

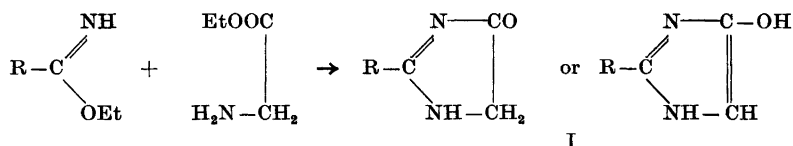
Reactions between Imino Esters and α -Amino Acid Esters

I. The Structure of Finger and Zeh's Benzylimidazolones

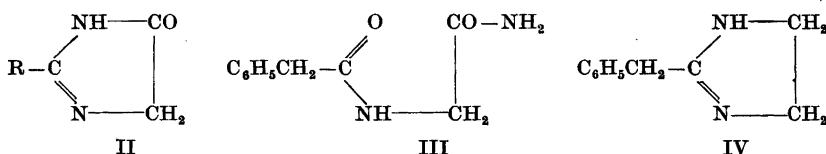
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The reaction between imino esters and α -amino acid esters was first studied by Finger ^{1,2}. He reported the formation of 5(4)-imidazolones (I, R = CH₃ or C₆H₅CH₂) when the reactants in molecular proportions were brought into contact at room temperature with or without ether as a diluent.



The formulation of the reaction products (I) was supported by their chemical reactions. In the case of R representing benzyl, however, two different products were isolated according to the experimental conditions selected ². They were considered to be isomerides and were formulated as (I) and (II), respectively.



Our present knowledge of tautomerism in amidines and imidazoles (*cf.* Ref. 3,4) renders the correctness of the proposed formulations highly questionable. This fact, in conjunction with a general interest in the chemistry of 5(4)-imidazolones, led to the present reinvestigation of the "isomerides" of Finger and Zeh ².

Attention was first directed to the reaction between molecular proportions of ethyl phenylacetimidate and glycine ethyl ester in ether solution at room temperature. Trituration of the crude, brown reaction product with hot

benzene gave a filtrate which deposited crystalline material on cooling. After purification, the pale yellow crystals melted at 138–139° (dec.) and gave analytical figures confirming the formula $C_{10}H_{10}ON_2$ of Finger and Zeh. A cryoscopical determination of the molecular weight gave values which agreed reasonably well with the empirical formula. Most of the chemical reactions previously reported were repeated and the results confirmed. Treatment of the imidazolone with boiling water resulted in hydrolysis to a crystalline compound, definitely proved to be phenaceturamide (III) on comparison with authentic material. This facile hydrolytic cleavage of the imidazole nucleus is paralleled in *e.g.* the work of Miescher *et al.*⁵ who found the salts of 2-benzylimidazoline (IV) very stable towards hydrolysis, whereas the free base was rapidly opened on boiling with water. The formulation of the compound above as 2-benzyl-5(4)-imidazolone (II, $R = C_6H_5CH_2$) is furthermore consistent with its solubility in alkali, its weakly basic properties, its ability to give condensation products with aldehydes and ketones as well as its ultraviolet absorption spectrum (Fig. 1). The latter may be considered as the spectrum of the imidazolone-ring showing only end-absorption, which has superimposed upon it the typical benzyl bands at *ca.* 250 $m\mu$. The similarity with the absorption spectra of benzylenillic acid and various benzylimidazolines is obvious⁶. The flat and low maximum at about 340 $m\mu$ may be attributable to traces of the higher melting reaction product discussed below. Benzoylation experiments in pyridine yielded a dibenzoyl-derivative, m.p. 138°, in accord with the previous results of Finger and Zeh. The molecular weight determination gave figures indicating the presence of two benzoyl groupings in the monomeric 2-benzylimidazolone.

The higher melting "isomeride" — Finger and Zeh's "Isoglyoxalidon" — was produced in rather poor yield on mixing ethyl phenylacetimidate and glycine ethyl ester in molecular proportions and initiating the reaction by local heating. An exothermic reaction took place, accompanied by extensive browning of the contents of the vessel. Treatment with hot benzene removed simultaneously formed 2-benzylimidazolone and left a crystalline residue which melted at 218–220° (vigorous decomposition) after repeated recrystallisations. The very pale yellow needles gave analytical figures indicating the composition $C_{20}H_{20}O_2N_4 \cdot H_2O$, apparently a monohydrate of a dimeride of 2-benzylimidazolone. Cryoscopical determinations of the molecular weight gave erratic and inconsistent results and hence provided no confirmatory evidence of the above empirical formula. The degradation experiments reported below, however, left little doubt as to the composition. The compound was sparingly soluble in water, cold ethanol and benzene and could conveniently be recrystallised from aqueous pyridine. Contrary to 2-benzylimidazolone, the dimeride proved stable in boiling water, while hydrolysis with hydrochloric acid at elevated temperature afforded ammonia, glycine and phenylacetic acid. Furthermore, the ability to condense with carbonyl-compounds was lost after dimerisation. Spectroscopically it could be shown that cold aqueous alkali caused a rather rapid and irreversible structural change. The dimeride produced a characteristic deep-blue colour with ferric chloride, while 2-benzylimidazolone gave only a weak brownish colour with this reagent.

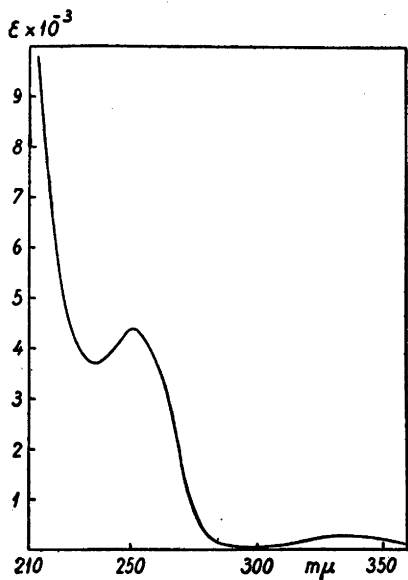


Fig. 1. Ultraviolet absorption spectrum of 2-benzyl-5(4)-imidazolone in water.

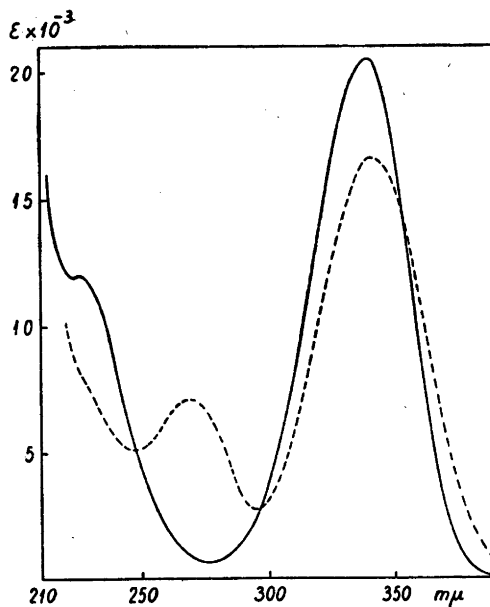
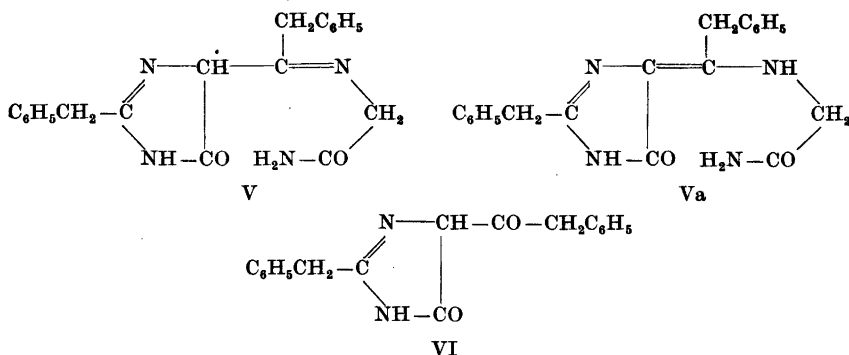


Fig. 2. Ultraviolet absorption curves of the dimeride (V or Va), — in 96% ethanol; - - - - in 0.05 N NaOH in 20% ethanol, measured immediately after dissolution.

An important clue to the nature of the dimeride was provided by treating it with cold 4 N hydrochloric acid, when a high-melting colourless compound, $C_{18}H_{16}O_2N_2$, resulted. The latter was soluble in sodium hydroxide and gave a pink colour with ferric chloride in neutral solution. It proved identical with an unidentified compound, described by Finger and Zeh, resulting from the rather drastic treatment of their "Isoglyoxalidon" with alkali. Inspection of the empirical formula indicated that glycine and ammonia had been lost during the mild acid hydrolysis of the dimeride. The C_{18} -formula of the remaining molecular fragment pointed to 2-benzylimidazolone, substituted by a phenylacetyl-grouping, as a likely structural possibility. No condensations were noticed between the acid degradation product and carbonyl compounds indicating the attachment of the phenacetyl-grouping to the reactive 4(5)-position of the intact imidazolone ring.

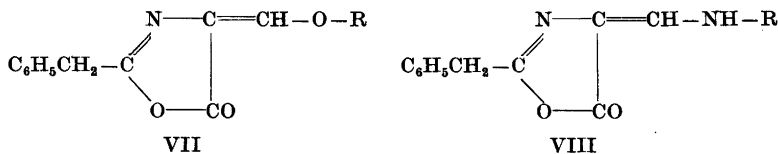
It will be recalled that the linkage in 1-2-position of the 2-benzylimidazolone (II, $R = C_6H_5CH_2$) was readily broken to give (III) upon boiling of its aqueous solution. Therefore, it seemed likely that the dimerisation reaction involved attaching the 2-carbon atom of one imidazolone nucleus, under simultaneous ring fission, to the active methylene group of another, intact 2-benzylimidazolone molecule. Thus the expression (V), possibly in equilibrium with (Va) for reasons to be discussed below, is presented as a tentative structure-

ral formulation of the "Isoglyoxalidon" of Finger and Zeh. This structure seems to accommodate satisfactorily the known facts and offers (VI), or possibly a tautomeride, as a likely formulation of the acid degradation product.



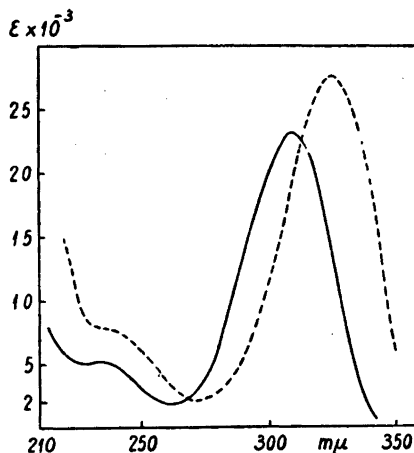
It should be noted that other structures have been considered for the dimeride. Although admittedly tentative, the formulae presented here seem to account better than any alternative ones for the experimental results. The possible participation of the methylene group of the benzyl substituent as a site of reaction could be ruled out, when it was found that 2-methyl-5(4)-imidazolone gave an analogous isomeride. The latter was prepared under different conditions and will be described in the following paper.

The above chemical evidence of the structures was strongly supported by studies of the ultraviolet absorption spectra. In ethanol solution the dimeride, (V) or (Va), exhibited a very strong absorption maximum at $340 \text{ m}\mu$ (ϵ 20 600); a secondary band at $226 \text{ m}\mu$ (ϵ 12 600) and a low minimum at $276 \text{ m}\mu$ (ϵ 720) were also apparent (Fig. 2). Whereas acidification resulted in no pronounced alteration of the spectrum, except for some hyperchromic effect, addition of alkali changed the absorption curve rather profoundly. At $270 \text{ m}\mu$ a new band appeared which, however, was destroyed when the alkaline solution was kept at ordinary temperature. The spectroscopical data are strikingly similar to the absorption spectra, determined during the penicillin work⁷, of the penicillanates and various model benzyloxazolones carrying a substituted hydroxy- or aminomethylene-grouping in 4-position (VII and VIII), (Fig. 3).



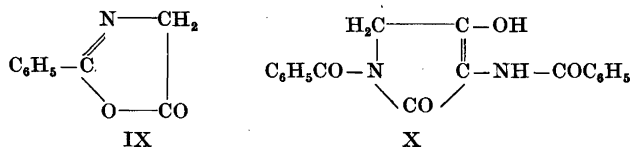
The bathochromic shift in the absorption spectra of the imidazolones compared with the corresponding azlactones is not surprising. It merely reflects the generally experienced progression of the absorption bands to longer wavelengths upon passing from heterocyclic oxygen-rings to the

Fig. 3. Ultraviolet absorption curves of: —: 2-benzyl-4(5)-aminomethylene-5(4)-oxazolone (VIII, R = H) in ethanol; - - - -: S-benzyl benzylpenicillic acid (VIII, R = CH(COOH)C(CH₃)₂-SCH₂C₆H₅) in ethanol.

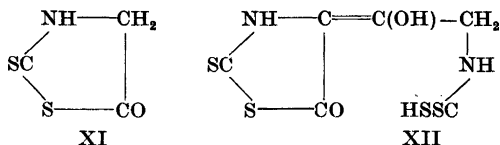


isosteric nitrogen-analogues. The spectroscopical studies therefore favor the substituted aminomethylene-structure (Va) while the acid hydrolysis to (VI) is more readily explained on basis of the tautomeric structure (V). An equilibrium between the two forms may conceivably exist. The acid degradation product gave an intense absorption band at 340 μ . This fact, in conjunction with the pink colour produced with ferric chloride, indicates the formula (VI), enolised in the side chain, as the most correct expression.

The above dimerisation reaction presents no essential novelty, being paralleled in other heterocyclic series. Thus it recalls a somewhat similar change which takes place when 2-phenyloxazolone (IX) is exposed to Grignard reagents or a mixture of triethylamine and hydrogen cyanide⁸. The intricate structural problem of this dimeride was eventually solved by Cornforth and Huang⁹, when they proved the formula (X) to be the correct expression.



A formally similar expression for the present dimeride would be incompatible with its chemical properties and therefore can be excluded. Cook and Levy¹⁰ found that 2-thio-5-thiazolidone (XI) underwent dimerisation under the influence of triethylamine. They established the expression (XII), formally similar to the one here proposed, as the most likely structure of their dimeride.



EXPERIMENTAL *

Ethyl phenylacetimidate. The hydrochloride was prepared from benzyl cyanide and ethanol in the usual way¹¹. The free ester was liberated on addition of NaHCO₃ and distilled. B.p. 87–88° at 1.8 mm, m.p. 5°. Contrary to the literature¹¹ it was observed that the free ester did not keep well at room temperature. In the following experiments freshly distilled ester or material which had been kept at dry ice temperature was used throughout.

2-Benzyl-5(4)-imidazolone (I, II, R = C₆H₅CH₂). Freshly distilled glycine ethyl ester¹² (4.0 g) was dissolved in anhydrous ether (20 ml). To this solution was added another, containing ethyl phenylacetimidate (6.4 g) in ether (10 ml), and the mixture was kept at room temperature. After a few hours, the separation of a crystalline solid started. Next day the crystals (4.8 g) were separated from the brown filtrate and thoroughly triturated with ether, when they appeared as a light brown powder. This was treated with hot benzene and an insoluble residue removed by filtration. On cooling, the filtrate deposited yellow crystals (1.5 g), m.p. 137–140°.

An analytical sample was prepared by an additional recrystallisation from methanol, containing ether and petroleum ether. Tiny, yellowish needles separated. M.p. 138–139° (dec.), (Finger and Zeh report the m.p. 143°).

C ₁₀ H ₁₀ ON ₂ (174.2)	Calc.	C 68.94	H 5.79	N 16.08
	Found	» 68.95	» 5.81	» 16.02

Cryoscopic determinations of the molecular weight (camphor) gave the values 166, 158, 188.

Addition of ferric chloride to an ethanolic solution produced an uncharacteristic, brownish colour.

Hydrolysis of 2-benzyl-5(4)-imidazolone. The above product (237 mg) was refluxed with water (10 ml) for one hour. Filtration of the hot solution removed traces of insoluble material. On cooling, the filtrate deposited crystals, which after recrystallisation from water with addition of a little charcoal, appeared as colourless plates. M.p. 178–179° alone or mixed with authentic phenaceturamide, prepared by ammonolysis of methyl phenaceturate.

Dibenzoyl derivative of 2-benzyl-5(4)-imidazolone. The benzylation of 2-benzyl-5(4)-imidazolone in pyridine solution was performed essentially as described by Finger and Zeh. The derivative separated from ethanol in clusters of colourless needles. M.p. 137–138°.

C ₂₄ H ₁₈ O ₂ N ₂ (382.4)	Calc.	C 75.37	H 4.74	N 7.33
	Found	» 75.50	» 4.91	» 7.55

Cryoscopic determinations of the molecular weight (camphor) gave the values 351, 362.

Preparation of the dimeride (V, Va). Ethyl phenylacetimidate (6.4 g) and glycine ethyl ester (4.0 g) were mixed and heated with a small free flame until the formation of a slightly yellow colour was observed. The flame was removed and a vigorous exothermic reaction took place, accompanied by a colour change to dark brown. After ca. 2 minutes, the reaction ceased and after cooling, ether (ca. 50 ml) was added when a light brown crystalline powder remained (5.0 g). This was refluxed with benzene (50 ml) for 0.5 hour, the benzene removed by decantation and the operation repeated with a portion of fresh benzene (20 ml). On concentration and cooling, crude 2-benzylimidazolone (1.0 g) separated from the benzene filtrates. The residue was recrystallised twice from aqueous ethanol, with addition of decolourising charcoal, to give slightly yellow needles (1.4 g), m.p. 211–213° (dec.). An analytical sample was recrystallised once more from aqueous pyridine and separated in small colourless needles. The m.p. values depended on the rate of heating. When rapidly heated, the sample melted at 216–220° under vigorous decomposition. The air-dried sample gave analytical figures indicating a monohydrate.

C ₂₀ H ₂₀ O ₂ N ₂ · H ₂ O (366.4)	Calc.	C 65.56	H 6.05	N 15.29
	Found	» 65.50	» 6.20	» 15.35

* All melting points are uncorrected and determined in capillary tubes in an electrically heated block.

The hydrate was dried at room temperature over P_2O_5 for 40 hours and the weight loss determined.

Calc.	for 1 H ₂ O	4.92 %	H ₂ O
Found		4.70 %	»

The anhydrous substance was analysed for nitrogen.

C ₂₀ H ₂₀ O ₂ N ₄ (348.4)	Calc.	N	16.08
	Found	»	16.01

On keeping in the open atmosphere, the anhydrous material rapidly reconverted into the monohydrate.

No reproducible results were obtained in the cryoscopical molecular weight determinations, neither in camphor nor in phenol.

Acid hydrolysis of the dimeride to (VI). When the dimeride (1.0 g) was added to 4 N hydrochloric acid (50 ml) a clear solution was obtained. Within less than one minute the separation of colourless crystals started. The product was isolated and carefully recrystallised from glacial acetic acid; prolonged heating or too high a temperature must be avoided. Otherwise the solution took on yellow and red colours indicating unwanted secondary transformations taking place. The crystalline powder was washed with ethanol and ether. M.p. 298–299° (dec.).

C ₁₈ H ₁₈ O ₂ N ₂ (292.3)	Calc.	C	73.96	H	5.52	N	9.59
	Found	»	73.70	»	5.27	»	9.82

Ultraviolet absorption spectra. The absorption spectra were determined in 1 cm cells with a Beckman model DU quartz spectrophotometer.

SUMMARY

The structures of two compounds, reported in the literature as isomeric 2-benzyl-5(4)-imidazolones, have been reinvestigated and the dimeric nature of the higher melting isomeride established.

Chemical and spectroscopical studies provide evidence for the proposed structural expressions (II) and (V), or their tautomeric forms.

Microanalyses have been performed in this laboratory by Mr. A. Grossmann.

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