Some Approaches to the Synthesis of Kainic Acid

Suren Husinec, Alexander E. A. Porter,* James S. Roberts, and Calum H. Strachan
Chemistry Department, University of Stirling, Stirling FK9 4LA

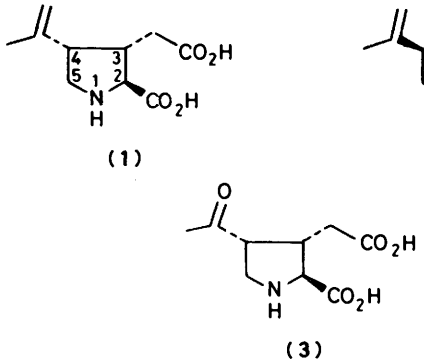
A strategy for the synthesis of the anthelmintic kainic acid is described, involving an investigation of the [3 + 2] cycloaddition reactions of some azomethine ylides obtained from the thermal ring opening of aziridines and 4,5-dihydro-1,2,3-triazoles, with cyclopentenone.

During the last decade considerable interest has been shown in the anthelmintic [1] and neurochemical [2] properties of the natural product kainic acid (1); this has culminated in a number of total syntheses [3] of compound (1) and the structurally related molecule (2).[4]

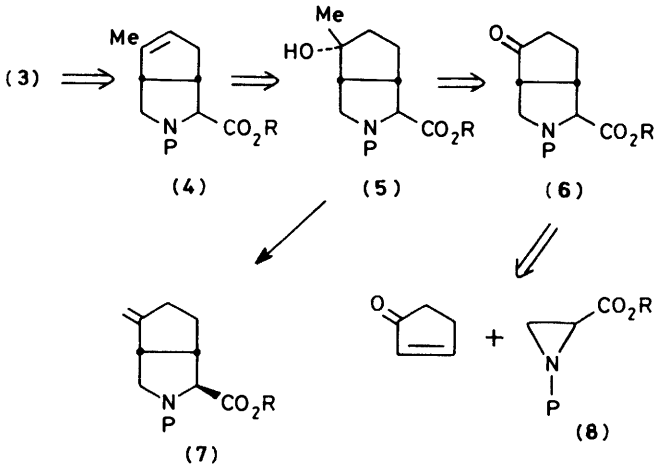
When contemplating the feasibility of producing a general method for the synthesis of kainic acid, which would also be of potential value for the production of analogues for evaluation in biological screens, attention must be directed towards the control of stereochemistry at C-3 and C-4, since the natural *cis* stereochemistry at these positions, which is crucial to the anthelmintic† function of (1), has presented a stumbling block in some earlier syntheses. Retrosynthetic analysis of the problem suggested that the ketone (3) which may be readily transposed‡ into kainic acid, should indeed represent our penultimate target, and should, in principle, be derivable (Scheme 1) by way of ozonolytic cleavage of the bicyclic dihydropyrrolidine (4). Furthermore the intermediacy of compound (4) should establish the stereochemical integrity at C-3 and C-4 in the target molecule. The bicyclic dihydropyrrolidine (4) might then be derived by pyrolysis of the acetate or xanthate ester of the tertiary alcohol (5) which is in turn the expected product from the addition of methyl-lithium or methylmagnesium halide to the ketone (6). Thus, addition of an organometallic reagent to compound (6) would be expected to occur from the least hindered face of the molecule resulting in compound (5), and acetate or xanthate ester pyrolysis of compound (5) can lead only to the *exo*-methylene isomer (7) or the thermodynamically favoured compound (4).

Construction of the bicyclic ketone (6) is not in itself a trivial problem since the relative stereochemistry at C-2, C-3, and C-4 must be controlled during its formation. However, incorrect stereochemistry at C-2 would not present a serious problem as epimerisation in such systems is easily effected. An elegant method of construction of compound (6) with the appropriate stereochemical control might be by way of a [3 + 2] cycloaddition between cyclopentenone and an *N*-protected aziridine (8). Such a cycloaddition might be expected to give compound (6) in a single step and, consistent with the intermediacy of an azomethine ylide [*e.g.* (9)], the regiochemistry of the cycloaddition reaction should be heavily biased towards its formation.

Initially, to test the viability of the route shown in Scheme 1, we decided to examine the synthesis of compound (8; P = $SiMe_3$) as this should furnish the bicyclic ketone (6; P = $SiMe_3$) in a single step. Aziridines are generally available by the thermolysis of 4,5-dihydro-1,2,3-triazoles[5-9] which are in turn



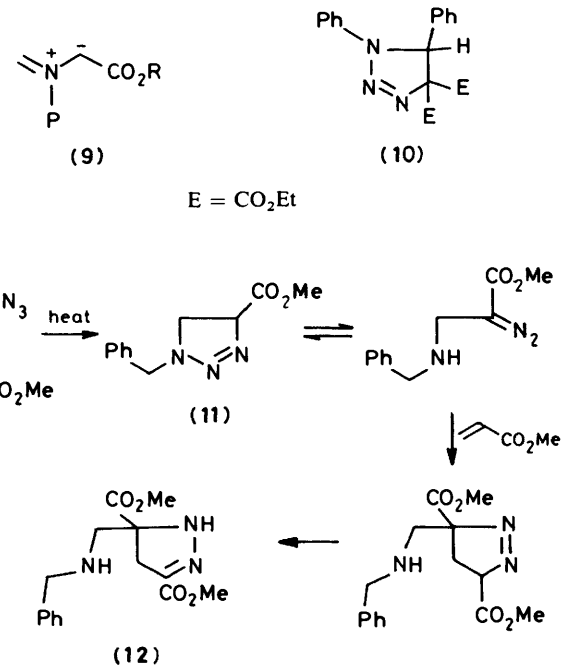
Scheme 1



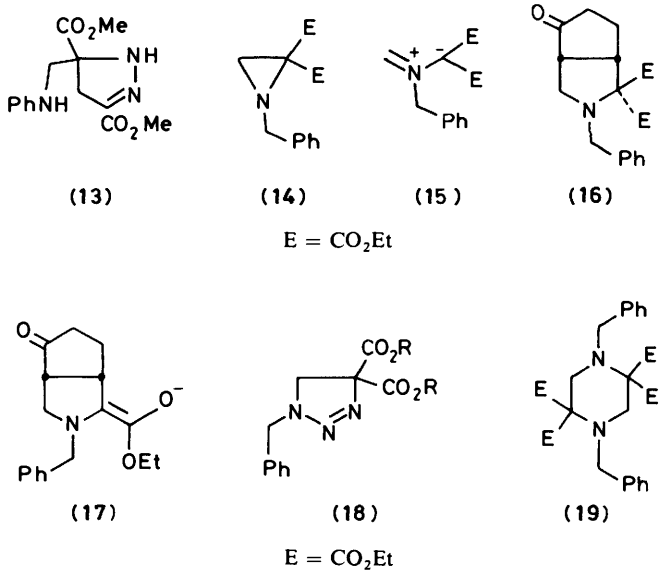
derived by a 1,3-dipolar cycloaddition between an alkene and an azide. Although precedent exists for the addition of trimethylsilyl azide [10] (TMSA) to dipolarophiles, in our hands the azide failed to react with methyl acrylate, even after protracted reaction times.

This result was unexpected as silicon, which is less electronegative than nitrogen, should have activated the azide towards cycloaddition. Butyl azide is known [7] to be much more reactive than phenyl azide [5] in cycloadditions with ethyl acrylate and this has been attributed to the $+I$ effect of the butyl group activating the α-nitrogen atom of the azide by increasing the electron density around it, where as the $-I$ effect of the phenyl ring tends to stabilise the azide group and so reduces its reactivity towards cycloaddition. It may be that the lack of reactivity in the case of TMSA is due to back bonding of the p electrons on the α-nitrogen atom of the azide into vacant d orbitals on silicon, depleting the electron density on nitrogen

† Of the known stereoisomers of kainic acid, all show considerably reduced anthelmintic activity compared with that of kainic acid itself.
‡ A referee has indicated that, although this transformation is claimed to work well, after extensive work his own group have never achieved a yield of greater than 20% in this reaction (*cf.* G. A. Kraus and J. O. Nagy, *Tetrahedron Lett.*, 1983, **24**, 3427.



Scheme 2.



and reducing the reactivity of the azide with electron deficient alkenes.

A further comparison of the reactivity of TMSA towards cycloaddition with diethyl phenylmethylenemalonate was made since this compound is known[11] to react with phenyl azide[12] and therefore provided another comparison of the effects imposed upon the azide group by trimethylsilyl and phenyl substituents. The azides were treated with diethyl phenylmethylenemalonate by stirring equimolar amounts of dipole and dipolarophile at 60 °C. For comparison, ethyl azidoformate,[12] which is known to be unreactive, was allowed to react under the same conditions. The mixtures were stirred at 60 °C for 1 month, after which time the phenyl azide had produced the dihydrotriazole (**10**). The other two reaction mixtures were found to contain only unchanged diethyl phenylmethylenemalonate and azide decomposition products.

It was considered that 2-alkoxycarbonyl-1-benzylaziridine (**8**; P = CH_2Ph) would serve as a convenient source of the azomethine ylide (**9**; P = CH_2Ph) in that the benzyl group should activate the benzyl azide in [3 + 2] cycloaddition reactions and in addition should be easily removable at a late stage in the synthesis.[13] Reaction of benzyl azide with methyl acrylate did not, however, yield the expected dihydrotriazole (**11**); instead the 4,5-dihydropyrazole (**12**) was the only isolable product. Huisgen and co-workers[5] have previously noted the formation of the 4,5-dihydropyrazole (**13**) during the reaction of phenyl azide with methyl acrylate and it seems probable that the 4,5-dihydropyrazoles arise by the initial ring opening (Scheme 2) of a dihydrotriazole to form a diazoester which subsequently reacts with a second molecule of the dipolarophile. In view of these problems, compound (**8**; P = CH_2Ph, R = Et) was prepared by an alternative route[14] in order to examine its reactivity in [3 + 2] cycloaddition reactions. On being heated with cyclopentenone in refluxing xylene, the aziridine progressively decomposed, but no cycloaddition of the azomethine ylide with the cyclopentenone was observed and only unidentified polymeric products were formed.

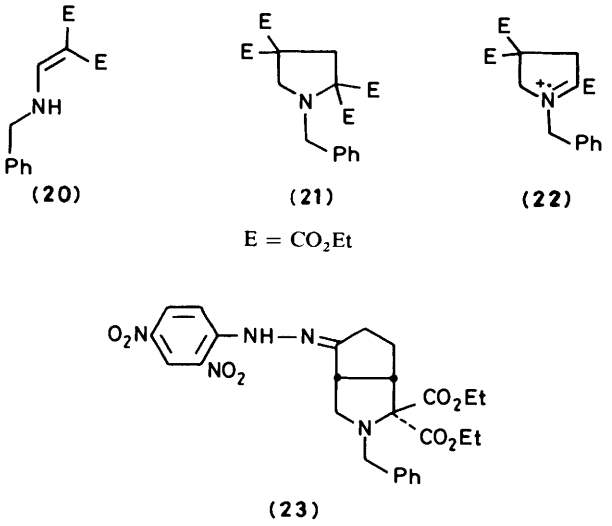
Similarly, no evidence of cycloaddition products was obtained with maleic anhydride or diethyl maleate under identical reaction conditions and it seems improbable that the aziridine was fragmenting by way of the azomethine ylide (**9**; P = CH_2Ph, R = Et). Heating of the aziridine in the absence of dipolarophile also resulted in extensive decomposition to the same polymeric products.

In order to reduce the amount of energy required to bring about aziridine ring fission, it was thought that an additional ester group on the aziridine ring might aid stabilisation of the azomethine ylide and bring about the interconversion at lower temperatures. With this aim in mind we decided to examine the synthesis of the aziridine (**14**), as conceptually this molecule has additional advantages. Cycloaddition of the azomethine ylide (**15**) with cyclopentenone would be expected to furnish compound (**16**) with two ethoxycarbonyl groups adjacent to the ring nitrogen atom, and if selectivity could be achieved in the monodecarboxylation, then the correct stereochemistry at C-2, C-3 and C-4 in the target molecule would result. Molecular models of compound (**16**) indicate that there is steric congestion of the α-ethoxycarbonyl group, and dealkoxycarbonylation using the NaCl–DMSO (dimethyl sulphoxide) procedure[15], which proceeds by way of the enolate (**17**), should lead preferentially to compound (**6**; R = Et, P = CH_2Ph).

The dihydrotriazole precursor (**18**) of the aziridine (**14**) was easily prepared by the reaction of benzyl azide with diethyl methylenemalonate.[16] The problem of dihydropyrazole formation encountered with the cycloaddition of benzyl azide and methyl acrylate did not occur in this instance, since the dihydrotriazole (**18**) has no proton at position-4 of the ring and hence is unable to isomerise to the diazoester.

In order to shorten the synthetic sequence, it was decided to generate the azomethine ylide (**15**) *in situ* from the dihydrotriazole (**18**) which was treated directly with cyclopentenone in refluxing toluene. T.l.c. of the reaction mixture on completion showed that three products were formed and a mass spectrum indicated that the bicyclic product (**16**) was present in the crude mixture. Separation of the reaction products was accomplished by p.l.c. and the product corresponding to the fastest-running spot was shown to be the piperazine (**19**) formed in 3.6% yield.

Certain types of aziridine are known to form piperazines in the presence of halide ions,[17,18] but the reaction usually requires polar solvents in order to be effective. Piperazines have also been obtained by the thermal dimerisation of aziridines[19] and this reaction has been described as a [3 + 3] cycloaddition



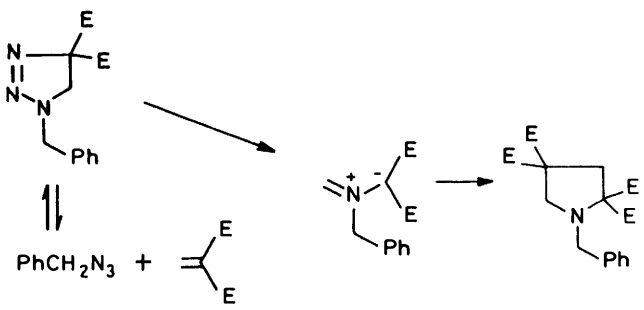
between two azomethine ylides. However, this is a symmetry-forbidden reaction and it would appear to be more probable that the reaction occurs by way of radical intermediates.

The material corresponding to the lower spot in the reaction mixture was shown to be diethyl benzylaminomethylenemalonate (**20**) (29% yield) and its structure was confirmed by comparison of its properties with those of the product from a reported synthesis using benzylamine and diethyl ethoxymethylenemalonate.[20] The formation of the enamine (**20**) was predictable, as it is well documented that, when dihydrotriazoles are thermolysed, they produce enamines or anils in addition to aziridines, the ratio of products being dependent upon the substituents on the dihydrotriazole.

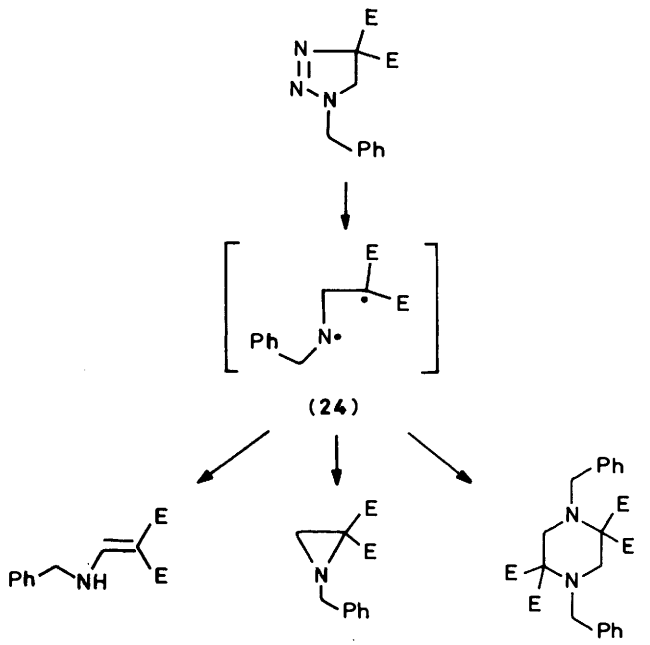
After removal of the by-products, a viscous oil remained which was chromatographically homogeneous and corresponded to the major product (67.6%) of the reaction. The mass spectrum of this oil showed a molecular ion corresponding to compound (**16**) and also a strong peak corresponding to (M^+ − CO_2Et). However, the ^1H n.m.r. spectrum was poorly resolved, indicating that this material was a mixture. The spectrum clearly exhibited benzyl, ethyl ester, and methylene resonances and there were also multiplets at δ8.0 which could be assigned to the cyclopentanone ring protons of (**16**), but the integral ratio for this region of the spectrum indicated the presence of a significantly greater number of protons than would be expected for this product. All attempts at chromatographic separation of this apparent mixture failed.

When the dihydrotriazole (**18**) was heated alone in toluene, a similar product mixture was obtained and, after removal of the piperazine (**19**) and the enamine (**20**), the residual gum had an R_F identical with that of the product from the cyclopentenone reaction. However, the mass spectrum did not show the peaks characteristic of compound (**16**). From the n.m.r. spectral data, the structure of the gum appears to be the pyrrolidine (**21**) which clearly could arise by the cyclo-reversion of compound (**18**) (Scheme 3) to give benzyl azide and diethyl methylenemalonate, followed by reaction of the latter intermediate with the azomethine ylide (**15**). Although compound (**21**) failed to show a molecular ion in the mass spectrum, a fragment ion at *m/z* 376 which corresponds to (M^+ − CO_2Et) (**22**) is related to the unobserved molecular ion (*m/z* 499) by a metastable peak at 314.87 a.m.u.

Further confirmation of the structure of (**21**) was obtained when compound (**18**) was heated with an excess of diethyl methylenemalonate. Comparison of the spectroscopic properties of compound (**21**) from this reaction showed that it is



Scheme 3. E = CO_2Et

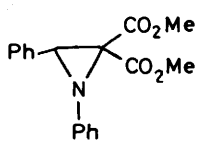


Scheme 4. E = CO_2Et

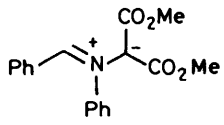
formed during the thermal decomposition of compound (**18**) and is present in the reaction product formed during the reaction of (**18**) with cyclopentenone.

In order to characterise the bicycle (**16**), the partially purified product from the cyclopentenone cycloaddition was treated with 2,4-dinitrophenylhydrazine and yielded a 2,4-dinitrophenylhydrazone (**23**) with spectral and analytical properties consistent with this structure, in 16% yield. This corresponds to an overall yield of 10% from the cycloaddition reaction and, because of the complexity of the reaction, does not offer a practical synthesis of compound (**16**).

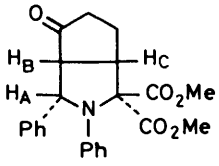
The low yield of the cycloaddition product (**16**) is almost certainly due to the side reaction occurring during the initial decomposition of the dihydrotriazole (**18**) to the aziridine (**14**) and in the subsequent ring opening reaction. In addition to the cyclo-reversion (Scheme 3), it would appear that compound (**18**) probably undergoes an initial decomposition (Scheme 4) to yield the diradical (**24**) which cyclises to the aziridine, dimerises to the piperazine (**19**), or undergoes hydrogen radical transfer to yield the enamine (**20**). With these competing pathways in operation, aziridine formation and subsequent ring opening to the azomethine ylide would appear to be only a minor reaction pathway. Indeed, when attempts were made to carry out cycloaddition reactions with strong dipolarophiles such as diethyl maleate, diethyl fumarate, and maleic anhydride, the



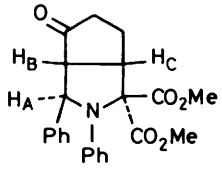
(25)



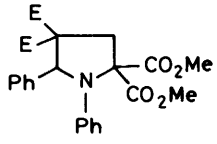
(26)



(27)



(28)



(29)

E = CO_2Et

reactions appeared to follow a similar course with the production of the by-products (**19**)—(**21**) in all reactions, along with minor quantities of the expected cycloaddition products.

Concurrent with our studies with the dihydrotriazole (**18**), we have also examined the reactivity of the known dihydrotriazole (**10**), since the reactivity of this compound is well established,[21-23] and we considered that it might serve as a useful model for our projected synthesis of kainic acid. On heating compound (**10**) under vacuum in a Kugelrohr apparatus until nitrogen evolution ceased, a deep purple oil remained. Raising the furnace temperature to 250 °C resulted in the distillation of this product as a purple viscous oil which changed to a deep red colour on cooling, and compound (**25**) was obtained in almost quantitative yield. The colour of the product is believed to be due to the azomethine ylide (**26**) which is in equilibrium with (**25**). No reports on the cycloaddition of compound (**26**) with cyclopentenone have appeared in the literature; thus, treatment of the dihydrotriazole (**10**) with cyclopentenone in refluxing toluene resulted in the formation of the cycloaddition products (**27**) and (**28**) in yields of 13.3 and 1.7% respectively. The stereochemical assignment was made on the basis of their ^1H n.m.r. spectral data since J_{AB} in the *cis*-isomer (**27**) is *ca.* 8 Hz, whereas in the *trans*-isomer (**28**) J_{AB} is *ca.* 4 Hz. These values are consistent with dihedral angles of *ca.* 10 and 130° respectively (molcular models) and support the above assignment.

By the simple expedient of carrying out the cycloaddition without solvent in an excess of cyclopentenone, the overall yield was increased to 44%, but somewhat curiously the product ratio of 27:28 was 1:1 under these conditions. In toluene solution the product ratio was 8:1, and in view of the lower reaction temperature it may be that compound (**27**) is a kinetic product, as molecular models indicate that in (**28**) there is less steric crowding and hence this molecule would be expected to be thermodynamically more stable.

The dihydrotriazole (**10**) also reacted with diethyl methylenemalonate to yield compound (**29**) in reasonable yield, indicating that the cyclo-reversion in this system (*cf.* Scheme 3) is not an important side reaction.

In view of the dramatically improved yield of compound (**27**) and (**28**) which was observed during the reaction of (**10**) with cyclopentenone in the absence of solvent, we re-examined the reaction of compound (**18**) with cyclopentenone under similar conditions in order to optimise the yield of (**16**). However, the same product mixture resulted with no indication of any significant improvement in the yield. We are currently examining alternative methods for the synthesis of compound (**16**).

Experimental

M.p.s were determined on a Kofler block and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 577 instrument for solutions in $CHCl_3$ unless otherwise stated. ^1H N.m.r. spectra were recorded on a Perkin-Elmer R32, ^{13}C n.m.r. spectra on a Bruker WP80, and mass spectra on a Jeol JMS D100 spectrometer.

Diethyl Phenylmethylenemalonate.—Diethyl malonate (100 g, 0.63 mol), benzaldehyde (71 g, 0.66 mol), piperidine (3.25 ml), and benzoic acid (2 g) were heated under reflux in benzene (200 ml) through a Dean-and-Stark water separator. The reaction was continued until no more was collected (18 h) and the reaction mixture was cooled and diluted with benzene (100 ml). The resultant solution was washed with saturated sodium hydrogen carbonate solution (50 ml) and dried ($MgSO_4$). Concentration of the resultant solution and distillation under reduced pressure gave the title compound (138 g, 90%), b.p. 124 °C/0.1 Torr (lit.,[11] 140—142 °C/4 Torr), δ($CDCl_3$) 7.58 (1 H, s), 7.22 (5 H, s), 4.15 (4 H, q), and 1.15 (6 H, t).

Cycloaddition of Benzyl Azide with Methyl Acrylate.—Benzyl azide (97 g, 0.073 mol) and methyl acrylate (7.3 g, 0.073 mol) were stirred together at room temperature under nitrogen and the reaction followed by ^1H n.m.r. After 4 days the methyl acrylate had been consumed and a viscous oil remained which was degassed to remove residual traces of the ester. The residual oil was triturated with methanol and a colourless crystalline solid (5.35 g, 48%) was obtained. Recrystallisation from ethanol gave 5-benzylaminomethyl-3,5-bis(methoxycarbonyl)-4,5-dihydropyrazole (**12**), m.p. 101.5—102 °C (lit.,[24] 100—101 °C), $\nu_{max.}$ 3 360, 1 740, and 1 580 cm^{-1}; δ($CDCl_3$) 7.25 (5 H, s), 6.98 (1 H, bs), 3.78 (3 H, s), 3.77 (2 H, s), 3.71 (3 H, s), 3.19 (2 H, d), 2.72 (2 H, d), and 1.6 (1 H, bs).

1-*Benzyl*-4,4-*bis*(*ethoxycarbonyl*)-4,5-*dihydro*-1,2,3-*triazole* (**18**; R = Et).—Benzyl azide (44 g, 0.331 mol) and diethyl methylenemalonate (57 g, 0.331 mol) were stirred together at room temperature and under nitrogen in dry benzene (250 ml). After 5 h, t.l.c. indicated that the reaction had gone to completion and addition of hexane caused the precipitation of *compound* (**18**; R = Et) as a colourless solid (86 g, 85%), m.p. 59.5—60 °C, $\nu_{max.}$ 1735 cm^{-1}; δ($CDCl_3$) 7.24 (5 H, s), 4.85 (2 H, s), 4.25 (4 H, q), 3.55 (2 H, s), and 1.28 (6 H, t); *m/z* 277 ($M^+ - N_2$) and 204 ($M^+ - N_2 - CO_2Et$) (Found: C, 59.1; H, 6.3; N, 13.8. $C_{15}H_{19}N_3O_4$ requires C, 59.02; H, 6.23; N, 13.77%).

1-*Benzyl*-4,4-*bis*(*methoxycarbonyl*)-4,5-*dihydro*-1,2,3-*triazole* (**18**; R = Me).—In a similar reaction to that described for the ethyl ester above, the title compound was obtained in 85% yield, m.p. 45—47 °C (isopropyl alcohol), $\nu_{max.}$ 1730 cm^{-1}; δ($CDCl_3$) 7.1 (5 H, s), 4.7 (2 H, s), 3.7 (6 H, s), and 3.5 (2 H, s); *m/z* 249 ($M^+ - N_2$) and 190 ($M^+ - CO_2Me$). (Found: C, 56.2; H, 5.5; N, 15.15. $C_{13}H_{15}N_3O_4$ requires C, 56.30; H, 5.45; N, 15.15%).

Reaction of 1-*Benzyl*-4,4-*bis*(*ethoxycarbonyl*)-4,5-*dihydro*-1,2,3-*triazole with Cyclopentenone.*—The dihydrotriazole (**18**; R = Et) (18.68 g, 60.98 mmol) was dissolved in dry toluene (150 ml) containing hydroquinone (10 mg). The apparatus was flushed with dry nitrogen and cyclopentenone (5 g, 60.97 mmol) was added. The mixture was heated under reflux overnight and

allowed to cool to room temperature; on concentration (Buchi) it gave a deep yellow oil (22.29 g). T.l.c. (ether–hexane, 4:1) showed that three components were present. However, attempts to separate these by column chromatography were unsuccessful. A sample (15.5 g) of the crude mixture was separated by p.l.c. (30, 40 × 20 cm plates) into two bands, a lower band which corresponded to the slowest-running spot on t.l.c. and a faster-running band which corresponded to the two faster-running spots on t.l.c. The purified material from the lower band was extracted from the silica to yield an oil (4.44 g, 28.8%) which on trituration with methylcyclohexane gave a waxy solid. Four crystallisations from hexane gave colourless crystals of diethyl benzylaminomethylenemalonate (**20**), m.p. 69—70 °C (lit.,[20] 74 °C); δ($CDCl_3$) 8.0 (1 H, d), 7.22 (5 H, s), 4.44 (2 H, d), 4.19 (2 H, q), 4.15 (2 H, q) 1.3 (3 H, t), and 1.26 (3 H, t); $\nu_{max.}$ 1 685, 1 655, and 1 609 cm^{-1}; *m/z* 277 (M^+) (Found, C, 65.2; H, 6.9; N, 5.2. $C_{15}H_{19}NO_4$ requires C, 64.98; H, 6.86; N, 5.05%).

The upper band from the p.l.c. was extracted from the silica with dichloromethane and concentrated to yield a deep yellow oil (11.0 g). This product was dissolved in ether and cooled in a deep freeze for 1 h. The resultant white precipitate (0.56 g, 3.6%) was isolated by filtration and was crystallised three times from methylcyclohexane to yield the piperazine (**19**) as colourless crystals, m.p. 136—137 °C; $\nu_{max.}$ 1730 cm^{-1}; δ($CDCl_3$) 7.17 (10 H, s), 4.80 (8 H, m), 3.86 (4 H, s), 3.26 (4 H, s), and 1.07 (12 H, t); *m/z* 554 (M^+) (Found: C, 65.1; H, 6.9; and N, 5.2. $C_{30}H_{38}N_2O_8$ requires C, 64.98; H, 6.86; N, 5.05%).

The remaining ether solution was concentrated to yield a chromatographically homogeneous gum (10.44 g, 67.6%). A portion of this material (1.85 g) was stirred with a solution of 2,4-dinitrophenylhydrazine as the sulphate salt in methanol overnight, evaporated to dryness, and the residual solid dissolved in CH_2Cl_2. The resultant solution was washed with water (2 × 20 ml), dried ($MgSO_4$), filtered and evaporated to yield the bicyclic hydrazone (**23**) (0.45 g), m.p. 170—171 °C (MeOH), $\nu_{max.}$ 1 750, 1 638, and 1 616 cm^{-1}; δ($CDCl_3$) 9.08 (1 H, d), 8.28 (1 H, dd), 7.84 (1 H, d), 7.32 (5 H, m), 4.34 (2 H, q), 4.3 (2 H, s), 4.2 (2 H, q), 3.91 (1 H, d), 3.26 (1 H, d), 3.06 (1 H, m), 2.72 (2 H, d), 2.55 (2 H, m), 1.92 (2 H, m), 1.36 (3 H, t), and 1.27 (3 H, t) (Found: M^+ 539.2023. $C_{26}H_{29}N_5O_8$ requires *M* 539.2017).

Reaction of 1-*Benzyl*-4,4-*bis*(*ethoxycarbonyl*)-4,5-*dihydro*-1,2,3-*triazole with Diethyl Methylenemalonate*.—The dehydrotriazole (3 g, 9.84 mmol) and diethyl methylenemalonate (1.72 g, 10 mmol) were heated in dry xylene (9 ml) under nitrogen until effervescence began. When no more gas was evolved (5 min), the source of heat was removed and the mixture concentrated to yield a viscous oil. A portion of this oil (1.05 g) was separated by p.l.c. (silica, hexane–ether 4:1) into two bands. The lower band (0.14 g) was shown to be compound (**20**) by comparison with an authentic sample. The upper band was extracted using CH_2Cl_2 and concentration followed by addition of ether resulted in the precipitation of the piperazine (**19**) (0.14 g, 13%). The residual oil (0.57 g, 54%) was purified by Kugelrohr distillation; $\nu_{max.}$ 1730 cm^{-1}; δ($CDCl_3$) 7.18 (5 H, s), 4.24 (4 H, q), 4.02 (4 H, q), 3.99 (2 H, s), 3.79 (2 H, s), 1.29 (6 H, t), and 1.08 (6 H, t). Highest observed ion, *m/z* 376, metastable scan from 376 detected a low intensity peak at *m/z* 449.

Reaction of 4,4-*Bis*(*methoxycarbonyl*)-1,5-*diphenyl*-4,5-*dihydro*-1,2,3-*triazole* (**10**) *with Cyclopentenone*.—The dihydrotriazole (**10**) (10 g, 29.5 mmol) and cyclopentenone (2.5 ml, 29.9 mmol) were dissolved in dry toluene (50 ml) containing a crystal of hydroquinone and the mixture was heated at reflux under nitrogen overnight. The mixture was concentrated and subjected to a short pressure column (Kieselgel HF254; 25 g) using ether–hexane (8:2). The fastest-running fraction (3.27 g) was isolated as a brown oil which, as judged by its mass spectrum, contained no cycloaddition products. The major fraction (5.57 g), which was obtained as a viscous brown gum on addition of ether, resulted in a colourless precipate (1.54 g, 13.3%), m.p. 167–169 °C (MeOH) which was assigned structure (**27**) on the basis of the following spectral and analytical data: $\nu_{max.}$ 1750 and 1605 cm^{-1}; δ($CDCl_3$) 7.5—6.5 (10 H, m), 4.79 (1 H, d, *J* 8 Hz), 3.90 (3 H, s), 3.44 (3 H, s), 3.05 (1 H, dd, *J* 8 and 12 Hz), and 2.7—1.97 (5 H, m); δ_C ($CDCl_3$) 23.54 (t), 36.79 (t), 49.96 (d), 52.30 (q), 53.24 (q), 58.61 (d), 71.16 (d), 79.56 (s), 117.55 (d), 119.59 (d), 126.05 (d), 127.47 (d), 128.17 (d), 129.01 (d), 142.55 (s), 144.55 (s), 168.20 (s), 170.61 (s), and 214.48 p.p.m. (s); *m/z* 393 (M^+) and 344 (base peak) (Found: M^+ 393.1544. $C_{23}H_{23}NO_5$ requires *M* 393.1576).

After 1 month the remaining gum crystallised and compound (**28**), (0.193 g, 1.7%) was obtained, m.p. 132—133 °C (MeOH), $\nu_{max.}$ 1 750 and 1 605 cm^{-1}; δ($CDCl_3$) 7.6—6.4 (10 H, m), 5.24 (1 H, d, *J* 4 Hz), 3.88 (3 H, s), 3.51 (3 H, s), 2.80 (1 H, dd, *J* 4 and 10 Hz), and 2.5—2.05 (5 H, m); δ_C($CDCl_3$) 21.48 (t), 36.11 (t), 49.49 (d), 52.04 (q), 52.95 (q), 60.16 (d), 66.76 (d), 78.33 (s), 115.74 (d), 118.71 (d), 125.95 (d), 127.22 (d), 128.40 (d), 128.98 (d), 143.06 (s), 144.55 (s), 168.93 (s), 170.41 (s), and 214.34 p.p.m. (s); *m/z* 393 (M^+) and 334 (base peak) (Found: M^+ 393.1560. $C_{23}H_{23}NO_5$ requires *M* 393.1576).

Reaction of 4,4-*Bis*(*methoxycarbonyl*)-1,5-*diphenyl*-4,5-*dihydro*-1,2,3-*triazole* (**10**) *with Cyclopentenone without Solvent*.—The dihydrotriazole (**10**) (14.5 g, 42.77 mmol) and cyclopentenone (7 g, 85.36 mmol) with a few crystals of hydroquinone were heated in a 100-ml flask with a bunsen flame until the internal temperature reached 160 °C. The mixture liquified giving an homogeneous pale yellow solution which turned deep red during the course of the reaction. The mixture was maintained between 150—160 °C until effervescing due to nitrogen evolution had subsided. The mixture was cooled to 100 °C and toluene (10 ml) was added and the reaction mixture was heated at reflux overnight. After removal of the toluene, the resultant brown gum was purified by column chromatography (*vide supra*) to yield compounds (**27**) (3.84 g) and (**28**) (3.63 g) with spectral and analytical properties identical with those described above.

Reaction of 4,4-*Bis*(*methoxycarbonyl*)-1,5-*diphenyl*-4,5-*dihydro*-1,2,3-*triazole* (**10**) *with Diethyl Methylenemalonate*.—The triazole (**10**) (0.5 g, 1.47 mmol) and diethyl methylenemalonate (0.275 g, mmol) were dissolved in dry toluene (2 ml) and the mixture heated at reflux overnight. The mixture was concentrated and the product isolated by column chromatography (Kieselgel HF 254 silica) using hexane–ethyl acetate (8:2), to give 4,4-(*ethoxycarbonyl*)-2,2-*bis*(*methoxycarbonyl*)-1,5-*diphenyl*-4,5-*dihydropyrrole* (**29**) (0.42 g), m.p. 102—104 °C, $\nu_{max.}$ 1739 cm^{-1}; δ($CDCl_3$) 7.6—7.7 (10 H, m), 5.9 (1 H, s), 4.25 (2 H, m), 3.95 (3 H, s), 3.58 (2 H, q), 3.57 (3 H, s), 2.14 (2 H, s), 1.78 (3 H, t), and 0.86 (3 H, t); *m/z* 483 (Found: M^+ 483.1845. $C_{26}H_{29}NO_8$ requires *M* 483.1894).

Acknowledgements

We thank the S.E.R.C. and Pfizer for a CASE Studentship (to C. H. S.) and the O.R.S. for support to S. H. who is on study leave from the University of Belgrade.

References

1 S. Marakami, T. Takemoto, and N. Shimiza, Jap. Pat., 1954, 4947 (*cf. Chem. Abstr.*, 1955, **49**, 13 604i).
2 J. W. Olney, *Adv. Biochem. Psychopharmacol.*, 1981, **27**, 375.
3 K. Tanaka, M. Miyarnato, M. Honjo, H. Morimoto, T. Sugawa, M. Uchibayashi, Y. Sanno, and S. Tatsuoka, *Proc. Jpn. Acad.*, 1957,

33, 47; Y. Ueno, K. Tanaka, J. Ueyangi, H. Nawa, Y. Sanno, M. Honjo, R. Makemori, T. Sugawa, M. Ichibayashi, K. Osugi, and S. Tatsuoka, *Proc. Jpn. Acad.*, 1957, **33**, 53; S. Fang and J. Chu, *Hua Hsueh Pao*, 1964, **30**, 266 (*cf. Chem. Abstr.*, 1964, **61**, 7359f).
4 (*a*) W. Oppolzer and H. Andres, *Tetrahedron Lett.*, 1978, 3397; (*b*) W. Oppolzer and H. Andres, *Helv. Chim. Acta*, 1979, **62**, 2282; (*c*) W. Oppolzer and V. Sniecus, *Angew. Chem., Int. Ed. Eng.*, 1978, **17**, 476.
5 R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.*, 1966, **99**, 475.
6 G. L'Abbe, *Chem. Rev.*, 1969, **69**, 345.
7 W. Breockx, N. Overbergh, C. Samyn, G. Smets, and G. L'Abbe, *Tetrahedron*, 1971, **27**, 3527.
8 F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 1971, 4119.
9 J. Bourgois, M. Bourgois, and F. Texier, *Bull. Soc. Fr.*, 1978, 485.
10 S. S. Washburne, W. R. Peterson, and D. A. Berman, *J. Org. Chem.*, 1972, **37**, 1738.
11 C. F. Allen and F. W. Sprangler, *Org. Synth.* Coll. Vol. III, 1955, 377.
12 L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, 1967, vol. I.
13 H. King and T. S. Work, *J. Chem. Soc.*, 1940, 1307.
14 M. A. Stolberg, J. J. O'Neill, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, 1953, **75**, 5045.
15 J. H. Markgraf, M. S. Ibsen, J. B. Kinney, J. W. Kuper, J. B. Luric, D. R. Marrs, C. A. McCarthey, J. M. Pile, and T. J. Pritchard, *J. Org. Chem.*, 1977, **42**, 2631.
16 W. Feely and V. Boekelheide, *Org. Synth.* Coll. Vol. IV, 1963, 298.
17 H. W. Keine, W. G. Kenyon, and E. M. Johnson, *J. Am. Chem. Soc.*, 1961, **83**, 2570.
18 C. R. Dick, *J. Org. Chem.*, 1967, **32**, 72.
19 R. Heisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 1966, 397.
20 Y. Shvo, E. C. Taylor, and J. Bartulin, *Tetrahedron Lett.*, 1967, 3259.
21 F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 1972, 258.
22 F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 1972, 2373.
23 F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 1974, 310.
24 R. Carrie, M. Vaultier, and M. S. Quali, *Tetrahedron*, 1980, **36**, 1821.

Received 5th March 1984; *Paper* 4/355