122. *Small-ring Heterocyclic Compounds. Part III.*[1] *Reactions of Aromatic Glycidic Esters with Thiourea and Thioacetic Acid.*

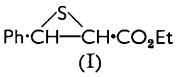
By T. C. Owen, C. L. Gladys, and L. Field.

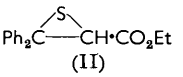
Conventional syntheses of episulphides from epoxides by means of thioacetic acid and thiourea have been applied to aromatic glycidic esters. The results suggest that the expected αβ-epithio-esters are unstable and lose sulphur, forming unsaturated esters. Condensation of a thioketone with ethyl chloroacetate after the manner of the Darzens condensation (which affords glycidic esters) apparently occurred, but only an unsaturated product was identified.

The route devised by L. N. Owen and his co-workers [2] for conversion of epoxides into episulphides by means of thioacetic acid seems most promising for the synthesis of epithio-esters such as (I) and (II). The epoxide ring of glycidic esters is, however, much more resistant to nucleophilic attack than is that of simple epoxides, and the aryl glycidic esters (III) and (IV) did not react with thioacetic acid in the absence of catalysts. Catalysis by mineral acids was ineffective, the glycidate (III) isomerising into ethyl phenylpyruvate

[1] Part II, *J.*, 1962, 501.
[2] Harding, Miles, and L. N. Owen, *Chem. and Ind.*, 1951, 887; Miles and L. N. Owen, *J.*, 1952, 817; Harding and L. N. Owen, *J.*, 1954, 1528.

(V) with sulphuric acid. Pyridine, either as solvent or in catalytic amounts, induced smooth addition at 25° (16 hr.), giving ethyl α-acetylthio-β-hydroxy-β-phenylpropionate (VI); prolonged reaction resulted in partial isomerisation of this hydroxy-ester (VI), probably into the β-acetoxy-α-mercapto-ester (VII) (cf. refs. 1 and 2). Acetylation of the hydroxy-ester gave ethyl β-acetoxy-α-acetylthio-β-phenylpropionate (VIII). As in the aliphatic series,[1] the assignment of the sulphur to the α-position is based on previous work [3,4] and confirmed by conversion of the diacetate (VIII) into the known α-mercaptocinnamic acid (IXa) (see below).


(I)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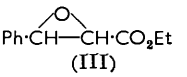
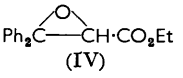

(III)


(IV)

$Ph \cdot CH_2 \cdot CO \cdot CO_2Et$
(V)

$Ph \cdot CH(OH) \cdot CH(SAc) \cdot CO_2Et$
(VI)

$Ph \cdot CH(OAc) \cdot CH(SH) \cdot CO_2Et$
(VII)

$Ph \cdot CH(OAc) \cdot CH(SAc) \cdot CO_2Et$
(VIII)

$Ph \cdot CH{:}C(SH) \cdot CO_2R$
(IXa, b)

$Ph \cdot CH(OH) \cdot CH(S \cdot CH_2Ph) \cdot CO_2Et$
(X)

$Ph \cdot CH(OH) \cdot CH(S \cdot C_6H_4 \cdot NH_2\text{-}o) \cdot CO_2Et$
(XI)

$Ph \cdot CH{:}CH \cdot CO_2R$
(XIIa, b)

$Ph_2C{:}CH \cdot CO_2R$
(XIIIa, b)

$Ph_2C(OH) \cdot CH(OH) \cdot CO_2Et$
(XIV)

$Ph_2C{:}S$
(XV)

a, R = H; b, R = Et.

Reaction of the glycidic ester (III) with thioacetic acid in boiling pyridine gave sulphur and ethyl cinnamate, probably *via* the epithioester (I) (see below). As evidence of the generality of such base-catalysed addition of thiols, the glycidic ester reacted smoothly with toluene-ω-thiol in the presence of pyridine, but not in its absence; reaction with *o*-aminobenzenethiol occurred without catalyst. [The products were not characterised but had infrared spectra consistent with structures (X and XI).] However a ββ-diarylglycidic ester (IV) was recovered unchanged after similar treatment with thioacetic acid and pyridine. This lack of reactivity, and the analogous behaviour of a ββ-dialkylglycidic ester,[1] indicate that such addition may be limited to glycidates having only one alkyl or aryl substituent in the β-position.

Earlier work [2,5] indicated the diacetate (VIII) to be a more promising starting material than the monoacetate (VI) for conversion into the epithioester (I) by treatment with alkali. Hot alkaline saponification of the diacetate gave unexpected results, however. Four equivalents of alkali were consumed rather than the three equivalents expected for saponification of the three ester functions. Acidification of the hydrolysate liberated hydrogen sulphide, indicating that at least part of the fourth equivalent had reacted with expelled sulphur (cf. ref. 6). With cold dilute alkali, the diacetate gave none of the expected epithioester but, instead, a mixture of approximately equal proportions of ethyl cinnamate (XIIb) and ethyl α-mercaptocinnamate (IXb), both of which, when an excess of alkali was used, were hydrolysed in part to the corresponding acids (XIIa and IXa). The proportion of cinnamate to α-mercaptocinnamate was somewhat dependent on the mode and speed of addition of the reactants; very slow addition of alkali to the diacetate favoured the cinnamate while the reverse addition to excess of alkali favoured the mercaptocinnamate (see Table).

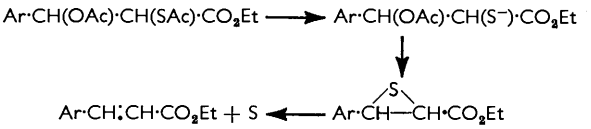
[3] Durden, Stansbury, and Catlette, *J. Amer. Chem. Soc.*, 1959, **81**, 1943.
[4] Culvenor, Davies, and Heath, *J.*, 1949, 278, 282.
[5] Goodman, Benitez, and Baker, *J. Amer. Chem. Soc.*, 1958, **80**, 1680.
[6] Toland, *J. Amer. Chem. Soc.*, 1960, **82**, 1911.

Reaction of diacetate (VIII) with dilute alcoholic alkali.

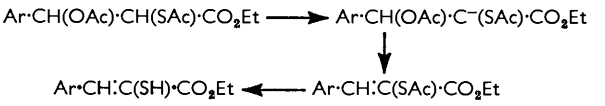
Equiv. of OH^-	Reaction time	Mode of addition	Yield (%) (IX) a & b	(XII) a & b	(IX) a	(IX) b	(XII) a	(XII) b
1·13	2 min.	Alkali added quickly to (VIII) in EtOH	48	24				
1·13	22 min.		48	31				
1·13 for 90 min. followed by 2·5 for 10 min.			53	47				
2	45 min.		45	38				
5	15 min.		43	34				
5	45 min.		43	34				
5	50 min.	(VIII) in EtOH added to OH^- in EtOH			6 *	41 *	25*	9 *
2	18·5 hr.	OH^- added very slowly to (VIII)	31	55				

* Actually isolated; other values estimated spectroscopically, cinnamic acid and its ester absorbing maximally at 2750—2780 Å with negligible absorption at 3100 Å, and α-mercaptocinnamic acid and its ester absorbing maximally at the latter wavelength.

The yields tabulated account for 70—100% of the diacetate used. It therefore seems unlikely that the epithioester (I) can be obtained by this approach. The products obtained probably arise by simultaneous reaction of the diacetate with base in two ways: (*a*) Formation and rapid spontaneous desulphurisation of the epithioester (I) gives cinnamate; the sulphur produced reacts with alkali to give sulphide, etc.:



(*b*) The mercaptocinnamate (IX) is formed by abstraction of the activated α-hydrogen atom, followed by electron redistribution with ejection of acetate ion. Hydrolysis of the *S*-acetyl group, probably after formation of the double bond, completes the formation of the enethiol (IX):



The dependence of the product ratio on the reaction conditions is consistent with the above mechanisms, as is the formation of cinnamate in high yield when the glycidate (III) is heated with thioacetic acid and pyridine. Similarly, reaction of this glycidate with alcoholic potassium thioacetate [excess, in an attempt to trap the epithioester (I) as the product of addition of thioacetate to the episulphide ring] gave cinnamate alone (80%), no mercaptocinnamate being detected. Culvenor *et al.*[4] have shown, and we have confirmed, that cinnamate, sulphur, and urea are obtained in high yield on reaction of this glycidate with alcoholic thiourea; the epithioester (I) presumably is an intermediate. No episulphide polymers were observed to result from these reactions, whereas in the aliphatic series [1] the ester–alkali reaction produced mercaptoacrylates and polymers but no simple acrylates.

The fact that many simple epoxides give episulphides by this route,[2,5] while only polymerised or desulphurised compounds are produced from glycidic esters, suggests that both aliphatic and aromatic epithioesters are unstable and, although probably produced, decompose spontaneously.

Reactions of the diacetate (VIII) with base in the presence of nucleophilic reagents in attempts to trap the intermediate epithioester by addition of the nucleophile to the episulphide ring were unsuccessful. Reaction with thioacetate and an excess of alkali

gave results similar to those obtained in the absence of thioacetate; with aqueous ammonia, liquid ammonia, and sodamide in liquid ammonia, the diacetate gave no products soluble in dilute acid such as should have resulted from the desired trapping.

Ethyl αβ-epoxy-ββ-diphenylpropionate (IV) did not react with thioacetic acid even in the presence of pyridine. Reaction occurred with thiourea in ethanol only during prolonged heating under reflux and gave a low yield of ethyl ββ-diphenylacrylate (XIIIb). This glycidate (IV) was also treated with thiourea and sulphuric acid (cf. ref. **3**) and gave ethyl αβ-dihydroxy-ββ-diphenylpropionate (XIV) (low yield). This behaviour is analogous to that of analogous aliphatic glycidates (cf. refs. **1** and **3**). Evidently the diphenylglycidate undergoes nucleophilic addition only under extreme conditions which force a variety of side reactions.

In an alternative approach to an αβ-epithioester, analogous to the Darzens reaction,[7,8] condensation of thiobenzophenone (XV) with ethyl chloroacetate was attempted. The starting materials were consumed but no pure products could be separated by distillation or by chromatography. However, saponification of the products gave ββ-diphenylacrylic acid (XIIIa) (30—35%), indicating that the carbon skeleton of the epithioester (II) had been produced. The possibility that this skeleton resulted from conversion of thiobenzophenone into benzophenone followed by conventional Darzens condensation of this was eliminated as the glycidate (IV) did not give the acid (XIIIa) on saponification. Presumably, therefore, the desired epithioester was produced but again desulphurised spontaneously. Attempts to trap the epithioester as an aminothiol by treatment of the reaction products with aniline (cf. ref. **9**) were unpromising. These results suggest that the epithioester (II), like (I), is unstable.

Experimental

Ultraviolet spectra were determined by using a Cary model **14**, and infrared spectra by using a Perkin-Elmer model **137** Infracord spectrophotometer. Fractional distillations were carried out through Nester and Faust spinning-band columns, 8″, 18″, and 36″ long, with estimated efficiences of **6**, **18**, and **40** theoretical plates, subsequently referred to as columns A, B, and C, respectively.

Reaction of Ethyl αβ-Epoxy-β-phenylpropionate (III) *with Thioacetic Acid.*—(a) *Without a catalyst.* An equimolar mixture of the reactants was kept at *ca.* 25° for 3 days. Its appearance and infrared spectrum were unchanged and titration with sodium hydroxide and with iodine showed that none of the thioacetic acid had been consumed. Heating at 100° also effected no change.

(b) *With sulphuric acid.* A mixture of the glycidate (20 g., 0·104 mole), thioacetic acid (8·5 g., 0·112 mole), and sulphuric acid (5 drops) was kept at 100° for 5 hr. It then gave a strong enol test with ferric chloride and its infrared spectrum showed development of a hydroxyl group and disappearance of the epoxide ring. Titration showed that 90% of the thioacetic acid was unconsumed. A portion (0·5 g.) of the mixture gave ethyl phenylpyruvate 2,4-dinitrophenylhydrazone (0·15 g., 22%), m. p. 125—128°; recrystallised from ethanol this had m. p. 133—135° (lit.,[10] m. p. 131—132°).

(c) *In boiling pyridine.* The ester (III) (5 g., 0·026 mole) and thioacetic acid (2·2 g., 0·029 mole) were heated in pyridine (10 ml.) under reflux for 2 hr. Isolation of product in ether gave an oil (6·2 g.), part (3 g.) of which was distilled, giving ethyl cinnamate (1·64 g., 74%), b. p. 101°/0·5 mm., n_D^{27} 1·5554 (lit., b. p. 273°, n_D^{20} 1·560), and sulphur.

(d) *In cold pyridine; preparation of ethyl α-acetylthio-β-hydroxy-β-phenylpropionate* (VI) *and ethyl β-acetoxy-α-acetylthio-β-phenylpropionate* (VIII). A solution of the glycidate (III) (19·2 g., 0·1 mole) and thioacetic acid (8·0 g., 0·105 mole) in pyridine (50 ml.) was kept at *ca.* 25° for 16 hr. and then poured into an ether–water mixture. The ether layer was extracted successively with aqueous potassium hydrogen carbonate and three portions of aqueous tartaric acid.

[7] Blicke and Faust, *J. Amer. Chem. Soc.*, 1954, **76**, 3156.
[8] Johnson, Belew, Chinn, and Hunt, *J. Amer. Chem. Soc.*, 1953, **75**, 4995.
[9] Martynov and Ol'man, *J. Gen. Chem.* (*U.S.S.R.*), 1957, **27**, 1881; 1958, **28**, 592.
[10] House, Blaker, and Madden, *J. Amer. Chem. Soc.*, 1958, **80**, 6386.

Evaporation of the dried ether layer gave an oil (25·5 g.) whose infrared spectrum showed OH and C=O absorptions and was consistent with ethyl α-acetylthio-β-hydroxy-β-phenylpropionate (VI). A portion (2 g.) of this oil was distilled (column A) unchanged (infrared), having b. p. 128°/0·2 mm., n_D^{25} 1·5289. Reaction proceeded equally satisfactorily in the presence of a catalytic amount of pyridine (*ca.* 0·1 mole per mole of each reactant). The crude hydroxy-ester (VI) (21·0 g.) was treated with acetic anhydride (8·8 g.) and pyridine (40 ml.) for 24 hr. at *ca.* 25°. The excess of anhydride was then decomposed by water (10 ml.), and the product isolated in ether and distilled (column A), giving *ethyl β-acetoxy-α-acetylthio-β-phenylpropionate* (VIII) (9·9 g., 39% from III), b. p. 131°/0·1 mm., n_D^{25} 1·5200, a pale yellow viscous oil (Found: C, 58·0; H, 6·1; S, 10·2, 10·5. $C_{15}H_{18}O_5S$ requires C, 58·0; H, 5·9; S, 10·3%).

Reactions of Diacetate (VIII) *with Alkali.*—(a) *Saponification.* The diacetate (0·2839 g.) was heated under reflux (3 hr.) with 0·618M-alcoholic potassium hydroxide (15·0 ml.). Titration with 0·0949M-hydrochloric acid (58·8 ml.) showed consumption of 4·05 equiv. of alkali per mole of the diacetate. Hydrogen sulphide was liberated on further acidification.

(b) *With cold dilute alkali.* The following experiment is typical: The diacetate (0·3942 g., 0·00127 mole) in 95% ethanol (5 ml.) was added to stirred 0·618M-alcoholic potassium hydroxide (10 ml.). After 1 hr., the deep yellow solution was poured into ether and water. Evaporation of the dried ether layer gave ethyl cinnamate (0·021 g., 9%), estimated to be 98% pure (ultraviolet absorption), identified by its ultraviolet spectrum and by conversion into cinnamamide (0·008 g., 4% overall), m. p. 145°. The aqueous layer was acidified and extracted with ether, and the dried ether layer evaporated, giving a sticky solid (0·2167 g.), a portion (0·2101 g.) of which was dissolved in ether and extracted with aqueous potassium hydrogen carbonate. Evaporation of the dried ether layer gave *ethyl α-mercaptocinnamate*, a pale yellow oil (0·1079 g., *ca.* 41%, estimated 97% pure from its ultraviolet spectrum, the molar extinction coefficient being assumed to be similar to that of the free acid). Its ultraviolet spectrum was very similar to that of the free acid,[11] and its infrared spectrum showed SH and conjugated C=C–C=O stretching frequencies. Saponification gave α-mercaptocinnamic acid (0·060 g., 26% overall), m. p. 128—132° (lit.,[11] m. p. 133—134°), the infrared and ultraviolet spectra being identical with those of an authentic specimen. Finally the aqueous potassium hydrogen carbonate layer, acidified and extracted with ether, gave crystals estimated (ultraviolet spectrum) to contain cinnamic acid (0·0467 g., 25% overall) and α-mercaptocinnamic acid (0·0137 g., 6% overall); cinnamic acid (0·02 g., 11% overall) was isolated by repeated crystallisation of this solid.

(c) *With alkali and potassium thioacetate.* To a solution of the diacetate (0·035 g., $1·13 \times 10^{-4}$ mole) in ethanol was added a solution of thioacetic acid (5 ml.; 0·05M) and potassium hydroxide (7·8 ml.; 0·0631M) in ethanol. Examination of acidified aliquot portions (ultraviolet) showed similar results to others obtained in the absence of the thioacetic acid.

(d) *With ammonia.* A solution of the diacetate (0·0142 g., $4·6 \times 10^{-5}$ mole) and aqueous ammonia (5 ml.; 0·0626M) in ethanol was heated under reflux for 4 hr. Spectroscopic examination then showed the absence of cinnamic and α-mercaptocinnamic acid derivatives. Extraction of an ether solution of the products with dilute hydrochloric acid separated no basic product. Similarly, no basic product was obtained after reaction of the diacetate with liquid ammonia or with sodamide in liquid ammonia.

Reaction of Ethyl αβ-Epoxy-β-phenylpropionate with Potassium Thioacetate.—A solution of thioacetic acid (0·4 g., 0·0052 mole) in ethanol (5 ml.) was neutralised (phenolphthalein) with 0·618M-alcoholic potassium hydroxide. A solution of the glycidic ester (0·48 g., 0·0025 mole) in ethanol (5 ml.) was added. The solution developed a deep wine-red colour and after 4 hr. was diluted to 25 ml. An aliquot part, acidified with hydrochloric acid, was examined spectroscopically; its ultraviolet spectrum was consistent with the presence of ethyl cinnamate (80% yield) as the sole product having absorption in the range 2600—3600 Å.

Reactions of Ethyl αβ-Epoxy-ββ-diphenylpropionate.—(a) *With thioacetic acid.* A solution of the glycidate (IV) (2·0 g., 0·0075 mole) and thioacetic acid (0·62 g., 0·00815 mole) in pyridine (3 ml.) was kept at *ca.* 25° for 24 hr. The infrared spectrum of the mixture was unchanged and the glycidate was recovered almost quantitatively.

(b) *With thiourea in ethanol.* Thiourea (1·40 g., 0·0184 mole) and the glycidate (5·0 g., 0·0186 mole) in ethanol (20 ml.), when heated under reflux (100 hr.) and subsequently cooled, deposited crystals, part of which (presumably urea) dissolved in water leaving a residue of sulphur, m. p. 119°. Evaporation of the supernate gave a yellow oil (infrared spectrum showed

[11] Campaigne and Cline, *J. Org. Chem.*, 1956, **21**, 32.

conjugated C=C–C=O absorption), saponified to ββ-diphenylacrylic acid (XIIIa) (60% from the yellow oil), infrared spectrum identified with that of an authentic specimen [m. p. 158—161°; prepared (low yield) by saponification and decarboxylation of ethyl diphenylmethylidenecyanoacetate kindly provided by Professor F. Prout, DePaul University, Chicago, U.S.A.].

(c) *With thiourea and dilute sulphuric acid.* Reaction of thiourea (1·42 g., 0·0186 mole) in dilute sulphuric acid (0·0186 mole) with the glycidate (5·0 g., 0·0186 mole) according to the procedure of Durden *et al.*[3] but with high-speed stirring and addition of detergent (Dreft; 0·01 g.) gave an oil (5·33 g.) from which was isolated ethyl αβ-dihydroxy-ββ-diphenylpropionate (XIV) (0·71 g., 13%), m. p. 125·5—129°. The same compound was isolated from a sample of the glycidate which had been stored under hot, humid conditions for several months; recrystallised from aqueous ethanol, it had m. p. 131—133° (Found: C, 71·3; H, 6·3. $C_{17}H_{18}O_4$ requires C, 71·4; H, 6·3%), with an infrared spectrum showing strong OH and C=O stretching frequencies.

Reaction of Thiobenzophenone (XV) *with Ethyl Chloroacetate.*—Thiobenzophenone, prepared by the procedure of Gofton and Braude,[12] was reasonably stable to potassium t-butoxide in t-butyl alcohol, its characteristic blue colour persisting for 15—20 min. at *ca.* 25°. Ethyl chloroacetate decomposed in a few seconds under similar conditions, as used in the Darzens condensation.[8] Potassium t-butoxide (0·043 mole; from potassium, 1·68 g.) in a mixture of t-butyl alcohol (40 ml.) and dimethylformamide (25 ml.) was added to a mixture of the thioketone (5·94 g., 0·03 mole) and ethyl chloroacetate (5·27 g., 0·043 mole) at 10—15°. Treatment of a portion of the organic product with aniline gave a solid product which contained nitrogen but no sulphur. Saponification of a further portion gave ββ-diphenylacrylic acid (32% overall), m. p. 161—162° (lit., m. p. 162°), mixed m. p. 159—162° [Found: C, 80·6; H, 5·5%; neut. equiv. (crude product), 219. Calc. for $C_{15}H_{12}O_2$: C, 80·3; H, 5·4%; neut. equiv., 224].

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[12] Gofton and Braude, *Org. Synth.*, 1955, **35**, 97.