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ISOTHIAZOLE CHEMISTRY—IX

SELECTIVITY IN CARBANION ATTACK ON N-ETHYL-3-ISOTHIAZOLONE

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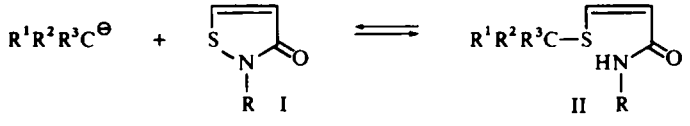
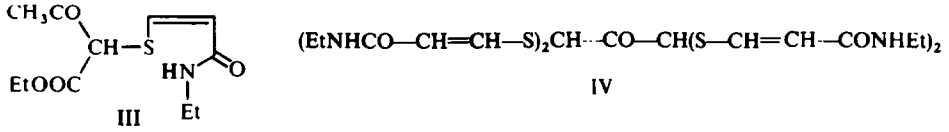
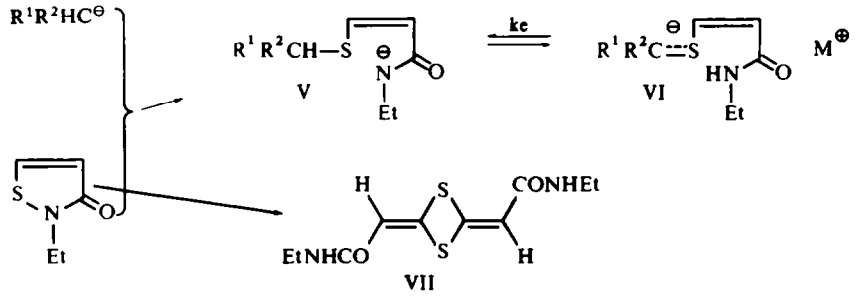
Abstract—Nucleophilic attack on the S-N bond in N-ethyl-3-isothiazolone has been studied with respect to the degree of substitution at the carbanion site. Attack by tertiary carbanions is not observed, the products reverting completely to starting materials under the reaction conditions. When dibasic carbon acids were employed, discrimination against the products of attack by a tertiary centre was observed. The expected products from tertiary attack have been independently synthesized, and shown to undergo intermolecular migration, yielding the products of attack by the less highly substituted carbanion centre. Reasons for this selectivity are discussed in terms of secondary stabilisation and leaving group efficiencies from sulphur.

INTRODUCTION

OUR early observations[1–3] on the lability of the S-N bond to nucleophilic attack in 3-isothiazolones (I) led to extension of this reaction into the use of carbanions,[4] with a view to establishing synthetic pathways. For this reason more detailed attention was directed to the use of the commonly available carbonyl-stabilized carbanions. We found that with primary (R—CO—Me) and secondary (R—CO—CH_2R) carbon acids substitution at the atom(s) adjacent to carbonyl could be achieved up







to the stage (III, IV) where only one H remained, but no further than this. The reaction was shown to be reversible, even in aprotic solvents, which suggested a good reason for the failure of full substitution in III and IV. It was proposed[4] that a major factor in reversion of V to generators could be the proton exchange V $\rightleftharpoons$ VI*, the latter being preferentially stabilised in aprotic media; recyclization of products such as V was observed in water, the rate depending upon the nature of the carbanion.

The apparent importance of an available carbanion site in the products II made it of some interest to study the reaction with tertiary carbanions. This could not be achieved directly, since the N-alkyl-3-isothiazolones are subject to dimerization[5] to 2,4-bismethylene-1,3-dithietanes (VII) by the action of bases—a convenient synthesis of this class of compound. In order to examine the reaction it was necessary to obtain the desired compounds by alternative methods.

Synthesis and stability of 3° cis-3-*alkylmercaptoacrylamides*

For this purpose we employed a series of insoluble salts VI (R_1, R_2 = all combinations of MeCO and COOEt) resulting[4] from the attack of 2° carbanions on I (R = Et), and alkylated the carbon acid moiety *in situ*. The reaction was not, however, free of complications. Attempted alkylation in hydroxylic solvents led only to recovery of I (R = Et), together with the alkylated carbon acid (probably alkylated in VI prior to ejection). The desired products IX were obtained, however, on alkylation of VI in DMF. Methylation of VI (R^1 = CH_3CO_2 R^2 = COOEt), gave, in addition to the expected C-methylation, an isomeric material showing a 3-proton PMR signal at τ 7·56 (—S—Me), to which we assign the ylid structure VIII,† in view of its relative instability. Analogous compound were not encountered in other cases.

The products which would have resulted from attack by tertiary carbanions (IX) decomposed rapidly when treated with aqueous alkali. Their behaviour in non-

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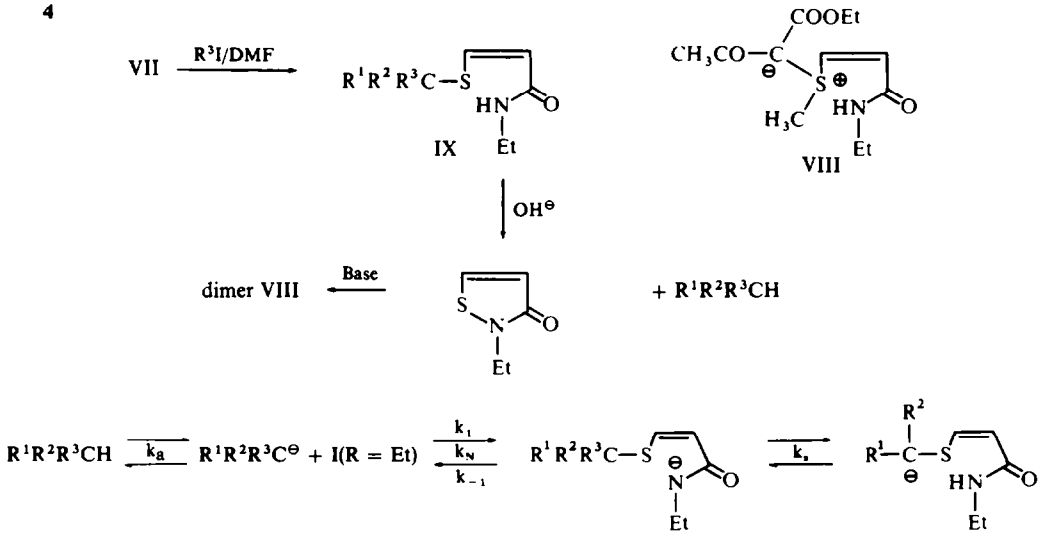


* This effect will be referred to as secondary stabilisation of the product.

† We thank Professor J. M. Swan for this suggestion.

aqueous base systems varied with the nature of the carbon acid—a subject discussed in detail below. Provided that no other carbanion site existed in the carbon acid chain (e.g. IX, $R^1 = R^2 = COOEt$, $R_3 = Me$), the dimer VII resulted from the N-ethyl-2-isothiazolone regenerated by ejection of the carbanion $R^1R^2R^3C^{\ominus}$. The situation can thus be summarised as follows: If one of $R^1R^2R^3 = H$, then the initially formed amide anion X is capable of secondary stabilization by proton exchange to XI (Ks is relatively large). Where none of $R^1R^2R^3 = H$ secondary stabilization cannot occur, and provided $k_{-1} \neq 0$, some regression will occur. This will ultimately lead to complete conversion to dimer VII (since this reaction is irreversible). This large disparity between the effectiveness of attack by tertiary and by primary or secondary carbanions meant that some interesting selectivity of reaction might be observed. In the usual carbanions employed in synthesis there are two carbanion sites: these generally differ substantially in *pKa*, and electrophilic substitution is normally observed only at the stronger acid site. We therefore made a more detailed examination of the behaviour of dibasic carbon acids in this system.

Competitive attack in diabasic carbon acids

Before considering the experimental results, it is worthwhile to examine the system in some detail. The reaction is essentially an electrophilic attack by N-ethyl-3-isothiazolone on the carbanion, and is in this respect comparable to alkylation. The reversibility of attack, however, coupled with the possibility of secondary stabilization of the products, introduce complexities not encountered in alkylation. Chart I summarizes the reactions expected between a dibasic carbon acid $HC_{1,2}$ and N-ethyl-3-isothiazolone. The carbanion C_2^- is defined as the stronger conjugate base, and

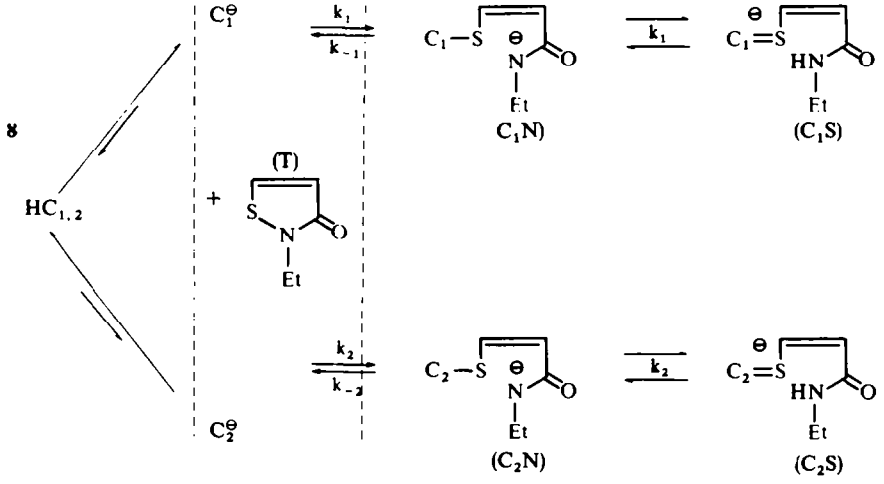


CHART 1

secondary stabilisation is ignored in the initial discussion ($K_1 = K_2 = 0$). At equilibrium $k_1[C_1^-][T] = k_{-1}[C_1N]$, $k_2[C_2^-][T] = k_{-2}[C_2N]$ and the product ratio $[C_1N]/[C_2N] = k_1/k_2 \cdot [C_1^-]/[C_2^-] \cdot k_{-1}/k_{-1}$ ----------1. Three factors

may be recognised in Equation 1:

a. *Comparative basicity* of the carbanions C_1^- and C_2^- towards H^+

b. Comparative nucleophilicity of C_1^- and C_2^- towards S (k_1/k_2)

c. *Comparative leaving group efficiency* of C_1^- and C_2^- (k_{-1}/k_{-2})

The situation can be seen more clearly as a competition between H-basicity and S-basicity if *b.* and *c.* are combined as the latter factor.

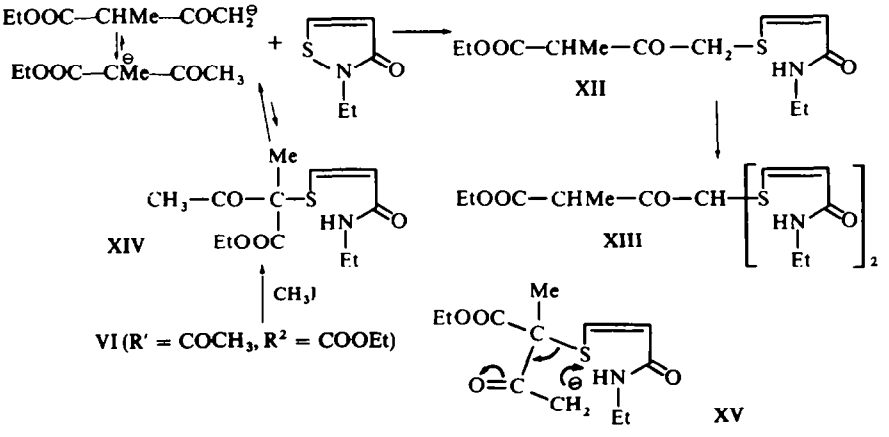
In the comparable case of carbanion alkylation, k_{-1} and $k_{-2} = 0$. and the product ratio is then subject to kinetic control. Experimental studies[6,7] tend to show that the rate of alkylation of an enolate is not grossly altered by changing the number of alkyl groups at the carbanion centre. This is a logical consequence of the perpendicular approach of the electrophile to the enolate π-plane, and the product ratio should reflect the equilibrium ratio of the enolates C_1^- and C_2^-; with 2-methylpentan-3-one, for example, this is the case.[8] Experimentally, this results at least in part from the fact that alkylation of the enolates is faster than the interchange between them;[8] as to how far this analogy can be extended to the reactions in Chart I is a matter for conjecture. It seems reasonable to assume, however, that k_1 and k_2 will not be grossly dissimilar, at least for small structural variations. It follows from this that, in cases where reversibility is encountered, as in Chart I, the product ratio can also reflect relative leaving group tendencies. We would therefore expect that the product from the minor enolate (less efficient leaving group) could predominate in the products.

Extending the analysis to cases where secondary stabilisation is involved, Equation I is modified by substitution to:

Product ratio =

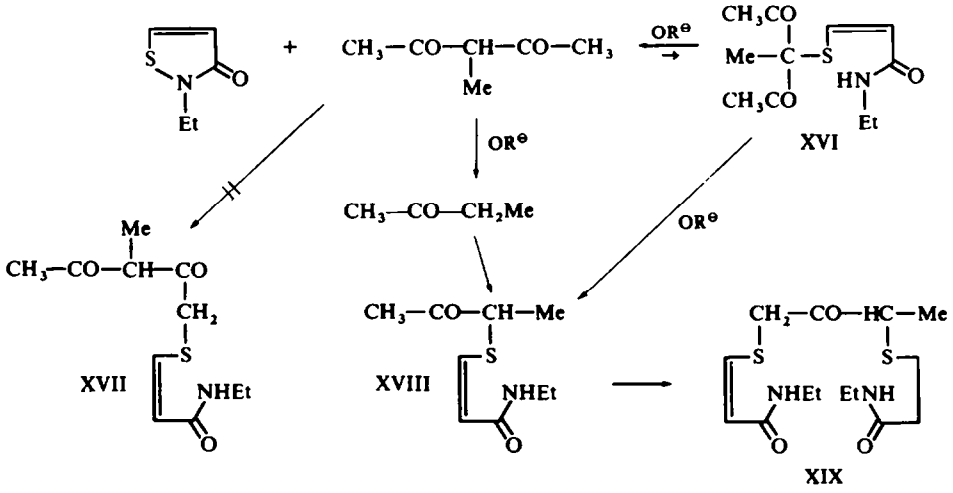
$$[C_1N + C_1S]/[C_2N + C_2S] = k_1/k_2 \cdot [C_1^-]/[C_2^-] \cdot k_{-1}/k_{-2} \cdot (1 + K_1)/(1 + K_2) \ldots 2$$

From equation 2 it is clear that the ratio $(1 + K_1)/(1 + K_2)$ could completely alter the situation, particularly in cases where either K_1 or K_2 = zero. This last situation, in which one of the acidic centres in $HC_{1,2}$ is tertiary, was the first to be examined. In doing so, we were aware of the need to ensure that equilibrium conditions were attained. House and Trost[9] showed that enolate production was kinetically controlled in aprotic media, and we therefore confined all work to the system t-butanol/t-butoxide. In passing we note that this choice of solvent may be expected to minimize the effects of secondary stabilization, but this is unavoidable.



Ethyl 2-methylacetoacetate represents a clear case where the stronger acidic centre is also tertiary, and therefore the better leaving group on all counts ($k_{-1} > k_{-2}$; $K_1 = 0$). The product obtained was the expected one, arising from attack by the primary centre, with a small amount of the disubstituted product XIII. As an additional check, the product of tertiary attack (XIV) was synthesised and separately subjected to the same reaction conditions. As before, XII and a little XIII were the only products. There remained a possibility that the conversion XIV → XII was an intramolecular rearrangement, proceeding through the 4-centre transition state XV. To seal off this loophole in the argument, we prepared XIV by reaction with trideuteromethyl iodide, and then subjected it to the same reaction in the presence of a mole equivalent of ethyl 2-methylacetoacetate. There was complete scrambling of the CD_3-group between XII and the recovered carbon acid. Furthermore, the transformation XIV → XII was carried out (d_4-MeOH/d_3-$MeO^{\ominus}$) in an NMR probe: the vinylic doublets of XIV disappeared very rapidly, being replaced by those of I(R = Et). A further set of vinylic doublets due to XII then appeared more slowly. There seems little doubt that the reaction sequence is XIV → I (R = Et) → XII.

In the completely analogous case of 3-methylpentan-2,4-dione it would seem that the same arguments should apply. When the reaction was carried out, the major product isolated (XVIII) had apparently lost an acetyl group, without any migration occurring to the primary carbon acid centre. As before, we prepared the product of tertiary attack (XVI) and showed that it also was transformed to XVIII. It became a matter of some importance to establish the stage at which acid cleavage of the β-diketone moiety had occurred. This was readily achieved by following the reaction in d_4-MeOH/d_3-$MeO^{\ominus}$ in the NMR probe. As in the case of 2-methylacetoacetic ester, the intermediacy of I (R = Et) was established, proving that cleavage was occurring in the isolated carbon acid after ejection, not in XVI itself. The apparent lack of migration was clearly due not to lack of ejection of the tertiary centre, but to preferential attack by the secondary carbanion site in the 2-butanone formed by cleavage. This point was confirmed by carrying out the corresponding carbanion attack with 2-butanone itself. The products obtained were XVIII, with a little XIX, as in the experiment with 3-methylpentan-2,4-dione itself.

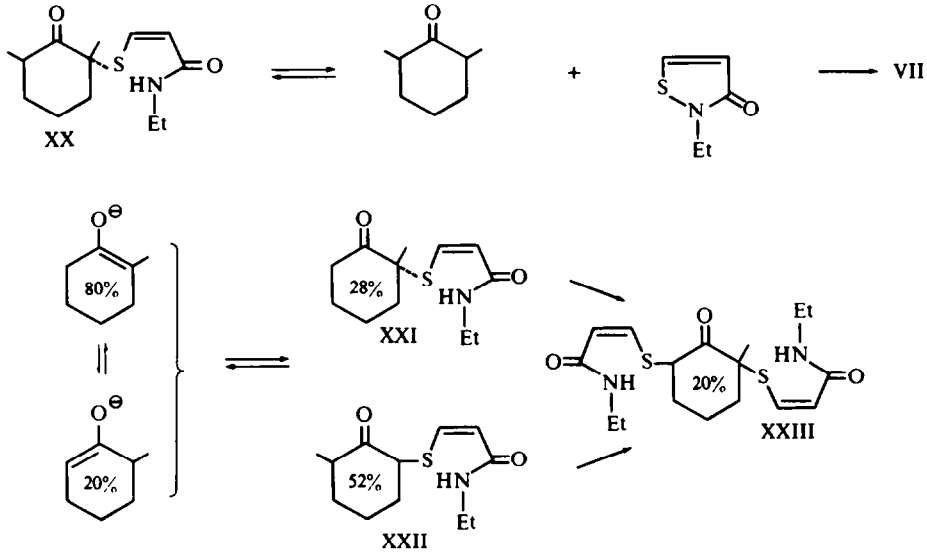


In this case, unlike that of 2-methylacetoacetic ester, no product from the original primary enolate (XVII) was observed. Evidently this route was too slow to compete with the cleavage of the carbon acid to 2-butanone, and re-attack by the new carbon acid.

In the two cases presented above, the possibility of secondary stabilisation does not arise in one of the products (that from attack from the 3° carbanion site) so that it is impossible to compare the significance of this factor against that of leaving group efficiency (k_{-1}, k_{-2}). The solvent system employed would tend to reduce the effect of secondary stabilisation, so should permit such comparison in suitable cases. In earlier work[4] we have shown that the equilibrium

$$\text{I} + \text{carbon acid} \rightleftharpoons \text{II}$$

exists even when secondary stabilisation is operative, and we now examined the cases of simple ketones R—CO—R, where there should be no extreme preference for the formation of one enolate over the other.



The symmetrical ditertiary carbon acid 2,6-dimethylcyclohexanone was first tested as a standard, using dithietane formation as a gauge of the extent of ejection. The product XX was obtained after a short reaction time; increased reaction time led to a slow increase in dithietane formation. That this was truly due to reversal of the formation of XX was shown by subjecting it to the same reaction conditions, with the same results. 2-Methylcyclohexanone was now reacted in the same manner, yielding three products XXI, XXII* and XXIII in the ratio shown. That the XXI : XXII ratio was a true equilibrium ratio was shown by its constancy with extended reaction time, and by subjecting XXI to the same reaction conditions, to provide the same XXI/XXII mixture.

The required XXI could not be satisfactorily separated from XXII, and was accord-

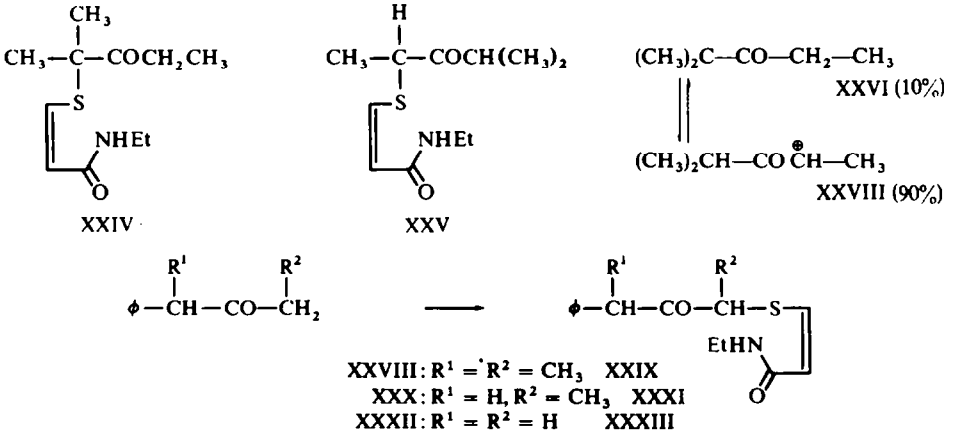
* NMR data indicated only one isomer of XXII, assigned the *cis* (diequatorial) configuration.

ingly synthesised by Michael addition of 2-methyl-2-mercaptocyclohexanone to N-ethylpropiolamide.

It is apparent that the monosubstitution products XXI and XXII contain a substantially greater proportion of XXII (65%) than would be expected from the equilibrium proportion (20%) of the corresponding enolate ion. The extent of the discrepancy, however, is not such as to warrant any attempt at a deep analysis of the situation. Although results of methylation and Michael addition[8,10] with the 2-methylcyclohexanone system have established that the rates for the two enolates are enolates are comparable *for these reactions*, it could well be that more selectivity is shown in the rates of attack on I. The fact that a product equilibrium XXI ⇌ XXII is being established, however, is beyond dispute. Since complete conversion XXI → XXII did not occur, we are able to establish that ejection of the carbanion from XXII is also occurring, despite the possibility of secondary stabilization in XXII. Thus we are able to conclude that secondary stabilization in XXII is not of overriding importance, as it apparently was in XII. The product ratio appears to be controlled by relative leaving group efficiencies (k_{-2}/k_{-1}) in this case.

The acyclic ketone 2-methyl-3-pentanone simiarly afforded two products (XXIV and XXV), with the product of attack at the tertiary centre predominating, in direct contrast to alkylation.[8] It is apparent in this case that secondary stabilisation cannot be playing any part in the determination of product ratio, since all factors except the unknown leaving group efficiencies of the two carbanions combine to indicate XXV as the major product. Thus the enolate ratio XXVII:XXVI is ~9, electrophilic attack on XXVII must be at least as fast as on XXVI, and secondary stabilization is not possible in the case of XXIV. The almost inescapable conclusion is reached that the product is determined by the relative leaving group efficiencies of the two carbanions, favouring the product from the stronger conjugate base of the parent carbon acid.

The final group of ketones selected for study consisted of the benzyl alkyl ketones XXVIII, XXXX and XXXII. In such compounds it has been shown that carbanion formation[8] (and alkylation) occurs almost exclusively at the benzylic position. They constitute a group in which a relatively strong acid centre (3° and 2°) is exposed to competition from a weaker centre (2° and 1°). In each case there was only one product



of reaction with N-ethyl-3-isothiazolone—that from the least favoured enolate (XXIX, XXXI and XXXIII). These results are again consistent with the idea that relative leaving group efficiencies are playing an important role in determining the product of the reaction.

CONCLUSIONS

In summary, we have seen that electrophilic attack by N-ethyl-3-isothiazolone results generally in the product from reaction at the less acidic site in a dibasic carbon acid. The single exception to this is seen in the stronger carbon acids (e.g. the β-diketones) and then only when the stronger acid site is not tertiary. This exception we ascribe to the existence of substantial secondary stabilisation. That it should occur only in the stronger carbon acids is seen as a function of competition between the amide anion V and the S-stabilized carbanion VI.

The equilibrium constant for this proton exchange will be related to the *pKa*'s of the respective conjugate acids. Only in products from the stronger carbon acids will Ke be so large as to control the product ratio. This situation evidently arises in the β-diketones, where the stronger acid centre is usually of p*Ka* 8–10. While it is not possible to reliably estimate the p*Ka*'s of the products, we may assume that the mercaptoacrylamide moiety will decrease these values by at least 1–2 p*K* units. The result should be that the carbon acid centre in the product will be substantially stronger than the nitrogen acid centre (estimated to be about p*Ka* 9–10).[2] The absence of secondary stabilisation effects in the products from simple ketones (p*Ka* 20–25) is to be expected, since the dissociations constant for the carbon acid centre will be some 10^{10} less than that of the nitrogen acid centre (i.e. the ratio V:VI $\sim 10^{10}$). Under these circumstances, final product ratios would tend to reflect leaving group tendencies, as discussed previously.

The benzyl ketones (p*Ka* 15–17[11]), although there are some 5 p*Ka* units stronger than the alkanones, still appear to lack secondary stabilization in the products from reaction with I. While this is consistent with the previous argument, it will be noted that we drew no detailed conclusion from the cyclohexanone case. The stereochemistry of electrophilic attack (and of its reversal) is presumably such that the C—S bond is formed in an axial manner,[12] yet there is every reason to believe that this C—S bond in XXII is equatorial. It is unfortunate that XXII, as well as being the product from the less favoured enolate, is also sterically more acceptable than the isomeric XXI. It is possible that steric factors may also be invoked to explain the results of reaction with the benzyl ketones, although we consider this unlikely.

Provided that secondary stabilisation effects can be shown to be absent, the reversibility of the systems described should permit a measure of the relative S-basicities of selected carbanions, and we hope to present information along these lines in a subsequent communication.

EXPERIMENTAL

M.ps are uncorrected. Microanalysis was carried out by the Australian Microanalytical Service at the University of Melbourne. IR spectra (Unicam SP200 or SP200G) refer to Nujol mulls unless otherwise stated, and UV spectra (Beckman DK-2A) were measured in 90% EtOH—extinction coefficients are given in parentheses. 60 Mhz spectra (Perkin–Elmer R-10) are quoted as τ-values, with coupling constants in

Hz. Mass spectra were measured on an AEI MS9 instrument. All sovents referred to were rigorously dried by standard procedures.[4]

1. N-*Ethyl*-cis-3-*t-alkylmercaptoacrylamides*

General procedure. The appropriate sodium salt VI, prepared as described earlier,[4] (0·005 mole) in DMF (15 ml) was stirred under N_2 while adding the required alkyl halide (excess, ~0·01 mole) at room temp. Stirring was continued overnight at 30–40°, the reaction mixture was poured into water, and the products recovered with ether. The conversion (NMR analysis) was 60–90%. Chromatography over silica in benzene/petroleum/ether mixtures gave the pure products.

(a) *Diethyl 2-methyl-2-(N-ethyl-cis-3-acrylamido)mercaptomalonate* crystallized from ether/hexane as colourless needles m.p. 58–60°. (Found: C, 51·2; H, 7·0; N, 4·8; S, 10·5. $C_{13}H_{21}NO_5S$ requires: C, 51·5; H, 7·0; N, 4·6; S, 10·6%); IR: ν_{max} 3300, 1735, 1640 cm^{-1}; UV: λ_{max} 275 *br* (12850) mμ; NMR ($CDCl_3$): 2·88 (d, H)–4·09 (d, H) (J = 10), 3·9 (br, NH), 6·6 (m, 2H), 8·25 (s, 3H), 8·73 (t, 3H); *mass spectrum.* M^+ = 303.

(b) *3-Methyl-3-(N-ethyl-cis-3-acrylamido)mercaptopentan-2,4-dione* (XVI). crystallized from benzene/hexane as colourless prisms m.p. 107–109°. (Found: C, 54·6; H, 7·2; N, 5·5; S, 13·1. $C_{11}H_{17}O_3NS$ requires: C, 54·3; H, 7·0; N, 5·8; S, 13·2%); IR: ν_{max} 3370, 1695, 1635 cm^{-1}; UV: λ_{max} 274 br (14280) mμ; NMR ($CDCl_3$): 3·84 (d, H)–4·11 (d, H) (J = 10), 4·0 (br, NH), 6·6 (m, 2H), 7·27 (s, 6H), 8·34 (s, 3H), 8·93 (t, 3H).

(c) *Ethyl 2-acetyl-2-(N-ethyl-cis-3-acrylamido)mercaptopropionate* (XIV) crystallized from ether as colourless plates m.p. 76–77°. (Found: C, 53·0; H, 6·9; N, 5·3; S, 11·8. $C_{12}H_{19}NO_4S$ requires: C, 52·7; H, 7·0; N, 5·1; S, 11·7%); IR: ν_{max} 3360, 1745, 1708, 1635 cm^{-1}; UV; λ_{max} 272 (12640) mμ; NMR ($CDCl_3$): 3·29 (d, H)–4·02 (d, H) (J = 10), 5·72 (q, 2H), 6·6 (m, 2H), 7·70 (s, 3H), 8·30 (s, 3H), 8·71 (t, 3H), 8·83 (t, 3H). A second *compound* (18%, believed to be the ylid VIII) was separated by preparative TLC (Kieselgel H; benzene/acetone/hexane 4:1:6). It darkened on standing and decomposed on heating alone or in solvents. *Mass spectrum* (Direct probe): M^+ = 273 ($C_{12}H_{19}NO_4S$ requires MW = 273); IR (film): ν_{max} 3420, 1705, 1670, 1625 cm^{-1}; NMR ($CDCl_3$); 2·3 (br, NH), 3·05 (d, H–4·76 (d, H) (J = 6·1), 5·66 (q, 2H), 6·8 (m, 2H), 7·56 (s, 3H), 7·72 (s, 3H), 8·63 (t, 3H), 8·79 (t, 3H).

2. *Reaction of N-ethyl-3-isothiazolone with 1,3-dicarbonyl compounds*

The essential experimental procedure for the reaction has been described.[4] t-BuOK and t-BuOH were used throughout.

(a) *With ethyl 2-methylacetoacetate.* The crude reaction product was chromatographed (SiO_2, benzene/chloroform 7:3) to give a colourless oil (65% yield). Crystallization from benzene/hexane gave *ethyl 2-methyl-3-oxo-4-(N-ethyl-cis-3-acrylamido)mercaptobutanoate* (XII) as colourless prisms m.p. 52–54°. (Found: C, 52·5; H, 6·9; N, 5·1; S, 11·4. $C_{12}H_{19}NO_4S$ requires: C, 52·7; H, 7·0; N, 5·1; S, 11·7%); IR: ν_{max} 3360, 1720, 1700 (w), 1635 cm^{-1}; UV: λ_{max} 274 (13240) mμ; NMR ($CDCl_3$): 3·28 (d, H)–4·02 (d, H) (J = 9·9), 3·4 (br, NH), 5·82 (q, 2H), 5·93 (q, H), 6·40 (s, 2H), 6·65 (m, 2H), 8·64 (d, 3H) (J = 7), 8·73 (t, 3H), 8·86 (t, 3H); *mass spectrum*: M^+ = 287.

Further elution (chloroform/ether 1:1) gave ethyl *2-methyl-3-oxo-4,4-bis(N-ethyl-cis-3-acrylamidomercapto)butanoate* (XIII) m.p. 144–146°; (Found: C, 50·5; H, 6·5; N, 6·7; S, 15·8. $C_{17}H_{26}O_5N_2S_2$ requires: C, 50·7; H, 6·5; N, 7·0; S, 16·0%); IR: ν_{max} 3360, 1740, 1705, 1640 cm^{-1}; UV λ_{max} 282 (28640) mμ: NMR ($CDCl_3$); 2·98, 3·80, 3·85 (overlapping pairs of doublets, 4H, J = 10), 4·92 (s, H), 5·84 (q, 2H) 6·7 (m, 4H), 8·7 (overlapping triplets, 12H), total integration 26H. The same products were obtained by stirring XIV at room temp under N_2 with t-BuOK.

(b) *With 3-methylpentan-2,4-dione.* The crude product (90% yield) was triturated with ether to give the insoluble disubstitution product. Purification by washing with hot alcohol gave *1,3-bis(N-ethyl-cis-3-acrylamidomercapto)butan-2-one* (XIX, 15%) as a colourless crystalline solid m.p. 165–167°. (Found: C, 50·6; H, 6·3; N, 8·5; S, 19·3. $C_{14}H_{22}N_2O_3S_2$ requires: C, 50·9; H, 6·7; N, 8·5; S, 19·4%); IR: ν_{max} 3370, 1695, 1640 cm^{-1}; UV: λ_{max} 282 (25480) mμ. The residual oil was chromatographed (SiO_2, benzene/chloroform 3:2) to yield *3-(N-ethyl-cis-3-acrylamido)mercaptobutan-2-one* (XVIII, 52%) as colourless prisms m.p. 68–71°. (Found: C, 53·7; H, 7·5; N, 6·6; S, 15·6. $C_9H_{15}NO_2S$ requires: C, 53·7; H, 7·5; N, 7·0; S, 15·9%); IR: ν_{max} 3360, 1705, 1635 cm^{-1}; UV: λ_{max} 276 (12400) mμ; NMR ($CDCl_3$): 3·26 (d, H)–4·07 (d, H) (J = 10), 3·7 (NH) 6·43 (q, H), 6·65 (m, 2H), 7·70 (s. 3H), 8·53 (d, 3H, J = 7), 8·83 (t, 3H).

The same products (XIX, 15%, and XVIII 62%) were identified from reaction of XVI with t-BuOK in t-BuOH at room temp, and from similar reaction of I(R = Et) with butan-2-one (XIX 12%, XVIII 60%).

3. *Isotopic scambling in* XIV

Preparation of XIV from VI (R^1 = Me, R^2 = COOEt) was carried out as described, using trideuteromethyl iodide. The product was identical with that described previously, but showed no NMR signal at 8·30. It was stirred in t-BuOH with one mole equiv each of t-BuOK and ethyl 2-methylacetoacetate for 16 hr at room temp, and the products were isolated in the usual way. The recovered ethyl 2-methylacetoacetate showed 50% 2-trideuteromethylacetoacetate content, and the isolated XII showed only 50% intensity in the NMR doublet at 8·64.

4. *Reaction of* N-*ethyl*-3-*isothiazolone with ketones*

(a) 2,6-*Dimethylcyclohexanone.* after stirring the reaction mixture for 2 hr and quenching in 2M HCl, the recovered products were triturated with chloroform. The insoluble dimer VII (28% yield) was filtered off and the residue chromatographed (SiO_2, benzene/hexane/ether 2:3:1) to give 2,6-*dimethyl*-2-(N-*ethyl*-cis-3-*acrylamido*)*mercaptocyclohexanone* (XX, 68%) crystallizing from benzene/hexane as colourless prisms m.p. 109–11. (Found: C, 61·3; H, 8·4; N, 5·5; S, 12·2. $C_{13}H_{21}NO_2S$ requires: C, 61·2; H, 8·3; N, 5·5; S, 12·5%); IR: ν_{max} 3370, 1705, 1635 cm^{-1}; UV: λ_{max} 276 (11210) mμ; NMR ($CDCl_3$): 3·40 (d, H)–4·09 (d, H) (J = 10), 3·8 (br, NH), 6·6 (m, 2H), 7·9 (br), 7·58 (s), 8·83 (t, 3H), 8·99 (d, J = 7·2).

Rearrangement of XX. 0·005 mole potassium t-BuOK in t-BuOH (10 ml) was cooled to 10°, and XX (1·28 g, 0·0005 mole) added. After short stirring under N_2 a turbidity developed; after 16 hr the dimer VII (0·61 g, 95%) was filtered off. 2,6-Dimethylcyclohexanone (0·54 g, 95%) was recovered from the filtrate.

(b) 2-*Methylcyclohexanone.* The reaction product was triturated with ether to give 2-*methyl*-2,6-bis-(N-*ethyl*-cis-3-*acrylamidomercapto*)*cyclohexanone* (XXIII, 20%), which crystallized from DMSO/water as a colourless amorphous solid m.p. 140–144°. (Found: C, 55·0; H, 6·9; N, 7·3; S, 17·0. $C_{17}H_{26}N_2O_3S_2$ requires: C, 55·1; H, 7·1; N, 7·6; S, 17·3%); IR: ν_{max} 3300, 1700, 1640 (br) cm^{-1}; UV: λ_{max} 280 (br) (26750) mμ; NMR (DMSO-d_6): 1·95 (br, t, 2H), 3·12 (d, H), 3·51 (d, H), 3·97 (d, H), 4·09 (d, H) (J = 10), 5·5 (br, t), 6·8 (m), 7·9 (br, m), 8·7 (s), 8·9 (t). Total integration 26H.

Chromatography (SiO_2, benzene/chloroform/ether 2:3:1) of the residual oil gave 2-*methyl*-6-(N-*ethyl*-cis-3-*acrylamido*)*mercaptocyclohexanone* (XXII, 48%), crystallizing from EtOH/hexane as colourless plates m.p. 163–164°. (Found: C, 59·4; H, 7·9; N, 5·5; S, 13·3. $C_{12}H_{19}NO_2S$ requires: C, 59·7; H, 7·9; N, 5·8; S, 13·3%); IR: ν_{max} 3370, 1710, 1635 cm^{-1}; UV: λ_{max} 276 (11820) mμ; NMR ($CDCl_3$): 3·27 (d, H)–4·11 (d, H) (J = 10), 3·7 (br, NH), 6·7 (m), 7–9 (br), 8·86 (t), 9·2 (d, J = 6), total integration 19H.

Further elution afforded a mixture (32%) of XXII (10–15% by NMR) and XXI. The latter was identified by comparison of its NMR spectrum with that of an authentic specimen (*vide infra*).

Repetition of the experiment with excess 2-methylcycloxanone greatly reduced the yield of XXIII, but did not alter the XXI:XXII ratio, showing that this was not due to faster disubstitution of one of the components.

Synthesis of XXI. NaOH (2 g, 0·05 mole) in water (40 ml) was saturated with H_2S at 5°, and 2-chloro-2-methylcyclohexanone (7·35 g, 0·05 mole) in EtOH (30 ml) was slowly added, stirring and cooling while still passing H_2S. After 2 hr the product was extracted into chloroform and distilled to give 2-*methyl*-2-*mercaptocyclohexanone* (6·4 g, 89%), b.p. 88–89°. (Found: C, 58·2; H, 8·4; S, 22·0. $C_7H_{12}OS$ requires: C, 58·3; H, 8·4; S, 22·2%); IR: ν_{max} (film) 2560 (w), 1705 cm^{-1}.

A catalytic amount of Na was added to this product (1·44 g, 0·01 mole) and N-ethylpropiolamide (0·98 g, 0·01 mole) in EtOH (20 ml). The mixture was cooled occasionally in ice, stirred for 1·5 hr, and the solvent removed under reduced press. Crystallization of the product from ether gave 2-*methyl*-2-(N-*ethyl*-cis-3-*acrylamido*)*mercaptocyclohexanone* (XXI, 78%) as colourless plates m.p. 120–121°. (Found: C, 59·4; H, 7·9; N, 5·5; S, 13·4. $C_{12}H_{19}NO_2S$ requires: C, 59·7; H, 7·9; N, 5·8; S, 13·3%); IR: ν_{max} 3320, 1695, 1635 cm^{-1}; UV: λ_{max} 277 (11320) mμ; NMR ($CDCl_3$): 3·41 (d, H)–4·04 (d, H) (J = 10), 3·3 (br, NH), 6·65 (m, 2H), 7·5–8·5 (br, 8H), 8·60 (s, 3H), 8·96 (t, 3H). The NMR spectrum was superposable on that of the major component of the mixture above.

Equilibration of XXI/XXII *by base.* XXI (0·005 mole) was stirred overnight under N_2 at room temp in t-BuOH with t-BuOK (0·005 mole). Analysis of the isolated XXI/XXII mixture achieved by comparison of the NMR signals at 3·27/4·11 and 3·41/4·04, indicated 30% XXI, 70% XXII. Examination by TLC confirmed the presence of both isomers, free from extraneous products.

(c) 2-*Methylpentan*-3-*one.* The total crude products (95% yield) showed only two components by TLC, and their proportions were estimated by NMR analysis of the vinylic doublets as 60% XXIV, 40% XXV. The products could not be completely separated, and structural assignments were based on ca. 80% pure fractions. The total mixture showed only one molecular ion (*m/e* 229) in the mass spectrum, and on treat-

ment with dilute aqueous alkali gave only I(R = Et) and 2-methylpentan-3-one. The IR spectrum showed ν_{max} 3370, 1695, 1640 cm^{-1}, and the UV spectrum showed λ_{max} 275 (12260). NMR assignments are given below.

XXIV: 3·39 (d, H)–4·14 d, H) (J = 10), 3·8 (br, NH), 6·65 (m, $NC\underline{H}_2$—), 7·28 (q, CO—$C\underline{H}_2$), 8·50 (s, $(C\underline{H}_3)_2C$), 8·83 (t, $C\underline{H}_3$—CH_2N), 8·98 (t, CO—$CH_2C\underline{H}_3$).

XXV: 3·25 (d, H)–4·06 (d, H) (J = 10), 3·5 (br, NH), 6·28 (q, CO—$C\underline{H}(CH_2)$—S), 6·65 (m, NH—$C\underline{H}_2$—), 6·9 (m, $(CH_3)_2C\underline{H}$—CO), 8·53 (d, CO—$CH(C\underline{H}_3)$S), 8·83 (t, $C\underline{H}_3CH_2N$), 8·92 (d, CO—$CH(C\underline{H}_3)_2$, J = 7·1).

(d) 1-*Phenylbutan-2-one.* The reaction product was triturated with ether to remove high mol wt material, and the residual oil chromatographed on SiO_2. (benzene/hexane/ether 2:3:1) to give 1-*phenyl*-3-(N-*ethyl*-cis-3-*acrylamido*)*mercaptobutan*-2-*one* (46%) crystallizing from ether (at −78°) as colourless prisms m.p. 126–128°. (Found: C, 64·7; H, 6·9; N, 4·8; S, 11·4. $C_{15}H_{19}NO_2S$ requires: C, 65·0; H, 6·9; N, 5·0; S, 11·5%); IR: ν_{max} 3340, 1750, 1635 cm^{-1}; UV: λ_{max} 278 (br) (17300) mμ; NMR ($CDCl_3$): 2·74 (br, 5H), 3·32 (d, H)–4·15(d, H) (J = 10), 3·8 (br, NH), 6·05 (s, $OC\underline{H}_2CO$), 6·36 (q, CO—$C\underline{H}(CH_3)$—S—), 6·65 (m, CH_3—$C\underline{H}_2N$), 8·58 (d, CO—$CH(C\underline{H}_3)$—S) (J = 6·6), 8·85 (t, $C\underline{H}_3$—CH_2N).

(e) 2-*Phenylpentan-3-one.* The crude product was chromatographed (SiO_2, benzene/hexane/chloroform 3:2:1) to give a colourless oil. Crystallization from ether afforded 2-*phenyl*-4-(N-*ethyl*-cis-3-*acrylamido*) *mercaptopentan*-3-*one* as a granular solid. (Found: C, 65·6; H, 7·2; N, 4·7; S, 11·1. $C_{16}H_{21}NO_2S$ requires: C, 66·0; H, 7·3; N, 4·8; S, 11·0%); IR: ν_{max} ($CHCl_3$) 3350, 1705, 1640 cm^{-1}; NMR ($CDCl_3$): 2·71 (br, 5H), 3·19 (d, H)–4·07 (d, H) (J = 10), 3·9 (br, N$\underline{H}$), 5·65 (q, O—C$\underline{H}$Me—CO), 6·41 (q, CO—C$\underline{H}$Me—S), 6·65 (m, CH_3—$C\underline{H}_2N$), 8·65 (d, J = 7·1), 8·68 (d, J = 7·0), 8·85 (t, $C\underline{H}_3$—CH_2N), total integration 21H.

(f) *Phenylpropan-2-one.* The oily reaction product was triturated with hexane and filtered. The insoluble solid (35%) was washed with hot EtOH to give a *compound* m.p. 165–170, presumed to be 1-phenyl-1,3,3-tris(N-ethyl-cis-3-acrylamido)mercaptopropan-2-one. (Found: C, 55·1; H, 5·9; N, 8·0; S, 18·4. $C_{24}H_{31}ON_3O_4S_3$ requires: C, 55·3; H, 6·0; N, 8·1; S, 18·4%); IR: ν_{max} 3340 (s), 1685 (w), 1640 (s) cm^{-1}; UV: λ_{max} 278 (br) mμ. The filtrates were chromatographed (SiO_2, benzene/methylene chloride 7:3) to give 1-*phenyl*-3-(N-*ethyl*-cis-3-*acrylamido*)*mercaptopropan*-2-*one* (58%) as a colourless oil, showing only one component by TLC. Treatment with aqueous base gave only N-ethyl-3-isothiazolone and phenylpropan-2-one; IR: ν_{max} (film) 3340 (br, 1700, 1635 cm^{-1}; NMR ($CDCl_3$): 2·7 (br, s, 5H), 3·29 (d, H)–4·09 (d, H) (J = 10), 4·1, NH), 6·09 (s, $OC\underline{H}_2CO$), 6·61 (s, CO—$C\underline{H}_2$=S), 6·7 (m, CH_3—CH_3—$C\underline{H}_2N$), 8·87 (t, $C\underline{H}_3$—CH_2N).

Further elution yielded a vitreous solid; crystallization from dioxan/hexane gave 1-*phenyl*-3,3-*bis*(N-*ethyl*-cis-3-*acrylamido*)*mercaptopropan*-2-*one* as colourless prisms m.p. 156–160°. (Found: C, 60·3; H, 6·2; N, 7·3; S, 16·8. $C_{19}H_{24}N_2O_2S_2$ requires: C, 60·6; H, 6·4; N, 7·4; S, 17·0%); IR: ν_{max} 3340, 1705 (w), 1635 cm^{-1}; NMR ($CDCl_3$): 2·7 (br, s, 5H), 3·08 (d, H)–3·93 (d, H) (J = 10), 3·4 (br, N$\underline{H}$), 5·15 (s, CO—C$\underline{H}$—S_2), 6·04 (s, O—$C\underline{H}_2$—CO), 6·65 (m, 2x $C\underline{H}_2N$), 8·86 (t, 2x $C\underline{H}_3$—CH_2N).

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REFERENCES

1 W. D. Crow and N. J. Leonard, *J. Org. Chem.* **30**, 2660 (1964).
2 W. D. Crow and I. Gosney, *Aust. J. Chem.* **19**, 1693 (1966).
3 W. D. Crow and I. Gosney, *Ibid.*, **20**, 2729 (1967).
4 W. D. Crow and I. Gosney, *Ibid.*, **22**, 765 (1969).
5 A. W. K. Chan, W. D. Crow and I. Gosney, *Tetrahedron* **26**, 1493 (1970).
6 H. Zook and W. L. Rellahan, *J. Am. Chem. Soc.* **79**, 881 (1957).
7 J. M. Conia, *Rec. Chem. Progr.* **24**, 43 (1963).
8 H. O. House and V. Kramer, *J. Org. Chem.* **28**, 3362 (1963).
9 H. O. House and B. M. Trost, *Ibid.*, **30**, 1341, 2502 (1965).
10 H. O. House, W. L. Roelofs and B. M. Trost, *Ibid.*, **31**, 646 (1966).
11 H. D. Zook, W. L. Kelley and I. Y. Posey, *Ibid.*, **33**, 3477 (1968).
12 E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analaysis* Ch. VII. Interscience, N.Y. (1965).