APPROACHES TO THE SYNTHESIS OF KAINIC ACID. A STUDY OF THE SYNTHESIS OF SOME 4,5-DIHYDRO-1,2,3-TRIAZOLES

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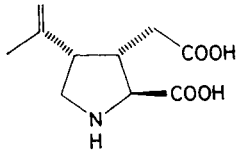
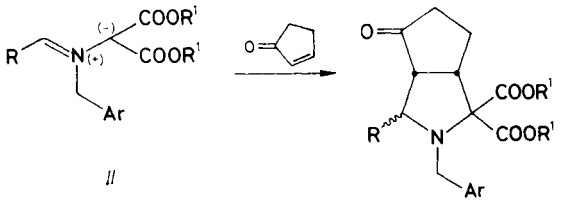
Two strategies for the synthesis of bicyclic pyrrolidine derivatives using [3 + 2]cycloaddition reactions of azomethine ylids are described.

As part of an ongoing interest in the synthesis of kainic acid (*I*) we have considered an approach[1] based upon the cycloaddition of azomethine ylids (*e.g. II*) to cyclopentenone (Scheme 1) to construct the basic nucleus *III* of kainic acid. Low yields in the cycloaddition step however have caused us to examine other azomethine ylid precursors and herein we described some of our results to this end.



I

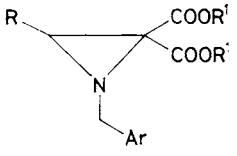


II *III*

SCHEME 1

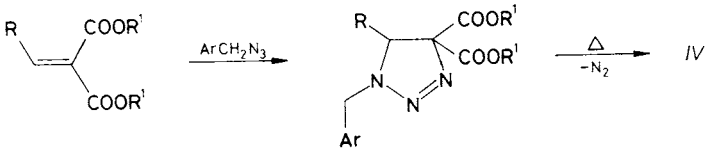
Aziridines such as *IV* have served as a starting point for the generation of azomethine ylids and when the substituent R in *IV* serves to stabilise the ylid, then good yields of [3 + 2]cycloaddition products have been obtained. We have attributed the low yields of *III*, ($R = H$, $R^1 = C_2H_5$) to the low stability of the azomethine ylid *II*, ($R = H$, $R^1 = C_2H_5$).

We have considered two alternative approaches to the synthesis of stabilised azomethine ylids which would facilitate the construction of bicyclic systems such as *III*. The first of these approaches involves the construction of aziridines, *e.g. IV*, where the substituent R would not only stabilise the intermediate azomethine ylid but also be (*a*) easily removed or (*b*) serve as a potential centre for further structural modification at later stages in the synthesis. Clearly, an S-phenyl substituent would serve both of these functions.



IV

One of the most satisfactory approaches to the synthesis of aziridines involves the thermal extrusion of nitrogen from 4,5-dihydro-1,2,3-triazoles which may be prepared by way of a [3 + 2]cycloaddition reaction between an alkene and an azide (Scheme 2), and logically the reaction of S-phenylmethylenemalonate (*V*, R = SC_6H_5) with 4-methoxybenzyl azide[2] is expected to furnish the triazoline *VI* (R = SC_6H_5).



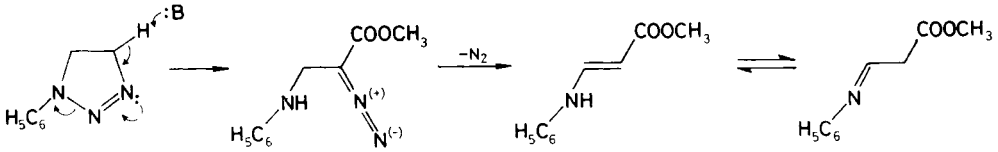
V *VI*

SCHEME 2

S-Phenylmethylenemalonate (*V*, R = SC_6H_5) was prepared by the reaction of ethoxymethylenemalonate with benzenethiol in toluene with continual removal of the eliminated ethanol[3]. The reaction of *V* (R = SC_6H_5, R^1 = C_2H_5) with 4-methoxybenzyl azide proved to be rather slow. However, after three weeks at 65°C the triazoline *VI* (R = SC_6H_5, R^1 = C_2H_5) was isolated in 30% yield. The structure of *VI* follows from elemental analysis and the characteristic chemical shift of the proton at C-5 which resonates at δ 5·40.

In addition to the triazoline *VI* (R = SC_6H_5, R^1 = C_2H_5) a second product was isolated. The IR spectrum indicated that a secondary NH absorption and two different carbonyl absorptions were present and these data coupled with the NMR spectrum suggested that the second product had the structure *VII*. This was con-

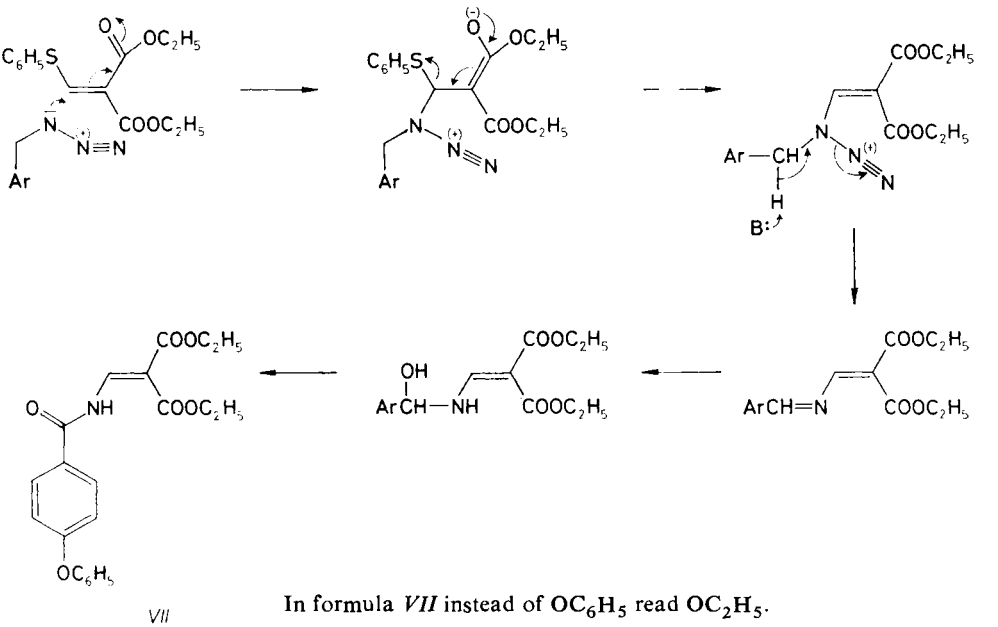
firmed by elemental analysis and an accurate mass measurement which revealed a molecular formula of $C_{16}H_{19}NO_6$.



In the first formula $COOCH_3$ should be placed in the position *4*.

SCHEME 3

In triazolines containing a single substituent at C-4, imine formation is common and Huisgen has proposed[4] a mechanism involving an initial proton abstraction from C-4 (Scheme 3) followed by nitrogen elimination to yield the enamine. However, this mechanism is dependent upon the initial proton abstraction. Clearly in the case of *VI* (R = SC_6H_5, R^1 = C_2H_5) such a fragmentation is not possible and an alternative mechanism (*e.g.* Scheme 4) may be in operation.



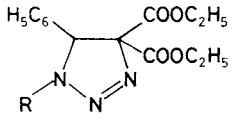
VII

In formula *VII* instead of OC_6H_5 read OC_2H_5.

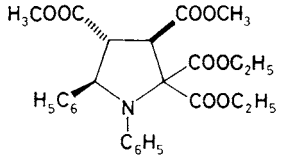
SCHEME 4

Texier and Carrie[5] have previously described reaction conditions for the thermolysis of 4,5-dihydro-1,2,3-triazoles in which nitrogen elimination and subsequent ring opening to the azomethine ylids are carried out in the presence of a suitable

1,3-dipolarophile providing a "one pot" synthesis of pyrrolidine derivatives and our initial studies on *VI* (R = SC_6H_5, R^1 = C_2H_5) were carried out under comparable conditions. In addition we have examined the thermolysis of the known triazoline *VIII* (R = C_6H_5 and R = 4-methoxybenzyl) under identical conditions for comparison purposes. 1,5-Diphenyltriazoline (*VIII*, R = C_6H_5) reacted smoothly with common dipolarophiles under previously described conditions; thus the reaction of *VIII* (R = C_6H_5) with dimethyl fumarate resulted in the formation of the pyrrolidine *IX* in good yield. However, under identical reaction conditions *VI* (R = = SC_6H_5, Ar = 4-$CH_3OC_6H_4$) and *VIII* (R = 4-$CH_3OC_6H_4CH_2$) failed to give any products of cycloaddition. In both cases the 4,5-dihydro-1,2,3-triazoles were recovered unchanged even when protracted reaction times, higher reaction temperatures and more potent dipolarophiles such as N-phenyltriazoline-dione or dimethyl acetylenedicarboxylate were employed.

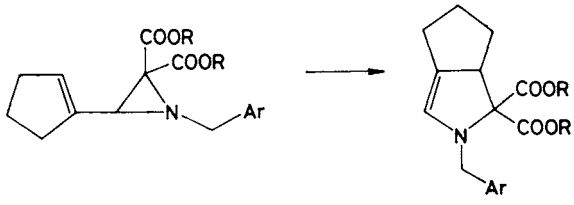


VIII



IX

As a second approach to the construction of a bicyclic framework (*e.g. III*) to use for subsequent elaboration to kainic acid we have considered the possibility of effecting an intramolecular [3 + 2]cycloaddition[6,7] reaction. Thus if a compound such as *X* (Scheme 5) could be constructed then intramolecular [3 + 2]cycloaddition

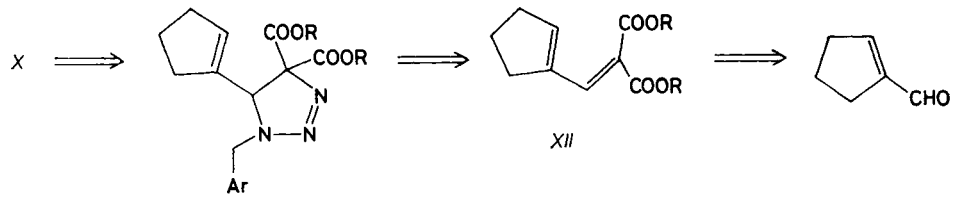


X *XI*

SCHEME 5

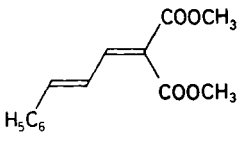
might be expected to yield *XI* which could be elaborated to kainic acid. In addition to the possibility of *X* undergoing ring opening of the aziridine to an azomethine ylid, *X* is formally a vinyl-cyclopropane analogue and as such an alternative mechanism for the rearrangement (*X* → *XI*) exists.

Retrosynthetic analysis of *X* suggests that it might be available through thermal extrusion of nitrogen from a 1,2,3-triazoline (Scheme 6) which is in principle available by [3 + 2]cycloaddition of a benzyl azide with diene-diester *XII*. Compound *XII*, which has not previously been described, is the anticipated product of a Knoevenagel condensation between cyclopentenecarboxaldehyde and malonic ester.

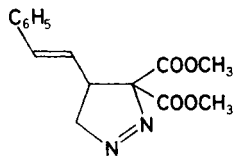


SCHEME 6

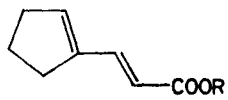
Initial attempts to effect the Knoevenagel reaction between diethyl malonate and cyclopentenecarboxaldehyde were complicated by low yields. However, using $TiCl_4$ as a catalyst, *XII* was obtained in 70% yield. Compound *XII* proved to be inert towards benzyl azide, 4-methoxybenzyl azide and phenyl azide even after eight weeks at elevated temperatures. This failure to undergo reaction is somewhat surprising particularly in view of the fact that the conjugated diene *XIII* is known[8] to undergo [3 + 2]cycloaddition with diazomethane to yield the pyrazoline *XIV*. Compounds *XII* and *XIII* might be expected to exhibit similar reactivity in view of their apparent electronic similarity and the failure of *XII* to react is not easily rationalised. We considered the possibility that steric congestion (space filling molecular models) might in part be responsible for this failure of *XII* to undergo reaction with azides and considered that the monoester *XV* might be more reactive. The acid *XV* (R = H) has previously been reported[9] and was prepared by Knoevenagel con-



XIII



XIV



XV

densation between cyclopentenecarboxaldehyde and malonic acid in pyridine. The literature report[9] did not indicate the stereochemistry of the product but only one product m.p. 162°C was obtained and precedent suggests that the *E* configuration should be observed. In our hands when this reaction was carried out two different crystalline solids were obtained and these were readily separable by their different solubilities in ethyl acetate. The NMR and mass spectra of the products were similar with *J* values for the α,β-unsaturated acid of 16 Hz. The melting points of the two samples were also similar and the major difference to be observed was in the TLC behaviour with the ethyl acetate soluble fraction having an R_F value of 0·83 and the insoluble material an R_F of 0·62 (silica, ether–hexane 80 : 20).

The less soluble of the two products which on the basis of its higher m.p. and an infra-red band at 982 cm^{-1} was assigned the *E* configuration was esterified using standard Fischer–Spier conditions to yield the ester *XV* ($R = CH_3$) which also proved to be unreactive towards benzyl azide even after heating for several weeks and no evidence for triazoline formation was observed. Again this failure to undergo [3 + 2]cycloaddition is surprising since under these conditions methyl cinnamate is known to yield the corresponding triazoline.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Perkin–Elmer R24 or Perkin–Elmer R32 at 60 and 90 MHz, respectively. Infra-red spectra were recorded on a Perkin–Elmer 577 grating instrument and mass spectra on a Jeol JMS D100. Melting points were determined on a Kofler block and are uncorrected.

Diethyl S-phenylmethylenemalonate: Ethoxymethylenemalonate (5 g), thiophenol (5·09 g) and a catalytic quantity of 4-toluenesulphonic acid were dissolved in toluene (20 ml) and heated so that the ethanol which formed during the reaction was distilled from the mixture. The mixture was heated until no further ethanol was evolved and the reflux temperature reached 110°C, then cooled and washed with sodium hydroxide solution (10 ml, 1 mol l^{-1}) and water (50 ml). The organic phase was dried over $MgSO_4$. Concentration of the resultant solution and distillation *in vacuo* gave the title compound 4·2 g (65%), b.p. 172–175°C/0·5 Torr. IR spectrum (film): ν_{max} 3 000, 1 720, 1 630, 1 300, and 840 cm^{-1}. ^{1}H NMR spectrum: $\delta(C^2HCl_3)$ 8·32 (1 H, s), 7·40 (5 H, m); 4·30 (4 H, m) and 1·35 (6 H, m). $C_{14}H_{16}O_4S$ requires *m/z* 280·0770; found: 280·0777.

1-(4'-Methoxybenzyl)-4,4-di(ethoxycarbonyl)-5-phenylthio-Δ^2-1,2,3-triazoline: Diethyl S-phenylmethylenemalonate (5 g) and 4-methoxybenzyl azide (2·4 g) were heated together at 65°C for 3 weeks in a flask protected from atmospheric moisture. Methanol was added and the resultant solution cooled at −20°C for two days. The resultant crystals were filtered, washed with cold methanol and dried *in vacuo* to yield the triazoline *VI* (Ar = 4-$CH_3OC_6H_4$, R = C_2H_5) 2·4 g (30%), m.p. 79–80°C. IR spectrum ($CHCl_3$): ν_{max} 2 950, 1 730, 1 600, and 1 110 cm^{-1}. ^{1}H NMR spectrum $\delta(C^2HCl_3)$: 7·35 (5 H, s), 6·95 (4 H, AA'BB', q), 5·40 (1 H, s), (2 H, q, J = 7 Hz), 4·20 (2 H, q, J = 7 Hz), 3·70 (3 H, s), 1·30 (6 H, t, J = 7 Hz). For $C_{22}H_{25}N_3O_5S$ (443·2) calculated: 59·59% C, 5·64% H, 9·48% N; found: 59·37% C, 5·55% H, 9·37% N.

The filtrate was left at −20°C for a further week and crystals (0·4 g, 7%) were deposited, m.p. 166°C. On the basis of the following data this compound was assigned structure *VII*: IR spectrum ($CHCl_3$): ν_{max} 2 980, 1 700, 1 680, and 1 600 cm^{-1}. ^1H NMR spectrum: $\delta(C^2HCl_3)$ 11·87 (1 H, broad d), 8·82 (1 H, d), 7·50 (4 H, AA'BB', q), 4·30 (4 H, m), 3·93 (3 H, s), 1·35, (6 H, m). For $C_{16}H_{19}NO_6$ (321·1) calculated: 59·85% C, 5·96% H, 4·36% N; found: 60·20% C 5·84% H, 4·36% N. $C_{16}H_{19}NO_6$ requires *m/z* 321·1213; found: 321·1218.

Ethyl 2-ethoxycarbonyl-3-cyclopentenylprop-2-enoate: A solution of titanium tetrachloride (12 ml) in CCl_4 (27 ml) was added dropwise to tetrahydrofuran (216 ml) cooled to 0°C. Diethyl malonate (8·6 g) and cyclopentenecarboxaldehyde (5·2 g) were added at once and a solution of pyridine (17·3 ml) in tetrahydrofurane was added dropwise over 30 min with the temperature mixture being maintained at 0°C. The mixture was stirred at room temperature for a further 30 min and then at room temperature for an additional 30 min. Water (50 ml) was continuously added followed by ether (50 ml). The mixture was stirred for an additional 15 min. The ethereal layer was separated and the aqueous phase extracted with ether (3 × 30 ml). The combined ethereal layers were dried over $MgSO_4$. Concentration and distillation of the residue *in vacuo* yielded 9 g (70%) of the title compound, b.p. 110°C/0·5 Torr. IR spectrum (film): ν_{max} 2 980, 1 780, 1 740, and 1 620 cm^{-1}. ^1H NMR spectrum: $\delta(C^2HCl_3)$ 7·35 (1 H, s), 6·35 (1 H, broad s), 4·22 (4 H, q, J = 7 Hz), 2·42 (4 H, m), 2·00 (2 H, m), 1·30 (6 H, t, J = 7 Hz). $C_{13}H_{18}O_4$ requires *m/z* 238·1206; found: 238·1208.

1-(4'-Methoxybenzyl)-4,4-di(ethoxycarbonyl)-5-phenyl-Δ²-1,2,3-triazoline: Diethyl benzylidenemalonate (5 g) and 4-methoxybenzyl azide (3·3 g) were heated together at 65°C for 3 weeks in a flask protected from atmospheric moisture. Methanol was added and the resultant solution was cooled at −20°C for two days. The resultant crystals were filtered, washed with a little ice-cold methanol and dried to yield 4·2 g (50%) of the title compound, m.p. 68°C. IR spectrum ($CHCl_3$): ν_{max} 2 980, 1 730, 1 600, and 1 120 cm^{-1}. ^1H NMR spectrum: $\delta(C^2HCl_3)$ 7·25 (5 H, m), 6·80 (4 H, AA'BB', q), 5·05 (1 H, s), 4·70 (2 H, q, J = 7 Hz), 4·30 (2 H, q, J = 7 Hz), 3·80 (3 H, s), 3·70 (2 H, m), 1·30 (3 H, t, J = 7 Hz), 0·80 (3 H, t, J = 7 Hz). For $C_{22}H_{25}N_3O_5$ (411·2) calculated: 64·23% C, 6·08% H, 10·22% N; found: 64·15% C, 6·16% H, 10·22% N. $C_{22}H_{25}N_3O_5$ requires *m/z* 411·1794; found: 411·1754.

1,5-Diphenyl-4,4-di(ethoxycarbonyl)-Δ²-1,2,3-triazoline: Diethyl benzylidenemalonate (45 g) and phenyl azide (21·5 g) were heated together at 65°C for 3 weeks in a flask protected from atmospheric moisture. Methanol was added and the resultant solution was left at −20°C for two days. The resultant crystals were filtered, washed with ice-cold methanol and dried to yield the title compound 32 g (48%), m.p. 94—96°C (ref.[3]. 98°C). IR spectrum ($CHCl_3$): ν_{max} 2 990, 1 740, 1 660, and 1 150 cm^{-1}. ^1H NMR spectrum: $\delta(C^2HCl_3)$ 7·30 (10 H, m), 5·90 (1 H, s), 4·40 (2 H, q, J = 7 Hz), 3·70 (2 H, q, J = 7 Hz), 1·2 (3 H, t, J = 7 Hz) and 0·85 (3 H, t, J = 7 Hz). $C_{20}H_{22}N_3O_4$ requires: *m/z* 339·1471; found 339·1473 ($M^+ - N_2$).

3-(Cyclopentenyl)prop-2-enoic acid: 2-Cyclopentenecarboxaldehyde (14·66 g) and malonic acid (47·64 g) were stirred in pyridine (16·94 g) at 100°C. The mixture effervesced slowly and continued to do so during the duration of the reaction. After 2·5 h the effervescence subsided and after 3 h the mixture was allowed to cool to room temperature and solidification occured. Sulphuric acid (30 vol. %) was added and the solid product was collected by filtration and washed with water. The resultant solid was dissolved in tetrahydrofurane and extracted with a saturated solution of $NaHCO_3$ (3 × 100 ml). The sodium hydrogen carbonate extracts were acidified to pH 1 with conc. HCl and the precipitated solid was collected by filtration, washed with water and dried *in vacuo* over P_4O_{10}, yield 13·44 g (63·8%). This product was stirred with ethyl acetate and filtered. The insoluble solid was dried giving 8·64 g (41·0%) of crystals which sublimed

above 100°C and then recrystallised as rhombic crystals which formed a glass at 139–140°C and melted at 140–145°C. ^{1}H NMR spectrum: $\delta(C^2HCl_3$ + hexadeuterodimethyl sulfoxide) 8·92 (1 H, bs), 7·46 (1 H, d, J = 16 Hz), 6·13 (1 H, s), 5·68 (1 H, d, J = 16 Hz), 2·45 (4 H, m), and 1·95 (2 H, m). IR spectrum ($CHCl_3$): ν_{max} 3 300–2 400, 1 685, 1 620, and 982 cm^{-1}. For $C_8H_{10}O_2$ calculated: 69·54% C, 7·30% H; found: 69·57% C, 7·42% H.

The filtrate was concentrated and the solid dried *in vacuo* giving 4·8 g (23%) of crystals m.p. 136–140°C. ^{1}H NMR spectrum: $\delta(C^2HCl_3)$ 11·13 (1 H, bs), 7·60 (1 H, d, J = 16 Hz), 6·28 (1 H, s), 5·74 (1 H, d, J = 16 Hz), 2·5 (4 H, m), and 2·02 (2 H, m). IR spectrum ($CHCl_3$): ν_{max} 3 300, 2 400, 1 685, 1 620, and 720 cm^{-1}.

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