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A NEW SYNTHESIS OF LUTIDONE DERIVATIVES

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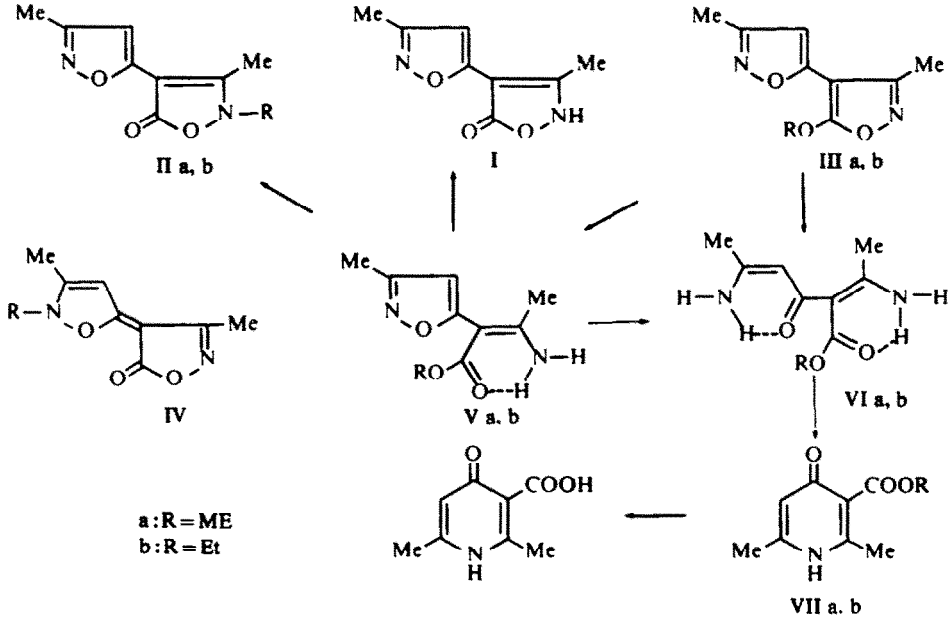
Abstract—The catalytic hydrogenation of some 4,5'-diisoxazole derivatives has been found to yield, through ring cleavage and recyclisation, γ-lutidone compounds. The structures of the intermediates are also discussed.

IN A previous paper[1] we reported a study of the tautomerism of the so-called "dimethyldiisoxazolone" I by comparison with the N- and O-alkyl derivatives II and III, whose structures could be ascertained from spectroscopic and chemical evidence. We report here on the ready hydrogenolysis of some derivatives of I to γ-lutidones.

Whereas catalytic hydrogenation of the O-alkyl derivatives IIIa, b in the presence of Pd/C cleaves only the alkoxy-activated isoxazole ring, as shown in Scheme I, hydrogenation in the presence of Raney nickel shows no selectivity and both isoxazole rings

SCHEME I



are cleaved, the absorption rate decreasing sharply after uptake of 2 moles of hydrogen, The hydrogenation solutions showed a large band at 290–335 mμ, consistent with an acyclic conjugated system of type VIa,b. This band gradually disappeared on heating and a new band at 257 mμ appeared, with evolution of ammonia. The high-melting products thus obtained showed analytical and spectroscopic data consistent with structures VIIa,b of lutidone carboxylates.[2,3] Further confirmation was derived by their

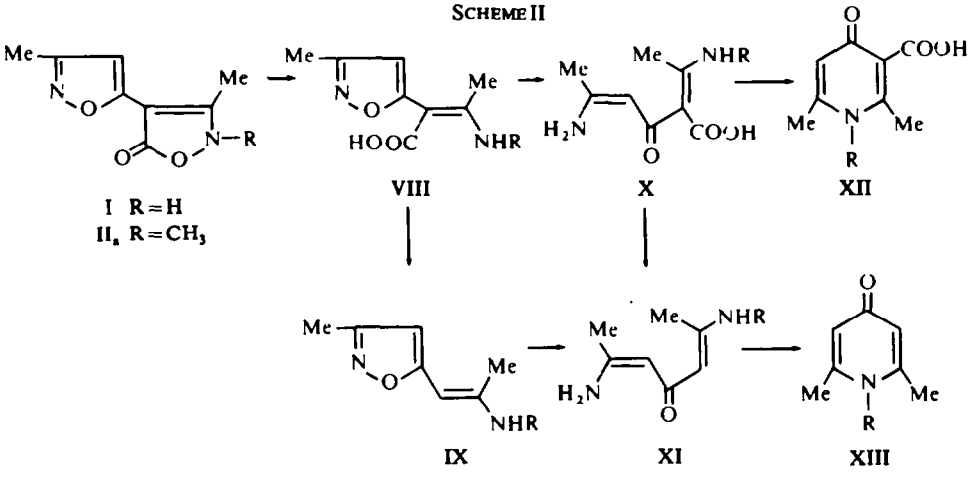
alkaline hydrolysis to the well-known lutidone carboxylic acid.[4] The same products VIIa,b were obtained by hydrogenolytic cleavage of the enamino-esters Va,b.

By hydrogenating 3-methyl-4-(3′-methyl-5′-isoxazolyl)-2H-isoxazolin-5-one (I) itself in the presence of Pd/C, cleavage of both isoxazole rings was achieved, although here a decrease of the hydrogen absorption rate was observed after uptake of 1 mole of hydrogen. The hydrogenation solution showed an absorption band at 356 mμ, consistent with the values reported for 2,6-bis-alkylaminohepta-2,5-dienes.[5, 6] Heating of the solution caused cyclization to γ-lutidone (XIII, R = H), besides which a small amount of lutidone carboxylic acid (XII, R = H) could also be detected.

Starting from the N-methylderivative IIa, we have isolated analogously N-methyl-lutidone (XIII, $R = CH_3$); careful chromatography of the mother liquor allowed us to separate a small amount of γ-lutidone (XIII, R = H).

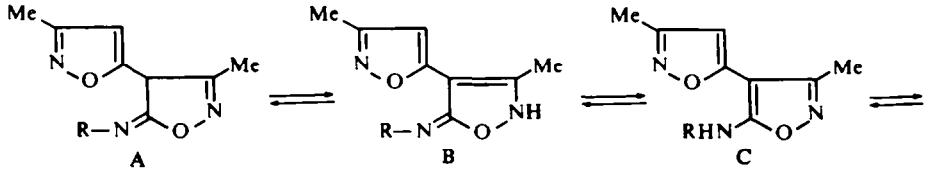
The predominant formation of the γ-lutidones rather than their carboxylic acids is not surprising in view of the known easy decarboxylation of intermediates such as VIII and X[5, 7] (Scheme II), consequently the hydrogenated solution should contain predominantly the 2,6-diaminohepta-2,5-dien-4-one XI, together with a small amount of the car

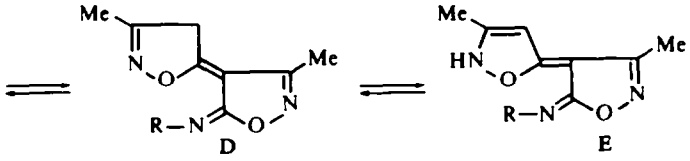
SCHEME II



boxylated product X, responsible for the formation of the lutidone carboxylic acid XII. It should also be mentioned that X and XI have been postulated as intermediates in the reaction of dehydroacetic acid with ammonia, but have never been reported.[5]

Next we investigated the hydrogenolysis of some amino-derivatives of I, which we prepared by nucleophilic substitution on 3,3′-dimethyl-5-chloro-4,5′-diisoxazole. Both primary and secondary amines reacted easily and gave quantitative yields of the expected products. The compounds XIVa,b obtained from primary amines, can exist in five tautomeric forms A–E:



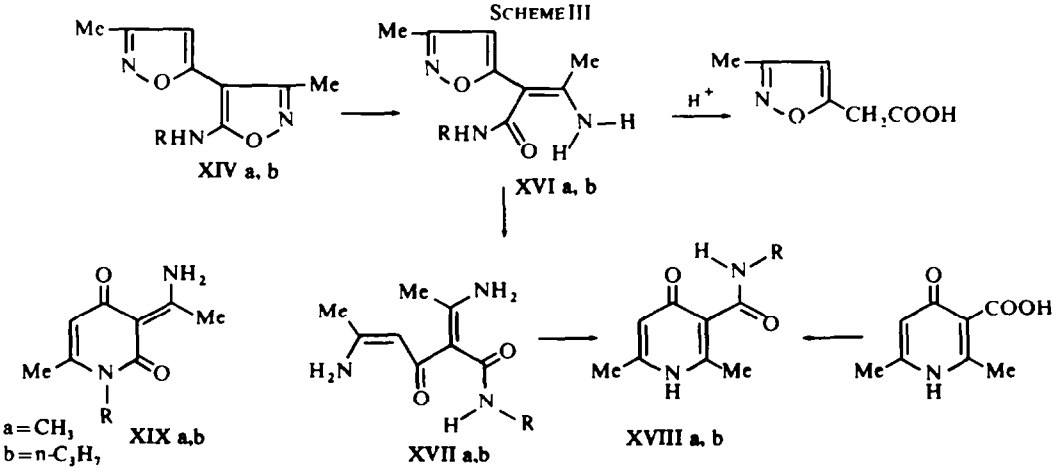


D E

The amino form C predominates, in accordance with the general trend already reported for 5-aminoisoxazoles.[8, 9] Supporting this is the observed coupling of the alkyl protons with the NH proton in the NMR spectra ($J = 5$ Hz for XIVa and 6·8 Hz for XIVb). Moreover the UV spectra of both compounds XIVa,b and compounds XV, where structure of type C is blocked, show a system of two bands, one at 253–260 mμ due to conjugation between the two heterocyclic rings* and the other at 279–286 mμ due to the 5-aminoisoxazole chromophore.[8]

Catalytic hydrogenation of compounds XIVa,b in the presence of Pd/C selectively cleaved the amino-substituted isoxazole ring and yielded the β-aminocrotonamides XVIa,b. The assigned structures are supported by spectroscopic data and by their hydrolysis to 3-methyl-5-isoxazolylacetic acid. As already observed in the case of the alkoxy-analogs, catalytic hydrogenation in the presence of Raney nickel caused non-selective cleavage of both isoxazole rings. Unlike the solutions obtained from the alkoxy-derivatives, which are stable for some days at room temperature. the solution from the hydrogenation of XIVb showed two bands at 310 and 356 mμ, consistent with an open-chain structure, which decreased sharply on evolution of ammonia. The somewhat surprising instability of intermediates such as XVIIb might be attributed to a chelation between the amide NH and the ketone CO,[10] which apparently gives rise to a geometry more favourable for cyclization. Working up of the solutions yielded the pyridone derivatives XVIIIa,b. These structures are consistent with spectroscopic data; in particular, the NMR spectra exclude the isomeric structures XIXa,b. The alkyl protons are coupled with the NH signal, which in turn is a broadened doublet (triplet for XVIIIb). shifted downfield by the chelation. Definitive confirmation of the structural assignement was achieved by synthesis from lutidone carboxylic acid (see Scheme III).

SCHEME III

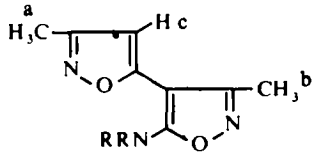


XIV a, b XVI a, b

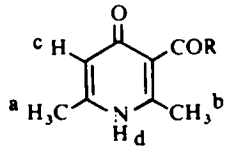
a = CH_3, b = n-C_3H_7 XIX a,b XVII a,b XVIII a, b

* Similar absorption bands are known for the alkoxy-derivatives IIIa,b 257 mμ (log ε = 4.20 and 4·22) and for 3,3'-dimethyl-5-chloro-4,5'-diisoxazole 249mμ (log ε = 4·03).[1]

TABLE 1. NMR SPECTRA OF DIISOXAZOLES AND γ-LUTIDONE DERIVATIVES
(τ values)



Compound	a, b	c	NH	Other signals
XIVa	7·66 s	4·12 s	3·66–4·12	N—CH_3: 6·87 d (J = 5 Hz)
XIVb	7·69 s	4·11 s	3·77–4·20	Propyl: CH_3 9·0 t (J = 7 Hz) CH_2 8·3 m, CH_2N 6·56 q (J = 6·8 Hz)
XVa	7·68 s; 7·78 s	3·98 s	—	Morpholino: 6·1–6·7 m (8H)
XVb	7·68 s; 7·83 s	4·02 s	—	Pyrrolidino: 6·4–6·7 m (4H); 7·9 8·2 m (4H)
XVc	7·67 s; 7·80 s	4·02 s	—	Piperidino: 6·5–6·8 (4H); 8·2–8·5 (6H)



Compound	a	b	c	d	Other signals
VIIa	7·72 s	7·59 s	3·88 s	no attribution	OCH_3: 6·24 s
VIIb	7·70 s	7·61 s	3·81 s	−1·7	CH_3 8·73 t (J = 7 Hz) CH_2O 5·76 q (J = 7 Hz)
XVIIIa*	7·78 s	7·37 s	3·88 s	−1·47	NH: −0·37 broad doublet (J = 5 Hz) N—CH_3: 7·24 d (J = 5 Hz)
XVIIIb	7·66 s	7·16 s	3·70 s	−0·8	NH: −0·55 broad triplet (J = 6 Hz) Propyl: CH_3 9·01 t (J = 7 Hz) CH_2 8·43 m CH_2-N. 6,63 t (J = 6 Hz)
XXIIa	7·72 s		3·92 s	−2·5	Morpholino: 6·17–6·8 (8H)
XXIIb	7·71 s		3·90 s	−2·2	Pyrrolidino: 6·3–6·9 (4H) 7·9–8·3 (4H)
XXIIc	7·70 s		3·93 s	−2·5	Piperidino: 6·55–6·85 (4H) 8·2–8·7 (6H)

* In DMSO solution

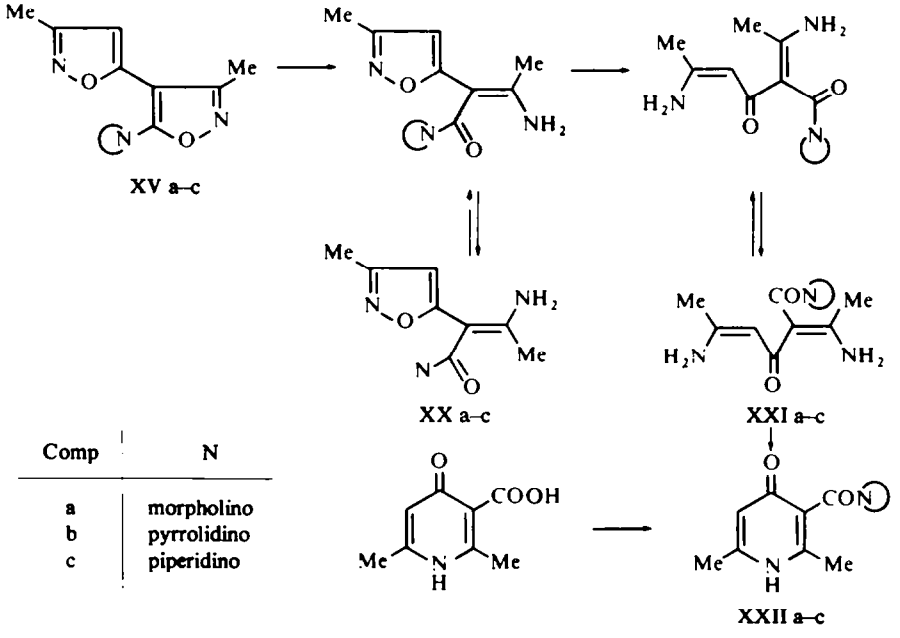
Hydrogenolysis of the amino-derivatives XV a–c (derived from secondary amines) in the presence of Pd/C led to uptake of two moles of hydrogen. Careful working up of the resulting solutions gave the open-chain crystalline products XXIa,b, whilst XXIc crystallized out directly towards the end of the hydrogenation.* For compound XXIb, which could be obtained with analytical purity, the proposed structure relies on its spectroscopic properties. The UV absorption maximum at 354 mμ is consistent with a

* By stopping the hydrogenation after uptake of only one mole of hydrogen, i.e. when the absorption rate decreases markedly, crude products were isolated whose NMR spectra indicated the presence of a mixture of *cis* and *trans* isoxazolylcrotonamides XXa–c. The absence of significant signals in the region 5–5·5 τ ruled out cleavage of the second ring, thus showing here the selectivity of the hydrogenolytic action.

dienaminoketone chromophore, whereas the NMR spectrum (see Table 1) shows a one-proton vinyl signal at 5·17 τ and two different methyl signals at 8·08 and 8·11 τ. Heating pure XXIb above its melting point or boiling its ethanol solution readily caused ring closure to give the corresponding lutidone derivative XXIIb in quantitative yield. Compounds XXIIa–c could be directly obtained by refluxing the hydrogenation solution (see Scheme IV). Their structures were confirmed by synthesis from lutidone carboxylic acid. It seems worth noting that the methyl groups in positions 2 and 6 are equivalent in compounds XXIIa–c, whereas compounds XVIIIa,b have two different methyl signals, owing to the downfield shift caused by the chelated amide group on the adjacent methyl group.

As is known, γ-pyridone derivatives are most usually prepared from pyrones (or their acyclic precursors) and ammonia or amines; lutidone carboxylic acid derivatives can

SCHEME IV



Comp	N
a	morpholino
b	pyrrolidino
c	piperidino

also be obtained by action of diketene on β-aminocrotonic acid derivatives.[11] Since 3-methyl-4-(3′-methyl-5′-isoxazolyl)-2H-isoxazolin-5-one (I) and its derivatives are easily accessible from acetoacetate, the hydrogenolytic process represents a convenient new route to lutidone derivatives. The method seems very promising as a general entry into γ-pyridone compounds and this study is being continued in order to investigate the range of applicability of the reaction.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra in abs. EtOH soln. on a Perkin–Elmer model 137 UV Spectrophotometer. IR spectra in Nujol mull on a Perkin–Elmer model 237 spectrophotometer. Microanalyses by Dr. L. M. Dacrema. NMR spectra: $CDCl_3$ soln, TMS as internal standard, τ values, Perkin–Elmer R 12 spectrometer (temp, 35°). Thin-layer chromatography: silica gel H plates. Characterization data and yields of all hitherto unknown compounds are collected in Table 2.

TABLE 2. CHARACTERIZATION DATA OF HITHERTO UNKNOWN COMPOUNDS

Compound	M.p.	Crystallisation solvent	Yield %	UV λ_{max}	UV log ε	Formula	Microanalysis Calc % C	Calc % H	Calc % N	Found % C	Found % H	Found % N
VIIa	194–196°	MeOH/iPr_2O	75	257	4·11	$C_9H_{11}NO_3$	59·66	6·12	7·73	59·63	6·17	7·68
XIVa	157–158°	C_6H_6/C_6H_{12}	86	260*; 284	3·78; 3·93	$C_9H_{11}N_3O_2$	55·95	5·74	21·75	56·10	6·02	21·62
XIVb	76–76·5°	C_6H_{12}	88	263*; 286	4·09; 4·25	$C_{11}H_{15}N_3O_2$	59·71	6·83	18·99	59·90	6·80	18·85
XVb	114–115°	C_6H_{12}	86	258; 281*	4·15; 4·06	$C_{12}H_{15}N_3O_2$	61·78	6·48	18·02	61·75	6·56	18·08
XVc	77·5–78°	n-C_5H_{12}	80	255; 284	4·06; 4·01	$C_{13}H_{17}N_3O_2$	63·14	6·93	16·99	63·11	7·13	17·08
XVIa	126–127	C_6H_{12}	70	280	4·22	$C_9H_{13}N_3O_2$	55·37	6·71	21·53	55·69	6·81	21·40
XVIb	104–105°	C_6H_{12}	86	280	4·23	$C_{11}H_{17}N_3O_2$	59·17	7·68	18·82	59·56	7·65	18·84
XVIIIa	258–259° dec	EtOH/iPr_2O	38	254; 281·5*	3·95; 3·61	$C_9H_{12}N_2O_2$	59·98	6·71	15·55	60·24	6·92	15·50
XVIIIb	169–170°	EtOAc	32	252; 281*	3·93; 3·62	$C_{11}H_{16}N_2O_2$	63·44	7·74	13·45	63·70	7·77	13·73
XXIIa	239–240°	EtOH/iPr_2O	84	260	4·07	$C_{12}H_{16}N_2O_3 \cdot H_2O$	56·68	7·14	11·02	56·40	7·19	11·03
XXIIb	223–224°	EtOH/iPr_2O	65	260	4·08	$C_{12}H_{16}N_2O_2$	65·43	7·32	12·72	65·30	7·36	12·96
XXIIc	214–215°	Me_2CO	69	260	4·08	$C_{13}H_{18}N_2O_2$	66·64	7·74	11·96	66·41	7·74	11·77

* Shoulder.

Materials. The 3-methyl-4-(3′-methyl-5′-isoxazolyl)-isoxazolin-5-one (I),[12] its N-methyl derivative (IIa)[1] and its O-alkyl derivatives (IIIa,b)[1] were prepared as in the literature. The 5-amino derivatives XIVa,b and XVa–c were obtained by nucleophilic substitution on 3,3′-dimethyl-5-chloro-4,5′-diisoxazole following the procedure already known for XVa.[1] The chloroderivative and an excess (5–10 equivalents) of amine are left at room temp in anhydrous benzene. The reactions, followed by TLC (eluant, ethyl acetate: cyclohexane = 7:3), were completed within 2–4 days, with the exception of the pyrrolidine reaction, which was completed in a few hours. In this latter case the hydrochloride did not separate, and therefore the solvent was removed and the residue treated with dil NaOH, leaving the crude compound XVb. For characterization data see Table 2.

Alkyl lutidone carboxylates (VIIa,b). (a) A soln of 1·0 g of IIIa[1] in 70 ml anhyd MeOH was hydrogenated over 2 ml Raney Ni for 3 h, until 2 equivs of H_2 were consumed. The catalyst was separated by filtration and the filtrate refluxed for 5h. After evaporation to dryness, the white residue was recrystallized to give VIIa as colourless needles, m.p. 194–196° (see Table 1). IR: ν_{CO} 1720 cm^{-1} (ester); $\nu_{C=C}$ 1645, 1625 cm^{-1} (pyridone ring stretch); ν_{CO} 1520 cm^{-1} (pyridone).

Analogously from 1·0 g of IIIb[1] in 70 ml anhyd EtOH a 73% yield of VIIb, m.p. 164–165° (from EtOAc), λ_{max}^{EtOH} 257 mμ (log ε 4·11) was obtained (lit[13,4] 163–164°; 161–162°).

(b) A soln of 0·5 g of either Va or Vb in 50 ml anhyd MeOH or EtOH over 1 ml Raney Ni consumed 1 equiv H_2 within 1–2 h. Working up as above afforded an 82% yield of VIIa or a 76% yield of VIIb.

Alkaline hydrolysis of VIIa,b. 60 mg (0·33 mmole) of VIIa were refluxed in 2 ml 4N alcoholic KOH for 1·5 h. After pouring the mixture onto 5 ml 1:1 HCl, 40 mg (65%) of lutidone carboxylic acid separated out, which after recrystallization from water melted at 257–258° dec, identical (mixed m.ps and IR) with an authentic sample prepared[5] from dehydroacetic acid.

Analogously, from VIIb (1·0 mmole) 100 mg (54%) of lutidone carboxylic acid were obtained.

Hydrogenolysis of "dimethyldiisoxazolone" I. A soln of 1·0 g (5·05 mmole) of I monohydrate[12] in 70 ml anhyd EtOH consumed in the presence of 0·1 g of 10% Pd/C, 200 ml H_2 within 4h. After filtration of the catalyst the soln was refluxed for 3 h. Evaporation to dryness left a white residue, m.p. 195–196° dec, which revealed two spots on TLC (eluant $CHCl_3$: MeOH = 80:20). A double crystallization from water yielded 20 mg of lutidone carboxylic acid, m.p. 256–257°, identical with an authentic specimen. The mother liquor was evaporated to dryness and the residue recrystallized from MeOH/EtOAc to give 0·5 g (81%) of γ-lutidone, m.p. 225–226°, identical (mixed m.ps and IR) with an authentic sample, prepared[5] from dehydroacetic acid.

Hydrogenation in 95% EtOH led to identical results.

Hydrogenolysis of N-methylderivative IIa. A soln of 400 mg (2·05 mmole) of IIa in 40 ml 95% EtOH when over 70 mg of 10% Pd/C, adsorbed 102 ml H_2 within 7 h. After filtration and brief heating, evaporation to dryness left 335 mg of a semisolid residue. Crystallization from water furnished 20 mg of N-methyl-γ-lutidone trihydrate, m.p. 106–108°, identical with an authentic specimen.[5] TLC of the mother liquor (eluant BuOH : AcOH : H_2O = 8:2:3) revealed the presence of equal amounts of N-methyllutidone ($R_f \sim 0·2$) and of γ-lutidone ($R_f \sim 0·4$). This latter compd was separated by preparative TLC and was identified by comparison with an authentic specimen.

α-(3-*Methyl-5-isoxazolyl*)-β-*amino-N-methylcrotonamide* (XVIa). A soln of 500 mg (2·58 mmole) of XIVa in 50 ml 96% EtOH and over 50 mg of 10% Pd/C consumed 65 ml H_2 in 25 min. After filtration and evaporation of solvent 350 mg of XVIa, m.p. 126–127°, were obtained. IR: ν_{NH} 3345, 3265, 3200, 3135 cm^{-1}; $\nu_{C=O}$ and $\nu_{C=C}$ 1628, 1523 cm^{-1}. NMR: 8·12 s (3H, lateral chain methyl group), 7·68 s (3H, isoxazole 3-methyl group), 7·22 d (3H, J = 5 Hz, N—Me), 4·22–4·81 broad (1H, amide NH), 4·02 s (1H, isoxazole 4-proton), 2·2–2·8 broad (2H, NH_2).

α-(3-*Methyl-5-isoxazolyl*)-β-*amino-N-n-propylcrotonamide* (XVIb). A soln of 350 mg (1·58 mmole) of XIVb in 40 ml 96% EtOH and 35 mg of 10% Pd/C consumed 37 ml H_2 in 40 min. After filtration and removal of solvent 300 mg of XVIb, m.p. 104–105°, were obtained. IR: ν_{NH} 3350, 3260, 3185, 3115 cm^{-1}; $\nu_{C=O}$ and $\nu_{C=C}$ 1612, 1518 cm^{-1}. NMR: 8·12 s (3H, lateral chain methyl group), 7·67 s (3H, isoxazole 3-methyl group), 4·3–4·7 broadened t (1H, J = 6Hz, amide NH), 4·00 s (1H, isoxazole 4-proton), 2·35–2·7 broad (2H, NH_2); N-propyl signals: 9·11 t (3H, J = 7 Hz, CH_3), 8·56 m (2H, CH_2) and 6·80 q (2H, J = 6 Hz, N—CH_2).

Acidic hydrolysis of XVIa,b. 100 mg of XVIa or XVIb in 7ml 1:1 h_2SO_4 were refluxed for 1 hr and the cooled mixture diluted with water and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$) and evaporated to dryness. A 80–85% yield of a crude product, m.p. 98–100° was obtained.

Crystallisation from benzene afforded pure 3-methyl-5-isoxazolylacetic acid as colourless needles, m.p. 106–107°, identical (mixed m.p. and IR) with an authentic sample obtained as previously described.[1]

γ-Lutidone carboxamides XVIIIa,b. (a) A soln of 1·0 g of XIVa or XIVb in 60 ml 95% EtOH and over 3 ml Raney Ni consumed 2 equivs H_2 within 2–4 h. After filtration and solvent removal the semisolid residue was crystallized from EtOH/iPr_2O or EtOAc to furnish the amides XVIIIa or XVIIIb, this latter being identical with the sample prepared by synthesis from lutidone carboxylic acid as described below. Refluxing the hydrogenation soln for 2 h did not improve the yields.

(b) A soln of 1·0 g of XVIb in 60 ml 96% EtOH over 3 ml Raney Ni consumed 1 equiv H_2 in 90 min. Working up as above yielded 0·5 g (54%) of XVIIIb, m.p. 164–166°.

γ-Lutidone carboxamides XXII a–c. A soln of 1·0 g of the aminoisoxazoles XVa–c in 60 ml 95% EtOH over 0·1 g 10% Pd/C consumed 2 equivs H_2 within 1·5–2 h. After filtration the solns were refluxed for 3–5 h, monitoring the course of the reaction by TLC or UV spectroscopy. Solvent removal left the high-melting crystalline γ-lutidone carboxamides XXIIa–c as residues (see Table 2).

2-(α-*Amino*) *ethylidene*-3-*oxo*-5-*amino*-*hex*-4-*enoamides* XXIa–c. A soln of 500 mg (2·15 mmole) of XVb in 30 ml anhyd EtOH over 50 mg 10% Pd/C consumed 2 equivs H_2 in 5 h. The catalyst was separated by filtration and the soln was cautiously evaporated to dryness. The oily residue soon solidified yielding 413 mg (82% yield) of colourless crystals, m.p. 158–159° dec. Cautious recystallization from acetone furnished an analytical sample, m.p. 161–162° dec. (Found: C, 60·58; H, 8·02; N, 17·65. Calc for $C_{12}H_{19}N_3O$: C, 60·73; H, 8·07; N, 17·71%). IR: ν_{NH} 3330, 3170 cm^{-1}; $\nu_{C=O}$ and $\nu_{C=C}$ 1630, 1578, 1530 cm^{-1}.

Analogous hydrogenation of XVa and XVc yielded crystalline compds, m.p. 157–158° dec (from MeOH/iPr_2O) and m.p. 191–192° dec. (from EtOH), slightly contaminated with the corresponding cyclized compd.

Thermolysis of XXIb. A sample of the open-chain amide XXIb was dipped into an oil-bath preheated to 180° for 5 min.: after foaming and evolution of ammonia, the residue was cooled and recrystallized from EtOH/iPr_2O to yield a compd, m.p. 216–218°, identified as XXIIb by comparison (m.p. and IR) with the product described above.

Syntheses of the γ-lutidone carboxamides. (a) To a cooled (−10°) and well-stirred suspension of 370 mg (2·0 mmole) of lutidone carboxylic acid monohydrate in 50 ml $CHCl_3$, first Et_3N (2·2 mmole) and then, in 15 min, a soln of ethyl chloroformate (2·5 mmole) in 6 ml $CHCl_3$ were added. After stirring at −10° for additional 30 min, morpholine (4·4 mmole) was added dropwise. The mixture was stirred for an additional hour, the solvent removed and the white solid residue was treated with EtOH. 50 mg of unsoluble lutidone carboxylic acid was thus recovered. The EtOH soln was evaporated to dryness and the residue (0·7 g) was thick-layer chromatographed (eluant $CHCl_3$:MeOH = 8:2). The faster running component was eluted with MeOH and 67 mg (14%yield) of XXIIa as colourless crystals, m.p. 220–222°, were thus obtained. The product is identical with the amide obtained by hydrogenolysis as described above.

(b) The amide XVIIIb has been analogously prepared in 10% yield, using N-propylamine, and was shown to be identical with the product obtained by hydrogenolysis.

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