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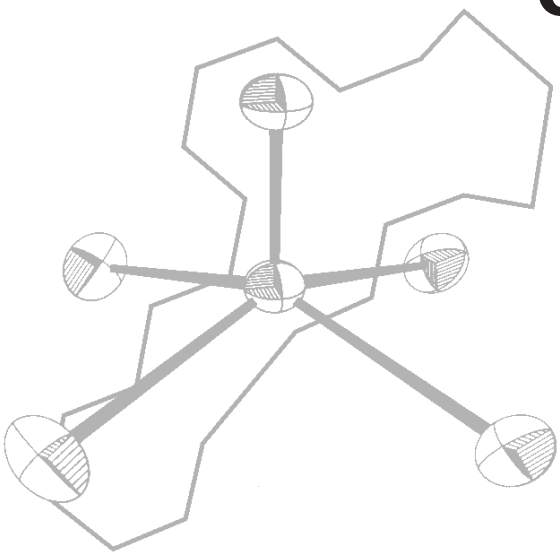

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Dihydro-1,2,4-triazin-6(1*H*)-ones. II* Synthesis of Several Methylated 3-Phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-ones

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Novel syntheses of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones were developed by use of imidoyl chlorides. The overall yield of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones prepared from amino acid imidates and hydrazines was improved by the development of a much more efficient synthesis of the imidates. The new 1,2-, 1,4- and 5,5-dimethyl dihydro-1,2,4-triazin-6(1*H*)-ones have been synthesized by cyclocondensation/cycloaddition pathways. Base-catalysed methylation of 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15) gave the 1-methylated derivative (8); under similar conditions 2-methyl-3-phenyl-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (9) afforded the 1,2-dimethyl derivative (7).

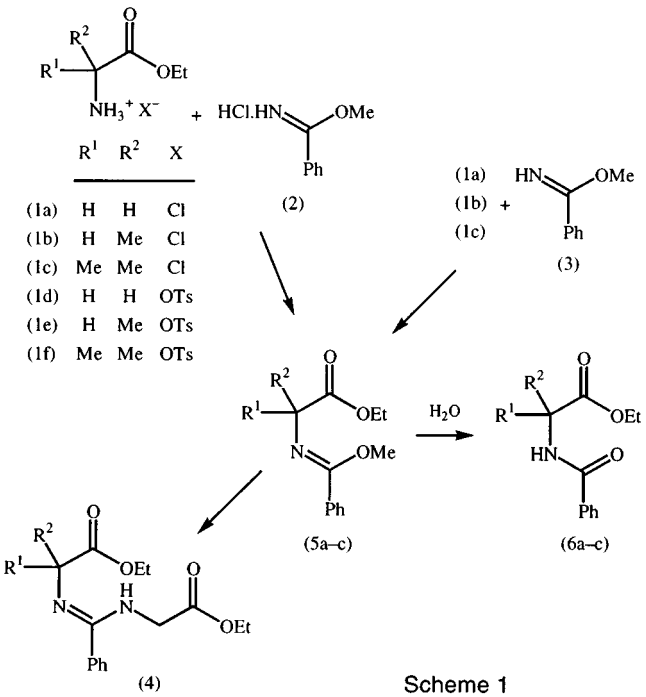
Introduction

In some of the literature on dihydro-1,2,4-triazin-6(1*H*)-ones doubts are raised as to whether some of the compounds described are actually imidazolones, and/or are different regioisomers to the one(s) described.[1] We have found that 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones have potential as crop protection agents and it was advantageous to develop unambiguous synthetic routes to a wide range of derivatives. Very few of the reported syntheses of dihydro-1,2,4-triazin-6(1*H*)-ones are for compounds with substituents attached at positions other than C3 or C5. Varying the substituents at C3 and C5 is relatively easy, since these positions originate from a modified α-amino acid. Those few examples[2] of dihydro-1,2,4-triazin-6(1*H*)-ones having *N*- or *O*-substituents have been prepared by ambiguous routes, with the exception of the work by El-Abadelah *et al.*[3] who reported the addition of nitrile imines to amino acid esters. It was therefore desirable to develop new routes for the regiospecifically substituted dihydro-1,2,4-triazin-6(1*H*)-ones.

Results and Discussion

Synthesis of Amino Acid Imidates (5)

The use of imidate esters (5) to prepare 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones has been demonstrated by Kjaer[4] and Camparini *et al.*[2] Imidate derivatives of the type (5) can be prepared from the reaction (Scheme 1) of the corresponding amino acid ester hydrochloride salts (1a,b) with triethylamine and the imidate ester hydrochloride salt (2).[5] A mixture of the amino acid ester hydrochloride salt (1a), methyl benzimidate hydrochloride (2) and 1 equiv. of 'laboratory grade' triethylamine in dichloromethane was stirred at room temperature overnight to give the corresponding amino acid imidate (5a) in 60% yield and 80% purity. When 2 equiv. of triethylamine were used, the product mixture contained some diaddition material (4). No reaction took place under anhydrous conditions, contrary to a report by Lerestif *et al.*[5] who



Scheme 1

* Part I, *Aust. J. Chem.*, 1996, **49**, 463.

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claimed that anhydrous triethylamine was required. Compound (5b) was also prepared in this manner.

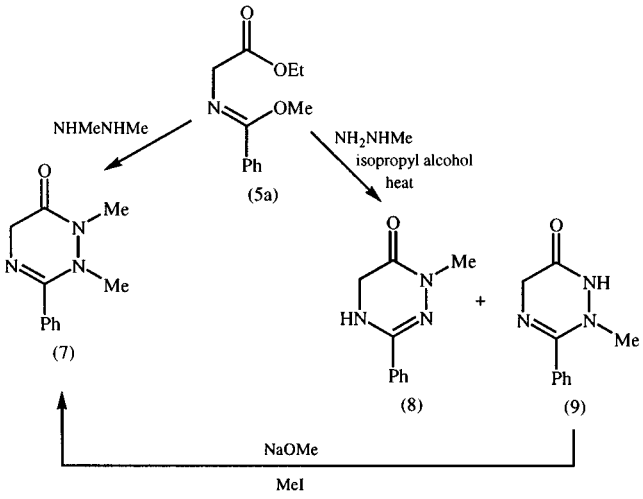
However, amino acid imidates (5) are usually prepared by the general procedure of Schmidt[6] or by a modification[7] in which an aqueous solution of the amino acid ester hydrochloride (1a–c) is shaken with a diethyl ether solution of the imidate ester (3) (Scheme 1). When ethyl glycinate hydrochloride (1a) was used, the yield of the desired imidate derivative (5a) was relatively low (59%) and it was accompanied by 12% of the hydrolysis product ethyl *N*-benzoylglycinate (6a) and 29% of unidentified products. It was therefore desirable to develop a new and improved route to this important intermediate. ^{1}H n.m.r. spectroscopic studies of the reaction of (1a) with (3) were carried out in deuterated dimethylformamide or in deuterated acetonitrile. They showed that the reaction progressed smoothly to a certain point, but then stopped. Prolonged reaction times led to decomposition products and the formation of some of the diaddition product (4) (Scheme 1). Preparative scale reactions carried out in anhydrous dimethylformamide or *N*-methylpyrrolidinone gave similar results. It appeared that there were two factors involved: (i) the reaction reached equilibrium in single-phase media; (ii) the chloride ion present in the reaction may be nucleophilic enough under these conditions to give rise to decomposition products. A possible solution to both of these problems was to use the *p*-toluenesulfonic acid salts (1d–f), first because the sulfonate anion is non-nucleophilic, and second, in an appropriate solvent, the reaction could be forced to completion by the precipitation of the insoluble ammonium *p*-toluenesulfonate.

The ethyl glycinate *p*-toluenesulfonic acid salt (1d) was prepared as described by Ueda.[8*] The *p*-toluenesulfonic acid salt (1e) of ethyl (*RS*)-alaninate and the corresponding salt (1f) of ethyl 2-amino-2-methylpropanoate were prepared similarly.[9,10]

Treatment of methyl benzimidate[11] (3) with the ethyl glycinate *p*-toluenesulfonic acid salt (1d) in dichloromethane under reflux gave the desired glycine imidate derivative (5a) in 81% yield and in greater than 97% purity (Scheme 1).[12] The ^{13}C n.m.r. spectrum of this material was consistent with that reported by Shi *et al.*[13] Our new procedure also worked well for the reaction of the *p*-toluenesulfonic acid salt (1e) of ethyl (*RS*)-alaninate with (3), but a longer reaction time was required (2–3 h). Hence the above procedure constitutes an improved synthesis of imidate esters.

*Preparation of 1- and 2-Alkylated 4,5-Dihydro-1,2,4-triazin-6(1*H*)-ones*

Not surprisingly, the reaction of the glycine imidate (5a) with methylhydrazine was not regioselective, giving a mixture of the regioisomers 1-methyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (8) (22%) and 2-methyl-3-phenyl-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (9) (70%) (Scheme 2) (cf. Camparini *et al.*[2]). These *N*-methyl derivatives were readily separated by chromatography due to their surprisingly very different chemical and physical properties. The 2-methyl derivative (9) was water-soluble and its infrared spectrum showed no carbonyl absorption, while the 1-methyl derivative (8) was not water-soluble and its infrared spectrum showed a strong carbonyl absorption. The 2-methyl derivative (9) was shown by single-crystal X-ray structure analysis to exist as a zwitterion in the solid state.[14] Spectroscopic analysis of (8) and (9) showed that they were respectively identical to the 1- and 2-methyl derivatives prepared previously by unambiguous routes.[12]



Scheme 2

*Preparation of 1,2-Dialkylated 4,5-Dihydro-1,2,4-triazin-6(1*H*)-ones*

In our quest for crop protection chemicals, 1,2-dialkylated 3-phenyl-2,5-dihydro-1,2,4-triazin-6(1*H*)-ones were of particular interest because this disubstitution precludes aerial oxidation to a 4,5-dehydro compound and aerial oxidation of 1,2-dialkylated triazinone derivatives to 5,6-dioxo compounds is less likely (see Scheme 4, below). The 1,2-dimethyl compound (7) and other dialkylated analogues were therefore of special interest. When a solution containing the freshly prepared imidate (5a) and 1,2-dimethylhydrazine was heated at 130°C for 2 h (Scheme 2), chromatography of the product afforded 34% of the new 1,2-dimethyl-3-phenyl-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (7). It is not clear whether the low yield was due to low conversion, or to loss of material when the 1,2-dimethylhydrazine dihydrochloride was neutralized with 2 equiv. of sodium methoxide. The ^{1}H and ^{13}C n.m.r. spectra of (7) showed the methyl resonances at δ 2·91 and 3·20, and 32·3 and 39·2, respectively, and the mass spectrum showed the expected molecular ion.

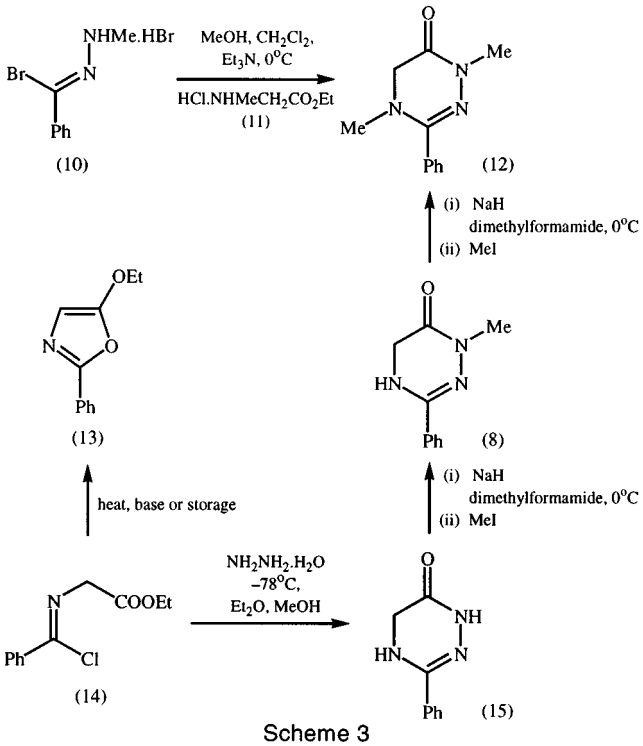
* Ueda reported that compound (1d) was an oil. However, in our hands, it was obtained as a solid, m.p. 80·5°, which gave the expected spectroscopic data and elemental analyses.

Methylation of the 2-Methyltriazinone (9)

Although the dimethyl compound (7) could be obtained from reaction of 1,2-dimethylhydrazine with the glycine imidate derivative (5a), the lack of availability of alkylated hydrazines and poor yield meant that this approach was restrictive. If the further alkylation of 2-methyl derivative (9), or other 2-substituted analogues, proceeded regioselectively at N 1 a range of 1,2-disubstituted derivatives of potential biological interest would be accessible. Treatment of the 2-methyltriazinone (9) with sodium methoxide and methyl iodide in dry methanol gave a good yield of the 1,2-dimethyl derivative (7) (Scheme 2). Indeed alkylation of 2-methyltriazinones proved to be an efficient and general procedure for producing 1,2-disubstituted compounds.

Synthesis of the 1,4-Dimethylated Triazinone (12)

The 1,4-dimethyl compound (12) (Scheme 3) was prepared by means of nitrile imine chemistry. An *N*-methyl nitrile imine was generated *in situ* by treating the *N*-methyl hydrazonoyl bromide hydrobromide[12] (10) with triethylamine. Cyclocondensation between the nitrile imine and ethyl sarcosinate hydrochloride (11) afforded, after chromatography, 1,4-dimethyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (12) in 73% yield. The ^{1}H and ^{13}C n.m.r. spectra of (12) showed two methyl resonances at δ 2·73 and 3·23, and 35·6 and 39·1, respectively. The mass spectrum of (12) showed the expected molecular ion. The 1,4-dimethyl derivative (12) was also the product formed on stepwise dimethylation of 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15) with sodium hydride and methyl iodide.



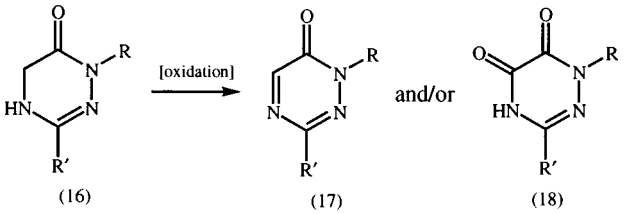
Scheme 3

Synthesis of the 5,5-Dimethylated Triazinone (20)

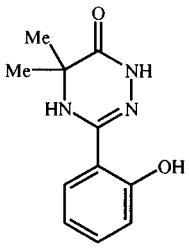
1-Alkyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-ones (16) were found to be susceptible to aerial oxidation to the corresponding dehydro derivatives (17) and 5,6-dioxo derivatives (18).* Therefore it was necessary to determine if the net biological activity observed for compounds of type (16) was due to the parent compound or its aerial oxidation products (Scheme 4). In this respect, it was of interest to prepare 5,5-dimethyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (20) in which aerial oxidation at C 5 is precluded.

Compound (19), a phenolic derivative of (20), has been reported by Chaloupka and Heimgartner,[15] but we required a synthetic route which is more direct and more amenable to the introduction of various substituents on the heterocyclic ring.

Theoretically the dihydrotriazinone (20) may be prepared by using the dimethyl imidate derivative (5c). However, this intermediate was unstable and difficult to prepare, so attention was directed to synthesis and use of the corresponding imidoyl chloride (21).



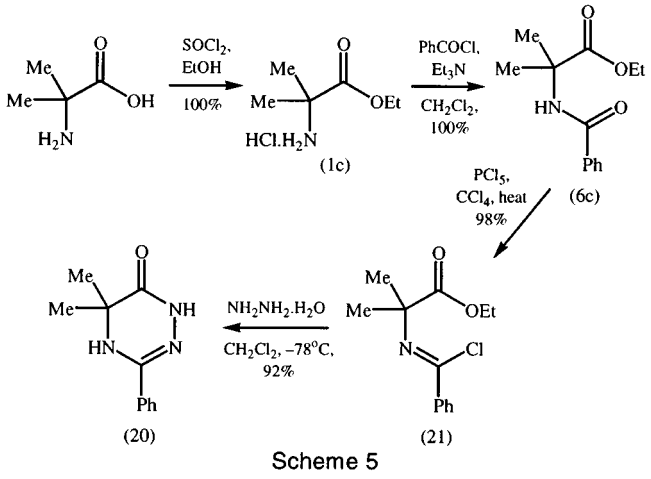
Scheme 4



The preparation of imidoyl halides is well documented,[16] and the desired imidoyl chloride (21) was prepared by a standard procedure (Scheme 5). 2-Amino-2-methylpropanoic acid was converted into ethyl 2-amino-2-methylpropanoate hydrochloride (1c) by treatment with thionyl chloride and ethanol. Reaction of (1c) with benzoyl chloride and triethylamine afforded the *N*-benzoyl derivative (6c), whose physical properties were consistent with those reported by Obrecht and Heimgartner.[17] Treatment of the amide (6c) with phosphorus pentachloride in carbon tetrachloride at reflux

* This oxidation will be reported in detail elsewhere by Collins, D. J., Hughes, T. C., and Johnson, W. M.

for 2 h afforded a product which contained 89% of the imidoyl chloride (21) and 11% of the starting amide (6c) (^{1}H and ^{13}C n.m.r. spectroscopic analysis). The ^{13}C n.m.r. spectrum of (21) showed no amide carbonyl resonance at δ 166·6, but a new resonance at δ 140·8 corresponding to the imine carbon atom. Unlike its glycine analogue (14), which is unstable and quickly forms 5-ethoxy-2-phenyloxazole (13) (Scheme 3), the dimethyl imidoyl chloride (21) was relatively stable.



Scheme 5

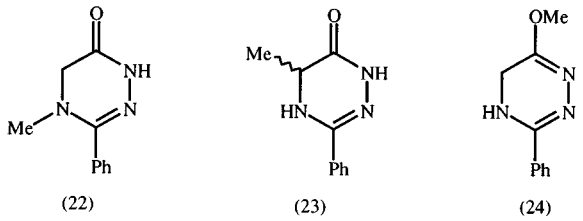
Reaction of an excess of hydrazine hydrate with the freshly prepared imidoyl chloride (21) in anhydrous dichloromethane gave the new 5,5-dimethyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (20) in 92% yield. The ^{1}H and ^{13}C n.m.r. spectra of (20) showed methyl resonances at δ 1·41 and 25·0, respectively.

New Synthesis of the 3-Phenyl Dihydrotriazinone (15)

The imidoyl chloride (14), previously synthesized by us,[12] is a highly reactive *N*-acyl amino acid equivalent which was expected to undergo cyclocondensation with a wide range of hydrazine derivatives to generate dihydro-1,2,4-triazin-6(1*H*)-ones. To our surprise, the highly exothermic reaction of the imidoyl chloride (14) in anhydrous diethyl ether/methanol with hydrazine monohydrate at room temperature gave poor yields (16–19%) of 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15), the major product being 5-ethoxy-2-phenyloxazole (13) (Scheme 3). However, when the reaction was repeated at −78°C the yield of 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15) was much better (59%). The melting point and spectroscopic data were consistent with those reported by Andersen *et al.*[18]

Methylation of the 3-Phenyl Dihydrotriazinone (15)

While 1,2,4-triazin-5(4*H*)-ones feature prominently in the reviews[19] of the alkylation of 1,2,4-triazine derivatives, the only papers found on the alkylation of 1,2,4-triazin-6(1*H*)-ones or their derivatives are those by Prokoféva *et al.*[20] and Camparini *et al.*[2] There are five possible monomethylation products of 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15), namely, (8), (9) and (22)–(24). We found that treatment of compound (15) with 1 mole equiv. of each of sodium hydride and methyl iodide at 0°C gave a single product in 93% yield (Scheme 3). This was identified as the 1-methyl derivative (8) by comparison of its spectral data and melting point with those of an authentic sample prepared by an unambiguous route.[12]



Conclusion

New routes to the dihydro-1,2,4-triazin-6(1*H*)-ones were developed by use of imidoyl chlorides. These compounds allowed a wider range of hydrazine derivatives to be cyclocondensed to form the desired ring compounds. An improved synthesis of amino acid ester derived imidates was developed by use of the corresponding *p*-toluenesulfonic acid salts under anhydrous conditions. This procedure avoided formation of hydrolysis and diaddition products observed when the conventional route was used. The new 1,2-, 1,4- and 5,5-dimethyl dihydro-1,2,4-triazin-6(1*H*)-ones have been synthesized by cyclocondensation/cycloaddition pathways. Methylation of 3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15) with methyl iodide and sodium hydride afforded the 1-methyl derivative (8) as the sole product. The position of alkylation was confirmed by comparison of the product formed with the five possible monomethylation products which had been previously unambiguously prepared. Methylation of the 2-methyl derivative (9) afforded the 1,2-dimethyl derivative (7) in a better yield than that obtained by reaction of the imidate (5a) and 1,2-dimethylhydrazine.

Experimental

Experimental and instrumental details were as described previously.[12]

The p-*Toluenesulfonic Acid Salt (1d) of Ethyl Glycinate*

A mixture of glycine (5·00 g, 66·5 mmol) and ethyl *p*-toluenesulfonate (14·8 g, 73·3 mmol) was suspended in anhydrous ethanol (150 ml) and heated under reflux for 36 h. Evaporation of the solvent under reduced pressure gave a white solid which was suspended in anhydrous diethyl ether (200 ml) and filtered to give the salt (1d) as a white solid (20·34 g, 100%), m.p. 80·5° (lit.[8] oil) (Found: C, 47·9; H, 6·2; N, 5·2. Calc. for $C_{11}H_{17}NO_5S$: C, 47·9; H, 6·2; N, 5·1%). ν_{max} (KBr) 3006s(br), 1746s, 1179s(br) cm^{-1}. ^{1}H n.m.r. δ 1·15, t, *J* 7·14 Hz, $OCH_2C\mathbf{H}_3$; 2·32, s, $ArC\mathbf{H}_3$; 3·66, br q, *J* 6·9 Hz, $^+NH_3C\mathbf{H}_2$; 4·03, q, *J* 7·2 Hz, $OC\mathbf{H}_2CH_3$; 7·08, d, *J* 8·2 Hz, H3′ and H5′; 7·68, d, *J* 8·2 Hz, H2′ and H6′; 7·95, br t,

J 6·9 Hz, $^{+}N\mathbf{H}_3CH_2$. ^{13}C n.m.r. δ 13·75, $OCH_2\mathbf{C}H_3$; 21·3, $Ar\mathbf{C}H_3$; 40·5, NCH_2; 62·2, $O\mathbf{C}H_2CH_3$; 126·0, C 2′, C 6′ or C 3′, C 5′; 128·9, C 2′, C 6′ or C 3′, C 5′; 140·7, C 1′ or C 4′; 144·6, C 1′ or C 4′; 167·3, C=O.

The p-*Toluenesulfonic Acid Salt (1e) of Ethyl* (RS)-*Alaninate*

The *p*-toluenesulfonic acid salt (1e) of ethyl (*RS*)-alaninate was prepared from (*RS*)-alanine by the same procedure as that used to prepare the analogous salt (1d) above. A mixture of (*RS*)-alanine (20·00 g, 224 mmol) and ethyl *p*-toluenesulfonate (49·4 g, 247 mmol) was suspended in anhydrous ethanol (400 ml) and heated under reflux for 36 h. Evaporation under reduced pressure gave a white solid which was suspended in anhydrous diethyl ether (200 ml) and filtered to give the salt (1e) (64·6 g, 99%) as a white solid. A sample was recrystallized from ethanol, m.p. 76–77° (lit.[9] 74–76°). ν_{max} (KBr) 3035s, 1750s, 1515m, 1223s, 1164s, 1037m, 685m cm^{-1}. ^{1}H n.m.r. δ 1·12, t, *J* 7·1 Hz, $OCH_2C\mathbf{H}_3$; 1·39, d, *J* 7·2 Hz, $CHC\mathbf{H}_3$; 2·32, s, $ArC\mathbf{H}_3$; 3·88–4·13, m, $OC\mathbf{H}_2CH_3$, $C\mathbf{H}CH_3$; 7·09, d, *J* 7·9 Hz, H 3′, H 5′; 7·70, d, *J* 7·9 Hz, H 2′, H 6′; 8·05, br s, NH_3. ^{13}C n.m.r. δ 13·8, $OCH_2\mathbf{C}H_3$; 15·7, $CH(\mathbf{C}H_3)_2$; 21·3, $Ar\mathbf{C}H_3$; 49·1, $\mathbf{C}H(CH_3)_2$; 62·2, $O\mathbf{C}H_2CH_3$; 125·9, C 2′, C 6′ or C 3′, C 5′; 128·9, C 2′, C 6′ or C 3′, C 5′; 140·5, C 1′ or C 4′; 141·1, C 1′ or C 4′; 169·8, C=O.

The p-*Toluenesulfonic Acid Salt (1f) of Ethyl 2-Amino-2-methylpropanoate*

A mixture of 2-amino-2-methylpropanoic acid (25·00 g, 242 mmol) and ethyl *p*-toluenesulfonate (53·4 g, 266 mmol) was suspended in anhydrous ethanol (400 ml) and heated under reflux for 36 h. Evaporation under reduced pressure gave a white solid which was suspended in anhydrous diethyl ether (200 ml) and filtered to give the salt (1f) as a white solid (73·2 g, 99%). A sample was recrystallized from ethanol/diethyl ether to afford a white solid, m.p. 121–123°.* ν_{max} (KBr) 2990s, 1744s, 1544m, 1190s, 815s, 766w, 681s, 570s cm^{-1}. ^{1}H n.m.r. δ 1·21, t, *J* 7·1 Hz, $OCH_2C\mathbf{H}_3$; 1·52, s, $C(CH_3)_2$; 2·35, s, $ArC\mathbf{H}_3$; 4·15, q, *J* 7·1 Hz, $OC\mathbf{H}_2CH_3$; 7·15, d, *J* 8·3 Hz, H 3′, H 5′; 7·75, d, *J* 8·3 Hz, H 2′, H 6′; 8·28, br s, $^{+}N\mathbf{H}_3CH_2$. ^{13}C n.m.r. δ 13·8, $OCH_2\mathbf{C}H_3$; 21·3, $Ar\mathbf{C}H_3$; 23·5, $C(\mathbf{C}H_3)_2$; 57·2, $\mathbf{C}(CH_3)_2$; 62·4, $O\mathbf{C}H_2CH_3$; 126·0, C 2′, C 6′ or C 3′, C 5′; 128·8, C 2′, C 6′ or C 3′, C 5′; 140·3, C 1′ or C 4′; 141·6, C 1′ or C 4′; 171·5, C=O.

Ethyl N-*[Methoxy(phenyl)methylidene]glycinate (5a)*[12]

Ethyl glycinate hydrochloride (1a) (1·63 g, 11·7 mmol) was added to a solution of methyl benzimidate hydrochloride (2) (2·00 g, 11·7 mmol) in dichloromethane (20 ml). Triethylamine (reagent grade, 1·62 ml, 11·7 mmol) was added and the solution was stirred at room temperature overnight. The mixture was adsorbed on a short column of silica gel which was eluted with dichloromethane. Concentration of the eluate gave (5a) (1·55 g, 60%) as a colourless oil. G.l.c. R_t 12·36 min, 97%. ν_{max} (film) 2984m, 2946m, 1746s, 1672s, 1435m, 1373m, 1282s, 1190s cm^{-1}. ^{1}H n.m.r. δ 1·20, t, *J* 7·1 Hz, $OCH_2C\mathbf{H}_3$; 3·85, s, $OC\mathbf{H}_3$; 4·05, s, $NC\mathbf{H}_2$; 4·13, q, *J* 7·1 Hz, $OC\mathbf{H}_2CH_3$; 7·25–7·39, m, Ar. ^{13}C n.m.r. δ 14·1, $OCH_2\mathbf{C}H_3$; 52·1, NCH_2; 53·5, OCH_3; 60·7, $O\mathbf{C}H_2CH_3$; 127·8, C 2′, C 6′ or C 3′, C 5′; 128·5, C 2′, C 6′ or C 3′, C 5′; 129·8, C 4′; 131·6, C 1′; 164·6, C=N; 171·2, C=O. Mass spectrum: *m/z* (c.i.) 222 ($[M+1]^{+\bullet}$, 100%), 190 (70), 155 (3), 148 (22), 135 (6), 118 (4), 104 (2), 86 (3).

Ethyl (RS)-N-*[Methoxy(phenyl)methylidene]alaninate (5b)*

The *p*-toluenesulfonic acid salt (1e) of ethyl (*RS*)-alaninate (6·70 g, 22·2 mmol) was added to a solution of methyl benzimidate (3) (3·00 g, 22·2 mmol) in dry dichloromethane (30 ml). The mixture was heated under reflux for 3 h under an argon atmosphere. During this time a white precipitate of ammonium *p*-toluenesulfonate formed. The mixture was cooled and then poured onto a short column of silica gel. Elution with dichloromethane afforded (5b) (3·77 g, 90%) as a colourless *oil*. The crude product was used immediately without further purification (Found: $[M+1]^{+\bullet}$, 236·130. $C_{13}H_{18}NO_3$ requires $[M+1]^{+\bullet}$, 236·129). ν_{max} (film) 2986m, 1739s, 1668s, 1447m, 1278s, 1199s, 1125s, 1051m, 889m cm^{-1}. ^{1}H n.m.r. δ 1·22, t, *J* 7·0 Hz, $CH_2C\mathbf{H}_3$; 1·32, d, *J* 6·8 Hz, $CHC\mathbf{H}_3$; 3·85, s, OCH_3; 3·98–4·19, m, $C\mathbf{H}_2CH_3$, $C\mathbf{H}CH_3$; 7·25–7·43, m, Ar. ^{13}C n.m.r. δ 14·0, $CH_2\mathbf{C}H_3$; 20·0, $CH\mathbf{C}H_3$; 53·3, $\mathbf{C}HCH_3$; 57·2, OCH_3; 60·5, $\mathbf{C}H_2CH_3$; 127·4, C 2′, C 6′ or C 3′, C 5′; 128·3, C 2′, C 6′ or C 3′, C 5′; 129·4, C 4′; 131·9, C 1′; 162·9, C=N; 173·4, C=O. Mass spectrum: *m/z* (c.i.) 236 ($[M+1]^{+\bullet}$, 56%), 204 (100), 162 (63).

*1-Methyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (8)*

Methylhydrazine (1·4 ml, 27·0 mmol) was added to a solution of the ethyl glycinate (5a) (3·98 g, 17·9 mmol) in isopropyl alcohol (15 ml). After the solution was stirred at room temperature overnight, the solvent and excess of methylhydrazine were removed leaving a yellow solid which was purified by chromatography over silica gel. Elution with dichloromethane/methanol mixtures (<5% methanol) gave a solid which was recrystallized from ethyl acetate/cyclohexane to give the 1-methyl triazinone (8) (747 mg, 22%). The melting point and spectroscopic data were identical to those of an authentic sample.[12] Further elution of the same column with increasing amounts of methanol (>5%) gave a solid which was recrystallized from methanol to afford 2-methyl-3-phenyl-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (9) (2·38 g, 70%). The melting point and spectroscopic data for this compound were identical to those of an authentic sample.[12] Most of the 2-methyl isomer (9) in the crude product can be easily isolated by trituration of the crude product with dichloromethane, in which it is insoluble.

*1,2-Dimethyl-3-phenyl-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (7)*

(i) *Reaction of (5a) with 1,2-dimethylhydrazine.* A solution of the ethyl glycinate (5a) (752 mg, 3·40 mmol) and 1,2-dimethylhydrazine (409 mg, 6·80 mmol) (prepared by neutralization of the dihydrochloride salt with sodium methoxide) in dry methanol (5 ml) was heated in a sealed Claris tube at 130° for 2 h. The mixture was cooled, the solvent was evaporated under reduced pressure, and the residue was chromatographed over silica gel. Elution with dichloromethane/methanol mixtures afforded the *1,2-dimethyl compound* (7) (240 mg, 34%). G.l.c. R_t 14·8 min, 100%; m.p. 88–89° (Found: C, 64·7; H, 6·5; N, 20·4%; $[M+1]^{+\bullet}$, 204·113. $C_{11}H_{13}N_3O$ requires C, 65·0; H, 6·5; N, 20·7%; $[M+1]^{+\bullet}$, 204·114). ν_{max} (film) 3056m, 2985w, 1670s, 1578w, 1449w, 1421w, 1266s, 781m, 739s, 706m cm^{-1}. λ_{max} 234 nm ($\log\epsilon$ 4·16). ^{1}H n.m.r. δ 2·91, s, $N(1)CH_3$ or $N(2)CH_3$; 3·20, s, $N(1)CH_3$ or $N(2)CH_3$; 4·20, s, CH_2; 7·27–7·50, m, 3H, Ar; 7·67–7·82, m, 2H, Ar. ^{13}C n.m.r. δ 32·3, $N(1)CH_3$ or $N(2)CH_3$; 39·2, $N(1)CH_3$ or $N(2)CH_3$; 50·5, CH_2; 128·6, C 2′, C 6′ or C 3′, C 5′; 128·9, C 2′, C 6′ or C 3′, C 5′; 131·6, C 4′; 132·5, C 1′; 160·7, C=N or C=O; 166·4, C=N or C=O. Mass spectrum: *m/z* (c.i.) 204 ($[M+1]^{+\bullet}$, 100%), 122 (6), 100 (2).

(ii) *Methylation of the 2-methyl compound (9).* A solution of 2-methyl-3-phenyl-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (9) (860 mg, 4·55 mmol) in anhydrous methanol (20 ml) was added dropwise with stirring to a freshly prepared solution of sodium methoxide (270 mg, 5 mmol) in anhydrous methanol

* Although the *p*-toluenesulfonic acid salt (1f) of ethyl 2-amino-2-methylpropanoate has been reported in two papers,[8,9] no spectroscopic data or physical properties have been reported other than its rate constant of saponification.

(10 ml) under argon. Freshly distilled methyl iodide (290 μl, 4·55 mmol) was then added and the mixture was stirred at room temperature for 2 days. The mixture was evaporated to dryness and the residue was triturated with ethyl acetate (3×30 ml). Evaporation of the filtrate and recrystallization of the residue from ethyl acetate/light petroleum afforded the 1,2-dimethyl triazinone (7) (595 mg, 64%) as a white solid, identical (m.p. and spectroscopic data) with the material described above.

*1,4-Dimethyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (12)*

Ethyl sarcosinate hydrochloride (11) (496 mg, 3·23 mmol) was added to a suspension of *N*-methylbenzohydrazonoyl bromide hydrobromide (10) (950 mg, 3·23 mmol) in anhydrous dichloromethane (50 ml) and anhydrous methanol (20 ml). The suspension was cooled to 0° and a solution of anhydrous triethylamine (2·69 ml, 19·4 mmol) in anhydrous methanol (30 ml) was added dropwise with stirring while the temperature was maintained at 0°. The mixture was allowed to warm slowly to room temperature while it was stirred overnight and then evaporated in vacuum. The residue was dissolved in dichloromethane (75 ml) and washed with water (30 ml). The aqueous layer was extracted with dichloromethane (25 ml) and the combined extract was washed with saturated sodium chloride solution, dried and concentrated to afford a yellow solid. Chromatography of the solid over silica gel and elution with dichloromethane/methanol afforded the *1,4-dimethyl triazinone* (12) (478 mg, 73%), m.p. 130–131°. G.l.c. R_t 20·1 min, 99% (Found: C, 64·6; H, 6·5; N, 20·9%; $[M+1]^{+\bullet}$, 204·113. $C_{11}H_{13}N_3O$ requires C, 65·0; H, 6·5; N, 20·7%; $[M+1]^{+\bullet}$, 204·114). ν_{max} (KBr) 2920w, 1660s, 1604s, 1468m, 1440m, 1392m, 1342m, 1221m, 808m, 760m, 733s, 706m cm^{-1}. ^{1}H n.m.r. δ 2·73, s, N(1)CH_3 or N(4)CH_3; 3·23, s, N(1)CH_3 or N(4)CH_3; 3·87, s, CH_2; 7·37, s, Ar. ^{13}C n.m.r. δ 35·6, N(1)CH_3 or N(4)CH_3; 39·1, N(1)CH_3 or N(4)CH_3; 51·0, CH_2; 128·9, C 2′, C 3′, C 5′, C 6′; 129·8, C 4′; 132·2, C 1′; 149·3, C=N; 158·5, C=O. Mass spectrum: *m/z* (c.i.) 204 ($[M+1]^{+\bullet}$, 100%), 122 (52), 105 (23).

Ethyl 2-Amino-2-methylpropanoate Hydrochloride (1c)

Thionyl chloride (20·9 ml, 360 mmol) was added dropwise to anhydrous ethanol (135 ml) at −15° under an argon atmosphere. 2-Amino-2-methylpropanoic acid (30 g, 288 mmol) was then added, the mixture was allowed to warm to room temperature and heated under reflux for 1 h. Evaporation of the solvent gave the ester hydrochloride (1c) (48·30 g, 100%) as a white solid. A sample recrystallized from anhydrous ethanol had m.p. 158·5–159·0° (lit.[21] 158–159°). ν_{max} (KBr) 2945s(br), 2645m, 2582m, 2035w, 1745s, 1593m, 1522m, 1473m, 1366m, 1309m, 1233m, 1188s cm^{-1}. ^{1}H n.m.r. δ ($(CD_3)_2SO$) 1·20, t, *J* 7·1 Hz, CH_2CH_3; 1·47, s, $C(CH_3)_2$; 4·16, q, *J* 7·1 Hz, CH_2CH_3; 8·86, br s, NH_3. ^{13}C n.m.r. δ ($(CD_3)_2SO$) 13·7, CH_2CH_3; 23·1, $NC(CH_3)_2$; 55·6, $NC(CH_3)_2$; 61·7, CH_2CH_3; 171·3, C=O.

Ethyl 2-Benzamido-2-methylpropanoate (6c)

Anhydrous triethylamine (20·8 ml, 150 mmol) was added dropwise to a solution of ethyl 2-amino-2-methylpropanoate hydrochloride (1c) (10·00 g, 60 mmol) in dichloromethane (50 ml). A solution of benzoyl chloride (7·6 ml, 66 mmol) in dichloromethane (20 ml) was added and the mixture was stirred at room temperature for 1 h. Evaporation of the mixture under reduced pressure gave a white solid which was dissolved in diethyl ether (100 ml) and washed with saturated sodium hydrogen carbonate solution (50 ml). The aqueous layer was extracted with diethyl ether (75 ml) and the combined extract was washed with saturated sodium chloride solution (50 ml), dried and evaporated under reduced pressure to give the 2-benzamido ester (6c) as a white solid (14·0 g, 100%). A sample recrystallized from toluene had m.p. 119·0–119·5° (lit.[17] 121·0–121·5°). G.l.c. R_t 13·239 min, 100%. G.l.c.m.s. R_t 17·409 min, 100%; mass spectrum: *m/z* (e.i.) 235 ($M^{+\bullet}$, 1%), 190 (1), 163 (4), 162 (33), 146 (1), 121 (1), 105 (100), 77 (35), 51 (11). ν_{max} (KBr) 3255s, 3065m, 2995m, 1737s, 1631s, 1547s, 1466m, 1386m, 1333m, 1272m cm^{-1}. ^{1}H n.m.r. δ 1·23, t, *J* 7·1 Hz, OCH_2CH_3; 1·64, s, $C(CH_3)_2$; 4·19, q, *J* 7·1 Hz, OCH_2CH_3; 6·98, br s, NH; 7·32–7·49, m, 3H, Ar; 7·73–7·79, m, 2H, Ar. ^{13}C n.m.r. δ 14·1, OCH_2CH_3; 24·6, $C(CH_3)_2$; 56·8, $C(CH_3)_2$; 61·5, OCH_2CH_3; 126·9, C 2′, C 6′ or C 3′, C 5′; 128·4, C 2′, C 6′ or C 3′, C 5′; 131·4, C 4′; 134·6, C 1′; 166·6, NC=O; 174·8, OC=O. Mass spectrum: *m/z* (c.i.) 236 ($[M+1]^{+\bullet}$, 100%), 218 (26), 162 (38), 130 (5), 115 (2), 105 (21).

Ethyl 2-([Chloro(phenyl)methylidene]amino)-2-methylpropanoate (21)

Phosphorus pentachloride (5·31 g, 25·5 mmol) was added to ethyl 2-benzamido-2-methylpropanoate (6c) (6·00 g, 25·5 mmol) in anhydrous carbon tetrachloride (100 ml) under argon. The mixture was heated under reflux for 2 h, cooled and filtered. Evaporation of the filtrate under reduced pressure gave 6·32 g of a colourless oil. The ^{1}H n.m.r. spectrum showed it to contain 89% of the imidoyl chloride (21) and 11% of the benzamido ester (6c). Compound (21) gave ν_{max} (film) 2991m, 1735s, 1662m, 1596w, 1535w, 1491m, 1268s, 1146s, 878m, 745s cm^{-1}. ^{1}H n.m.r. δ ($CCl_4/CDCl_3$) 1·28, t, *J* 7·1 Hz, OCH_2CH_3; 1·63, s, $C(CH_3)_2$; 4·19, q, *J* 7·1 Hz, OCH_2CH_3; 7·31–7·47, m, Ar, 3H; 7·95–8·94, m, Ar, 2H. ^{13}C n.m.r. δ ($CCl_4/CDCl_3$) 14·3, OCH_2CH_3; 26·4, $C(CH_3)_2$; 60·9, OCH_2CH_3; 64·6, $C(CH_3)_2$; 128·1, C 2′, C 6′ or C 3′, C 5′; 129·1, C 2′, C 6′ or C 3′, C 5′; 131·5, C 4′; 136·3, C 1′; 140·8, C=N; 174·2, C=O. The crude material was used directly in the next step.

*5,5-Dimethyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (20)*

Hydrazine monohydrate (3 ml, 53 mmol) was added dropwise* to a freshly prepared solution of the imidoyl chloride (21) (3·3 g, 13 mmol) in anhydrous dichloromethane (100 ml) cooled to −78° under argon. The mixture was allowed to warm slowly to room temperature and stirred overnight. It was then diluted with dichloromethane (100 ml), washed with saturated sodium hydrogen carbonate solution (50 ml) and saturated sodium chloride solution. The dried extract was evaporated under reduced pressure to give a white solid which was recrystallized from ethyl acetate/light petroleum to give the *5,5-dimethyl triazinone* (20) (2·46 g, 92%) as a white solid, m.p. 223–225°. G.l.c. R_t 14·62 min, 100% (Found: C, 65·2; H, 6·5; N, 20·9%; $[M+1]^{+\bullet}$, 204·113. $C_{11}H_{14}N_3O$ requires C, 65·0; H, 6·5; N, 20·7%; $[M+1]^{+\bullet}$, 204·114). ν_{max} (KBr) 3197m(br), 3066m, 1664s, 1622s, 1407m, 989w, 775w, 692w cm^{-1}. λ_{max} 225 ($\log\epsilon$ 4·21), 297 nm (3·92). ^{1}H n.m.r. δ 1·41, s, $C(CH_3)_2$; 6·39, br s, NH; 7·25–7·43, m, 3H, Ar; 7·63–7·75, m, 2H, Ar; 9·58, br s, NH. ^{13}C n.m.r. δ 25·0, CH_3; 52·5, $C(CH_3)_2$; 126·1, C 2′, C 6′ or C 3′, C 5′; 127·8, C 2′, C 6′ or C 3′, C 5′; 129·5, C 4′; 132·2, C 1′; 146·0, C=N; 167·2, C=O. Mass spectrum: *m/z* (c.i.) 204 ($[M+1]^{+\bullet}$, 100%), 188 (4), 176 (3).

*3-Phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15)*

A solution of hydrazine monohydrate (1·0 ml, 20 mmol) in anhydrous methanol (10 ml) was added dropwise with stirring to a freshly prepared solution of the imidoyl chloride ester (14)[12] (1·09 g, 4·8 mmol) in anhydrous diethyl ether (20 ml) at −78°

* Warning—addition of hydrazine to imidoyl chlorides was found to be highly exothermic.

under argon. The mixture was then allowed to warm to room temperature and stirred for 1 h. The solvents were evaporated and a solution of the residue in ethyl acetate (200 ml) was washed successively with saturated sodium hydrogen carbonate (75 ml) and saturated sodium chloride solution (30 ml). Evaporation of the dried extract gave a solid which was recrystallized from ethyl acetate to afford the 3-phenyl triazinone (15) (495 mg, 59%), m.p. 221–222° (lit.[18] 209–215°). ν_{max} (KBr) 3371s, 3211m(br), 3059m, 2913w, 1657s, 1628s, 1573m, 1540m, 1419s cm^{-1}. ^1H n.m.r. δ ($(CD_3)_2SO$) 3·82, s, CH_2; 7·36, br s, N(1)H; 7·37–7·46, m, 3H, Ar; 7·67–7·78, m, 2H, Ar; 10·44, N(4)H. ^{13}C n.m.r. δ ($(CD_3)_2SO$) 42·7, C5; 125·7, C2′, C6′ or C3′, C5′; 128·2, C2′, C6′ or C3′, C5′; 129·6, C4′; 132·4, C1′; 144·9, C3; 161·0, C6. Mass spectrum: *m/z* (c.i.) 176 ($[M+1]^{+\bullet}$, 100%), 153 (3), 135 (15), 104 (10), 87 (3). A similar reaction carried out at room temperature gave a lower yield (16–18%) of the 3-phenyl triazinone (15); the major product was 5-ethoxy-2-phenyloxazole (13), m.p. 35–36° (lit.[22] 38–39°).

*Methylation of 3-Phenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (15)*

A solution of the 3-phenyl triazinone (15) (1·00 g, 5·7 mmol) in anhydrous dimethylformamide (10 ml) was added dropwise with stirring to an ice-cold suspension of sodium hydride (171 mg, 80%, 5·7 mmol) in anhydrous dimethylformamide (2 ml) under argon. The cooling bath was removed and the mixture was stirred for 1 h, then it was then recooled to 0° and a solution of freshly distilled methyl iodide (355 μl, 5·7 mmol) in anhydrous dimethylformamide (5 ml) was added dropwise. The mixture was stirred for 2 h at 0°, and then evaporated to dryness (eventually 25°/0·05 mmHg). The ^1H and ^{13}C n.m.r. spectra and t.l.c. indicated that the crude product contained the 1-methyl 3-phenyl triazinone (8) (93%) and the 3-phenyl triazinone (15) (7%). This mixture was dissolved in water (30 ml) and extracted with ethyl acetate (3×50 ml). The extract was washed with brine, dried and evaporated under reduced pressure to give a yellow solid. Recrystallization of this from ethyl acetate/light petroleum gave the 1-methyl 3-phenyl triazinone (8) (940 mg, 87%). This was identical (m.p., ^1H and ^{13}C n.m.r. spectra) with the material prepared previously.[12] Compound (12) was prepared by repeating the above methylation procedure on compound (8). Spectra for compound (12) are reported above.

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