541. *Reactions of Ethylene Oxides. Part III. Syntheses of Some Heterocyclic Compounds from Glycidic Esters and Related Compounds.*

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A novel synthesis of 2 amino-4-keto-thiazolines substituted in the 5-position is effected by reaction of thiourea with glycidic esters. After the initial opening of the ethylene oxide ring, cyclisation is effected by loss of the alkoxy-group of the ester and not by loss of water; *e.g.*, methyl dimethylglycidate yields 2-*amino*-4-*keto*-5-(1-*hydroxy*iso*propyl*)*thiazoline* (IV), readily dehydrated to the 5-*iso*propylidene derivative (V). The ethylene sulphide corresponding to the glycidic ester is not formed, but when the temperature of the reaction is too high, the corresponding unsaturated ester and sulphur are produced. The thiazolines of type (V) rapidly form characteristic derivatives with primary and secondary aromatic amines with loss of ammonia. 1-Benzoyl-2-phenylethylene oxide reacts with thiourea to give a compound analogous to (IV), *i.e.*, 2-*amino*-4-*phenyl*-5-(α-*hydroxybenzyl*)*thiazole* (XV; R = Ph). *o*-Phenylenediamine and ethyl phenylglycidate form *ethyl* α-(*o*-*aminoanilino*)-β-*hydroxy*-β-*phenylpropionate* (XVI), which is converted into 2-*keto*-3-(α-*hydroxybenzyl*)-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (XVII).

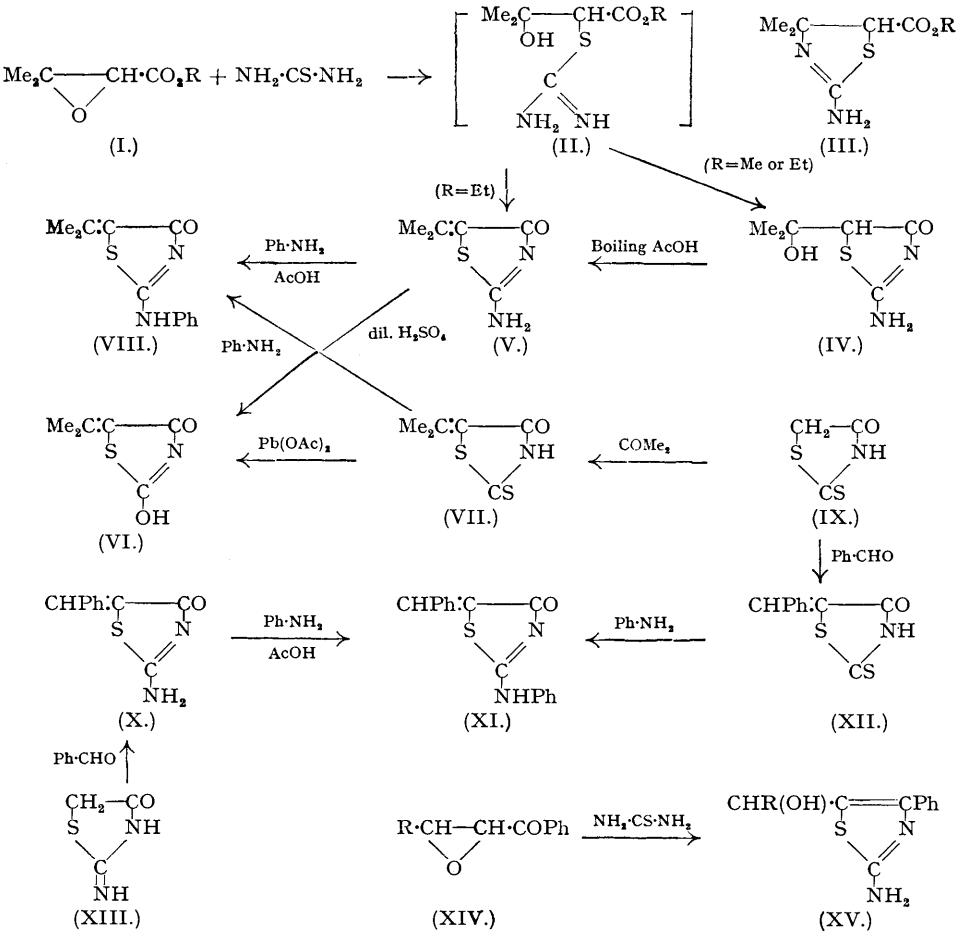
The reaction of thiourea with glycidic esters might be expected (Culvenor, Davies, and Pausacker, *J.*, 1946, 1050) to produce ethylene sulphide derivatives analogous to the original glycidic ester. Although this has not been realised, the decomposition products of such an ethylene sulphide, *viz.*, the corresponding unsaturated ester and sulphur, are readily formed as well as urea. However, when suitably low temperatures are used, *methyl dimethylglycidate* (I; R = Me) and thiourea in aqueous alcohol form a thiazoline derivative. The probable intermediate product (II; R = Me) could theoretically cyclise either by loss of water to form the thiazoline ester (III), or by loss of alcohol to give 2-*amino*-4-*keto*-5-(1-*hydroxy*iso*propyl*)-*thiazoline* (IV), which is the product isolated. This water-soluble compound readily gives acetone by alkaline hydrolysis, and is easily dehydrated by boiling acetic acid to form 2-*amino*-4-*keto*-5-iso*propylidenethiazoline* (V), m. p. 285°, which is also formed, along with (IV), when ethyl dimethylglycidate (I; R = Et) is condensed with thiourea.

The determination of the constitution of (V) presented difficulties. Its solubility is too low to admit of a satisfactory molecular-weight determination, and direct unambigous methods of synthesis are ineffective. Its structure, which may have the 2-imino-4-hydroxy- and other tautomeric forms, has been established as follows. It does not contain an alkoxy-group, and the sulphur atom must be in the ring, since it cannot be removed by the usual desulphurising agents such as aqueous sodium plumbite. The compound, m. p. 285°, gives acetone with aqueous permanganate, and it is amphoteric, though insoluble in weak bases such as aqueous sodium hydrogen carbonate or ammonia. Since ψ-thiohydantoins and 4-hydroxythiazoles are soluble in alkali (Renard and Chabrier, *Compt. rend.*, 1948, **226**, 582), the weakly acidic nature of (V) may be due to its tautomerism into a 4-hydroxy-derivative. This is probable, since the imino-form of (V) has the ·CO·NH·C(:NH)· group. (V) is a sufficiently strong base to form a methosulphate and a *picrate*, but 2-*acetamido*- and 2-*phenylureido*-4-*keto*-5-iso*propylidenethiazoline* are without basic properties. Acid hydrolysis of (V) converts it into 2-*hydroxy*-4-*keto*-5-iso*propylidenethiazoline* (VI), identical with the desulphurisation product of 5-iso*propylidenerhodanine* (VII), made by condensation of acetone with rhodanine (IX). This condensation of rhodanine with aliphatic ketones is apparently novel. Moreover, the action of anilide on (V) and (VII) gives the same product, *viz.*, 2-*anilino*-4-*keto*-5-iso*propylidenethiazoline* (VIII). Attention is directed to the convenience of the rapid reaction in glacial acetic acid of primary and secondary aromatic amines with derivatives of ψ-thiohydantoin (XIII), whereby loss of ammonia affords the substituted 2-aminothiazoline derivative. The great activity of the methylene group in rhodanine makes it generally more useful than ψ-thiohydantoin for the production of thiazolines substituted in the 5-position.

The condensation of ethyl phenylglycidate and thiourea at room temperature has been shown (Culvenor, Davies, and Heath, this vol., p. 278) to yield only ethyl cinnamate, sulphur, and urea, but it is now found that below 0° it gives a 17% yield of 2-amino-4-keto-5-benzylidenethiazoline (X), identical with the condensation product from benzaldehyde and ψ-thiohydantoin (Stieger, *Monatsh.*, 1914, **35**, 144). It is converted by aniline into 2-anilino-4-keto-5 benzylidenethiazoline, which is similarly obtained from 5-benzylidenerhodanine (XII) and aniline.

1-Benzoyl-2-phenylethylene oxide (XIV; R = Ph) reacts with thiourea to form 2-amino-4-phenyl-5-(α-hydroxybenzyl)thiazole (XV; R = Ph), which is converted by fission with alkali

into benzaldehyde and 2-amino-4-phenylthiazole, already made from thiourea and ω-bromoacetophenone (Traumann, *Annalen*, 1888, **249**, 38). Similarly, the nitrothiazolidine, m. p. 176°,

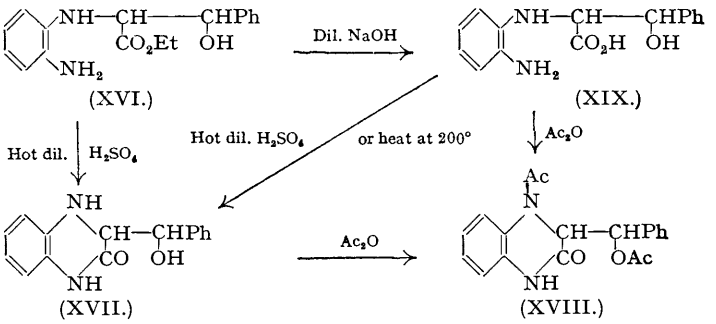


formed in very small yield from 1-benzoyl-2-(*m*-nitrophenyl)ethylene oxide (XIV; R = *m*-$NO_2 \cdot C_6H_4$) and thiourea (Bodforss, *Ber.*, 1918, **51**, 212; Culvenor, Davies, and Heath, *loc. cit.*), is probably not one of the two 2-imino-benzoyl-*m*-nitrophenylthiazolidines suggested by Bodforss but 2-amino-4-phenyl-5-(α-hydroxy-*m*-nitrobenzyl)thiazole (XV; R = *m*-$NO_2 \cdot C_6H_4$). It is formed in such minute amount that this deduction has not been experimentally verified by fission with alkali (p. 2576).

Reaction of Ethyl Phenylglycidate with o-*Phenylenediamine.*—It has been shown by Fourneau and Billeter (*Bull. Soc. chim.*, 1940, **7**, 593) that primary aromatic amines open the ethylene oxide ring in ethyl phenylglycidate to form derivatives of α-amino-β-hydroxypropionic acid. It is now found that *o*-phenylenediamine reacts in the same way to form *ethyl α-(o-aminoanilino)-β-hydroxy-β-phenylpropionate* (XVI), the direction of the ring opening being apparent from the loss of benzaldehyde when (XVI) is heated with concentrated alkali. The structure of the ester, which forms a *triacetyl* derivative in which the acetyl groups may be attached to the two nitrogen atoms and the β-oxygen atom, is shown by its conversion, and that of the corresponding *acid*, by heat into *2-keto-3-(α-hydroxybenzyl)-1 : 2 : 3 : 4-tetrahydroquinoxaline* (XVII). This forms a *diacetyl* derivative in which the two acetyl groups may have replaced a hydrogen atom on the hydroxyl group and on the 4-nitrogen atom, as shown in (XVIII). The formulation is in agreement with the fact (Motylewski, *Ber.*, 1908, **41**, 801) that the parent 2-keto-1 : 2 : 3 : 4-tetrahydroquinoxaline is substituted by only one acetyl group, which is probably in position 4.

It is seen from the present investigation that glycidic esters condense with compounds of

dual function to give rise to various heterocyclic compounds. Derivatives of thiazole are formed from thiourea, of quinoxaline from *o*-phenylenediamine, and of benzthiazine from



o-aminothiophenol (Culvenor, Davies, and Heath, *loc. cit.*, p. 279). In all these cases, cyclisation is effected by loss of the alkoxy-group of the ester, and the newly formed hydroxy-group takes no part in the ring closure; similarly, with 1-benzoyl-2-phenylethylene oxide (XIV; R = Ph), where the oxygen of the carbonyl group, and not the ring oxygen, is eliminated. When the side chain contains a hydroxyl group [*e.g.*, in (IV), (XV), or (XIX)], it readily suffers fission with aqueous alkali to form the corresponding carbonyl compound. This mode of hydrolysis is in contrast to that of the 5-arylidenerhodanine derivatives; *e.g.*, (XII) reacts with alkali forming α-mercaptocinnamic acid [CHPh:C(SH)·CO_2H] (Gränacher, *Helv. Chim. Acta*, 1922, **5**, 616). It is noteworthy that the conjugated chain CHPh:Ċ·CO·, as in (X) and (XII), does not add water to form the CHPh(OH)·ĊH·CO· derivative, since attempted hydrolysis with aqueous alkali or acid fails to give benzaldehyde. Aqueous potassium permanganate, however, produces benzaldehyde from such compounds as (X) and (XII).

Experimental.

Methyl dimethylglycidate (I; R = Me), b. p. 66—68°/20 mm., n_D^{23} 1·4180, was obtained in 40% yield by gradually adding sodium methoxide solution (from 23 g. of sodium in 200 ml. of methanol) to molar quantities of acetone and methyl chloroacetate, the temperature being kept below 5°. The solution was then kept for two days at room temperature, heated under reflux for one hour, neutralised with acetic acid, diluted with water, and extracted with benzene. The benzene extract was dried (Na_2SO_4) and fractionated (Found: OMe, 24·6. $C_7H_{10}O_3$ requires OMe, 23·9%). The other main fraction consisted of methyl methoxyacetate, b. p. 42·5—44°/26 mm., n_D^{22} 1·4000. Ethyl dimethylglycidate, b. p. 69—74°/12 mm., n_D^{18} 1·4202, was obtained similarly in 50% yield.

Reaction of Thiourea with Glycidic Esters.—A solution of methyl dimethylglycidate (2 g.) and thiourea (2 g.) in methanol (40 ml.) was kept for two weeks at 30°; when filtered from an insoluble black solid and then concentrated, it gave colourless needles, readily soluble in water, alcohol, and hot acetone, but sparingly soluble in cold acetone, from which 2-*amino*-4-*keto*-5-(1-*hydroxy*iso*propyl*)*thiazoline* (IV) separated in plates which charred at about 200° (Found: C, 41·6; H, 5·81; N, 16·3; O, 18·3. $C_6H_{10}O_2N_2S$ requires C, 41·4; H, 5·76; N, 16·1; O, 18·4%). With boiling 10% sodium hydroxide solution it gave acetone, and when heated under reflux with glacial acetic acid for one hour it was quantitatively converted into the 5-*iso*propylidene derivative (V). With phenyl *iso*cyanate in acetone solution, it formed carbanilide and the same phenylureido-derivative as that from (V).

Sulphur was formed in yields up to 0·78 g. when thiourea (7 g.) was heated under reflux with ethyl dimethylglycidate (7 g.) in 96% ethanol (50 ml.) for various periods up to 16 hours.

2-*Amino*-4-*keto*-5-iso*propylidenethiazoline* (V) was obtained in 92% yield when the above reactants were allowed to stand at 35° for 10 weeks, the solution filtered and evaporated to dryness, and the resulting brown solid boiled with glacial acetic acid (50 ml.), whereupon the initially clear solution rapidly became semi-solid through the deposition of crystalline (V) (10·2 g.). Small amounts of *ψ*-thiohydantoin and sulphur were also isolated. (V) was insoluble in water, sparingly soluble in organic solvents, and separated from a large volume of glacial acetic acid or ethanol in plates which at the m. p. (285°, decomp.) gave a garlic-like odour (Found: C, 46·15; H, 5·2. $C_6H_8ON_2S$ requires C, 46·2; H, 5·1%). It was insoluble in aqueous ammonia, and was precipitated by carbon dioxide from its solution in sodium hydroxide. It reacted with aqueous potassium permanganate to form acetone (identified as the *p*-nitrophenylhydrazone). Ammonia was slowly evolved when solutions of (V) in alkali or mineral acid were boiled. It was converted by heating under reflux for 8 hours with 14N-sulphuric acid into 2 : 4-*diketo*-5-iso*propylidenethiazolidine* (VI), needles, m. p. 166°, readily soluble in hot, sparingly soluble in cold water (Found: C, 45·9; H, 4·67. $C_6H_7O_2NS$ requires C, 45·9; H, 4·46%). This was also formed from ethyl dimethylglycidate and aqueous alcoholic thiourea in the presence of hydrochloric acid at 36° (Found: N, 9·10. $C_6H_7O_2NS$ requires N, 8·92%). The *monoacetyl* derivative of (V), needles, m. p. 285° (decomp.), from ethanol, was formed by heating it under reflux with excess of acetic acid and anhydride for 3 hours (Found: C, 49·0; H, 5·51; N, 14·3; S, 16·6. $C_8H_{10}O_2N_2S$ requires C, 48·5; H, 5·0; N, 14·1; S, 16·2%). The *picrate* of (V), yellow needles, m. p. 220°

(decomp.), from ethanol or acetic acid, was formed by admixture of the components in glacial acetic acid (Found : N, 18·0. $C_{12}H_{11}O_8N_5S$ requires N, 18·2%).

2-*Phenylureido*-4-*keto*-5-iso*propylidenethiazoline*, pale yellow rosettes, m. p. 273° (decomp.), was obtained by heating a mixture of (V) (0·25 g.), phenyl *iso*cyanate (1·25 ml.), and xylene (4 ml.) in a sealed tube at 140—150° for 2 hours, and was recrystallised from a large volume of glacial acetic acid (Found : C, 56·2; H, 4·58. $C_{13}H_{13}O_2N_3S$ requires C, 56·8; H, 4·74%); some carbanilide (m. p. 237°) was also isolated from this reaction. This phenylureido-derivative was insoluble in mineral acid, and did not form a picrate, but dissolved readily in warm 10% sodium hydroxide solution.

The aromatic amine derivatives were made by heating both (IV) and (V) under reflux for 30 minutes with a small excess of amine in glacial acetic acid, followed by crystallisation of the product from ethanol. 2-*Anilino*-4 *keto*-5-iso*propylidenethiazoline* (VIII) forms small needles, m. p. 236—237° (Found : N, 12·1; S, 14·3. $C_{12}H_{12}ON_2S$ requires N, 12·0; S, 13·8%); 2-(p-*chloroanilino*)-4-*keto*-5-iso*propylidenethiazoline* forms plates, m. p. 233—234° (Found : C, 54·15; H, 4·23; Cl, 13·5. $C_{12}H_{11}ON_2SCl$ requires C, 54·1; H, 4·13; Cl, 13·3%); the 2-(p-*methoxyanilino*)-analogue forms faintly yellow needles, m. p. 210—211° (Found : OMe, 12·0. $C_{13}H_{14}O_2N_2S$ requires OMe, 11·8%); and the 2-N-*methylanilino*-compound forms pale yellow needles, m. p. 171—172° (Found : N, 11·3. $C_{13}H_{14}ON_2S$ requires N, 11·4%). The primary amine derivatives were soluble in warm 10% sodium hydroxide solution, but that from the seconary amine was insoluble.

5-iso*Propylidenerhodanine* (VII).—Rhodanine (2 g.), acetone (5 ml.), and anhydrous sodium acetate (1 g.) were dissolved in the minimum amount of glacial acetic acid and heated under reflux for 4 hours beneath an efficient condenser. The *rhodanine* crystallised from alcohol in orange yellow needles, m. p. 197—198° (Found : N, 8·29; S, 37·3. $C_6H_7ONS_2$ requires N, 8·10; S, 37·0%). When (VII) (0·4 g.) was heated for one hour at 160—170° with aniline (1 ml.), hydrogen sulphide was evolved and the product crystallised from alcohol in needles, m. p. 236—237° undepressed by the aniline derivative (VIII) obtained from (V).

Although many different experimental conditions were tried, a similar condensation between acetone and ψ-thiohydantoin (XIII) to yield (V) could not be effected.

The rhodanine (VII) (0·5 g.) was heated under reflux with lead acetate (5 g.) in 50% alcohol, and the lead sulphide formed was repeatedly filtered off. After 48 hours the excess of lead salts was removed by precipitation with hydrogen sulphide, and the filtrate on evaporation yielded (VI), which recrystallised from water as needles, m. p. 165—166°.

Reaction of Thiourea with Ethyl Phenylglycidate.—Ethyl phenylglycidate (2 g.) and thiourea (0·8 g.) were dissolved in ethanol (90 ml.) and kept at −3° to 0° for 7 weeks. Sulphur, m. p. 122—126° (60% yield), was collected, the filtrate concentrated almost to dryness, the ethyl cinnamate extracted with ether, the residue digested with warm 10% sodium hydroxide solution, and the filtered alkaline extract neutralised with acid, yielding 2-amino-4-keto-5-benzylidenethiazoline (X) (0·35 g., 17%). This was soluble in mineral acid and alkali, and recrystallised from acetic acid in long yellow needles, m. p. 294° (decomp.) (Found : N, 13·56; S, 16·0. Calc. for $C_{10}H_8ON_2S$: N, 13·7; S, 15·7%); and in exactly the same manner as (V), it formed two derivatives, *viz.*, a *picrate*, m. p. 232°, yellow needles from acetic acid (Found : N, 16·2. $C_{16}H_{11}O_8N_5S$ requires N, 16·2%), and an aniline derivative (XI), m. p. 256°, yellow micro-rosettes from acetic acid (Found : N, 9·8. Calc. for $C_{16}H_{12}ON_2S$: N, 10·0%), shown by mixed m. p. to be identical with 2-anilino-4-keto-5-benzylidenethiazoline, made by the action of aniline on the condensation product (XII) of rhodanine and benzaldehyde (Gränacher, *Helv. Chim. Acta*, 1920, **3**, 152).

2-*Amino*-4-*phenyl*-5-(α-*hydroxybenzyl*)*thiazole* (XV; R = Ph).—1-Benzoyl-2-phenylethylene oxide (5 g.) and thiourea (10 g.) were heated under reflux in alcohol (75 ml.) for 7 minutes, the solution poured into water, and the non-viscous portion (1·3 g.; 20% yield) of the product separated by decantation. Recrystallisation from alcohol gave the *thiazole* (XV) in glistening plates, m. p. 207° (Found : C, 67·9; H, 5·1; N, 10·1. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 5·0; N, 9·9%). It was converted by boiling with 10% sodium hydroxide solution for a few minutes into benzaldehyde and 2-amino-4-phenylthiazole, m. p. 147°, identical (mixed m. p.) with a specimen made from ω-bromoacetophenone and thiourea (Traumann, *loc. cit.*). This aminothiazole was analogous to the minor product, m. p. 176°, from benzoyl-*m*-nitrophenylethylene oxide and thiourea, since both gave a purple colour when a solution in acetic acid was treated with a trace of sodium nitrite. The compound, m. p. 176°, very soluble in alcohol, insoluble in water, was probably (XV; R = *m*-$NO_2{\cdot}C_6H_4$).

Condensation of Ethyl Phenylglycidate and o-*Phenylenediamine.*—*o*-Phenylenediamine (5·4 g.; 0·05 mole) and ethyl phenylglycidate (9·6 g.; 0·05 mole) in ethanol (35 ml.) were heated under reflux for 9 hours. Crystals separated on cooling, and more on concentration of the mother-liquor, and after recrystallisation from aqueous alcohol a total yield of 7·5 g. of *ethyl* α-(o-*aminoanilino*)-β-*hydroxy*-β-*phenylpropionate* (XVI), m. p. 130·5°, was obtained (Found : C, 68·2, 68·1; H, 6·74, 6·57. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·67%). It was readily soluble in organic solvents and cold dilute mineral acid. Boiling with excess of acetic anhydride for ½ hour gave the *triacetate*, short needles, m. p. 189°, from alcohol (Found : N, 6·68, 6·77. $C_{23}H_{26}O_6N_2$ requires N, 6·57%. $C_{21}H_{24}O_5N_2$ requires N, 7·29%). The ester (XVI) (0·5 g.) was hydrolysed (ethanol being isolated) by 20 minutes' boiling with 10% aqueous sodium hydroxide (15 ml.), the cooled yellow solution neutralised to Congo-red with hydrochloric acid, and the precipitated amino-acid (XIX) (0·4 g.) recrystallised from aqueous alcohol, forming micro-crystals, m. p. 176° (decomp.), apparently the *dihydrate* (Found : C, 58·55; H, 6·40. $C_{15}H_{16}O_3N_2,2H_2O$ requires C, 58·4; H, 6·49%). It was readily soluble in hot and sparingly soluble in cold water, was amphoteric, and like the parent ester (XVI) it gave red solutions with aqueous mineral acid which deposit, especially after boiling or standing, a red amorphous product (apparently from oxidation), insoluble in water and in ether. Fission as well as hydrolysis of the ester (XVI) was effected when 0·4 g. was heated under reflux for 7 hours with potassium hydroxide (5 g.) in aqueous alcohol (10 ml.). Even after this prolonged treatment, a large amount of (XIX) was recovered on subsequent neutralisation. The steam-distillate yielded a few drops of benzaldehyde, identified by its odour and *p*-nitrophenylhydrazone, m. p. 190·5° alone or mixed with an authentic specimen.

2-*Keto*-3-α-*hydroxybenzyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (XVII), short needles, m. p. 167·5° (Found : N, 11·1. $C_{15}H_{14}O_2N_2$ requires N, 11·0%), was obtained when the amino-acid (XIX) or the ester (XVI) (2 g.) was heated under reflux with 2N-sulphuric acid (50 ml.) for 20 minutes, the red precipitate filtered off, the filtrate neutralised with ammonia, and the new precipitate recrystallised from ether and then from alcohol. It was also obtained by heating (XIX) for 15 minutes at 190—200°. It dissolved in cold dilute acids or warm sodium hydroxide solution, and when heated under reflux with excess of acetic anhydride for ½ hour gave the *diacetyl* derivative (XVIII), plates, m. p. 171—172° (Found : C, 67·35; H, 5·40. $C_{19}H_{18}O_4N_2$ requires C, 67·45; H, 5·33%), from alcohol. This was also obtained when the amino-acid (XIX) was similarly treated with acetic anhydride.

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