit.[6] The major fraction distilled at 145–150°C/0·2 mm.

50 g (0·3 mole) of the substance were dissolved in 150 ml of dry pyridine and 56·5 g (0·4 mole) of benzoyl chloride were added dropwise under ice cooling. The mixture remained at room temp overnight. After the usual workup, chromatography on silicic acid yielded a substance crystallizing from EtOH. 46 g (57%); m.p. 91–92°; IR (KBr): 2245 cm^{-1} (C≡N), 1650 cm^{-1} (C=O); Analysis: (Found: N, 10·24. Calc for $C_{15}H_{11}ClN_2O$: N, 10·35%).

3-p-Chlorophenyl-2-phenyl-5-trifluoroacetylimino-ψ-oxazole (**7a**). 5·4 g (0·02 mole) of **8a** were added to a mixture of 25 g trifluoroacetic anhydride and 15 g of CF_3COOH. The mixture became warm and reddish and was left for 30 min at room temp before evaporation *in vacuo* to a residue crystallizing from ether. The shining yellow crystals were recrystallized from toluene. 5·7 g (78%); m.p. 209–211° (dec); Analysis: (Found: C, 55·88; H, 2·73; N, 8·04. Calc for $C_{17}H_{10}ClF_3N_2O_2$: C, 55·68; H, 2·75; N, 7·64%).

N-Acetylmethaminoacetonitrile (**8b**). 42·0 g (0·6 mole) of methylaminoacetonitrile **7** were added in portions to 45 ml of acetic anhydride. After 1 h the excess anhydride was evaporated *in vacuo*, the resin chromatographed on silicic acid and the fractions eluting with benzene/20% MeOH were distilled at 138–140°C/11 mmHg. 39·0 g (58%); Analysis: (Found: C, 53·82; H, 7·19; N, 25·18. Calc for $C_5H_8N_2O$: C, 53·55; H, 7·19; N, 24·99%).

2,3-Dimethyl-5-imino-ψ-oxazole hydrochloride (**9**). The solution of 11·2 g (0·1 mole) of **8b** in 175 ml of CH_2Cl_2 was saturated with HCl at 0° and dil with 1000 ml of ether. The ppt was filtered off, washed with ether and recrystallized from AcOH/ether. 7·6 g (51%); m.p. 189–190° (dec); Analysis: (Found: C, 40·70; H, 6·15; Cl, 23·58; N, 18·61. Calc for $C_5H_8N_2O \cdot HCl$: C, 40·41; H, 6·10; Cl, 23·86; N, 18·85%).

2,3-Dimethyl-5-trifluoroacetylimino-ψ-oxazole (**7b**). 1·1 g (0·01 mole) of **8b** were added to 2 ml of CF_3COOH

and 3 ml of trifluoroacetic anhydride. The mixture was evaporated to dryness *in vacuo* and the resin crystallized from acetonitrile/ether. 1·2 g (58%); m.p. 217–218° (dec); Analysis: (Found: C, 40·59; H, 3·46; N, 13·60. Calc for $C_7H_7F_3N_2O_2$: C, 40·39; H, 3·39; N, 13·46%).

2,3-*Dimethyl-5-trifluoroacetylimino-ψ-oxazole* (**7b**). 1·5 g (0·01 mole) of **9** were added to 2·5 ml of CF_3COOH and 4·5 ml of trifluoroacetic anhydride. The mixture was evaporated to dryness *in vacuo* and the residue crystallized from acetonitrile/ether. 1·6 g (76%); The compound is identical with **7b** (described in the preceding paragraph) in IR, UV and NMR spectra and by m.p. and m.m.p.

Acknowledgement—We would like to thank Mr. J. Furlan for technical assistance and Dr. H. Pook of C. H. Boehringer Sohn, Ingelheim, West Germany, for providing the NMR spectra. The microanalyses were performed by Dr. A. B. Gygli, Toronto.

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