

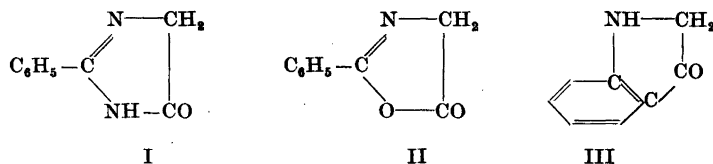
Reactions between Imino Esters and α -Amino Acid Esters

III. 2-Phenyl-5(4)-imidazolone and its Reactions

ANDERS KJÆR

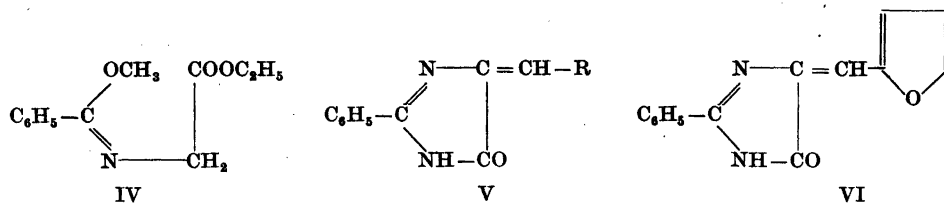
Chemical Laboratory, University of Copenhagen, Denmark

The reaction between iminoesters and α -amino acid esters as the free bases to give 5(4)-imidazolones was first reported from Finger's laboratory. The two documented examples of the reaction^{1,2} were supplemented by additional ones in a thesis by Zeh³. He demonstrated the applicability of ring-substituted alkyl benzimidates in the above reaction but gave no notice to the simple 2-phenyl-5(4)-imidazolone (I). Karrer and Gränacher⁴ later reported a compound, m.p. 141–143°, prepared by treating hippuramide with phosphorus pentachloride, to which they ascribed the structure (I). In a previous communication⁵ we showed their product to be hippuronitrile.



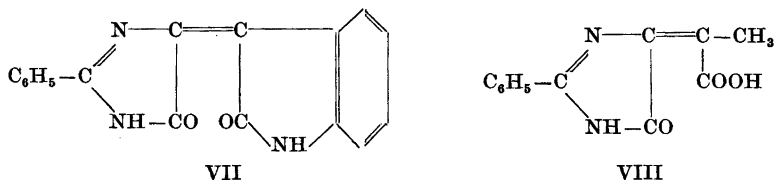
For several reasons a special interest was attached to the imidazolone (I) in the current studies. First, its formal resemblance to the highly reactive and synthetically important hippuric acid azlactone (II) made its synthesis and a closer investigation of its properties and possible preparative applications desirable. Secondly, the apparent structural analogy of (I) to indoxyl (III) allowed one to expect interesting indigoid properties of 2-phenyl-5(4)-imidazolone, an assumption which has been experimentally borne out.

In the preceding paper⁶ the failure to achieve ammonolysis of methyl α -methoxybenzylideneaminopropionate to a crystalline imidazolone was reported. No better results attended attempts to ring-close the corresponding glycine-derivative (IV) on treatment with ammonia. The high reactivity of the expected reaction products may explain these negative results, secondary reactions leading to complex by-products being predominant under the experimental conditions employed.



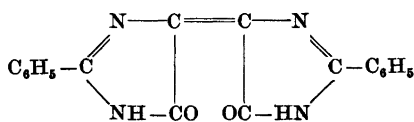
When ethyl benzimidate in ether solution was allowed to react with a molecular proportion of glycine ethyl ester, preferably in a nitrogen atmosphere, the mixture gradually deposited a light brown crystalline solid. The reaction was accompanied by the formation of an intensely red substance, the amount of which could be somewhat diminished by careful exclusion of oxygen. Crystallisation from benzene, followed by sublimation in high-vacuum, finally afforded a crystalline substance $\text{C}_9\text{H}_8\text{ON}_2$, m.p. $165-167^\circ$ (dec.). That this compound was the desired 2-phenyl-5(4)-imidazolone (I) was proved from its reactions.

Upon treatment with benzaldehyde and a trace of morpholine in glacial acetic acid, (I) gave 2-phenyl-4(5)-benzylidene-5(4)-imidazolone (V, $\text{R} = \text{C}_6\text{H}_5$), identical with a specimen prepared by the Erlenmeyer synthesis ⁷ (*cf.* Ref. 8). With furfural under similar conditions, the analogous 2-phenyl-4(5)-furfurylidene-5(4)-imidazolone (VI), m.p. $268-269^\circ$ (dec.), was obtained. Its m.p. agreed with the value ($266-267^\circ$) reported by Cornforth and Huang ⁹ for the same compound, while Ekeley and Ronzio ¹⁰ found the m.p. 293.5° and Erlenmeyer and Stadlin ¹¹ reported the value 241° (dec.). This divergency may be attributable to the presence of varying amounts of the two geometrical isomerides in the various preparations. Again, on reaction with 1-naphthaldehyde the unknown 4(5)-naphthylidene-5(4)-imidazolone (V, $\text{R} = \text{C}_{10}\text{H}_7$) was obtained. Condensation with isatin afforded a dark-red, high-melting condensation product. In view of the well-established reactivity of the β -position in isatin towards reactive methylene groups ¹², the structure (VII), or a tautomeride, is proposed for the condensation product. Pyruvic acid and (I) yielded a dark-violet reaction product possessing the structure (VIII).

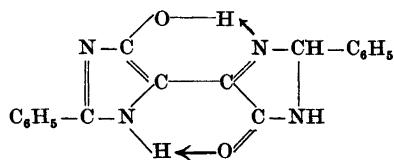


2-Phenyl-5(4)-imidazolone proved to be a highly reactive substance, particularly sensitive to oxygen. Even in the crystalline state it was transformed into a yellow substance, while its solutions in various solvents rapidly turned cherry-red, apparently as a result of oxidation. This phenomenon drew our attention to an older observation by Ruhemann and Stapleton ¹³. They isolated from the reaction between benzamidine and acetylenedicarboxylic acid diethyl

ester a product, forming "ruby-red crystals", which they named "glyoxaline red" and to which they ascribed the bicyclic structure (IX), formally similar to pyrazole blue and indigotin. Ekeley and Ronzio¹⁴ discussed the complex reactions between benzamidine and glyoxal in alkaline solution, yielding a series of differently composed red substances, one of which was "glyoxaline red".



IX



X

Therefore, it was not surprising to find that the red by-product in the condensation above consisted of essentially pure "glyoxaline red". In view of modern concepts of the indigoid structures, the formulation (X) is proposed for the red pigment. The latter was best prepared upon treatment of a solution of (I) in glacial acetic acid with oxygen. The identity with Ruhemann and Stapleton's pigment followed from the coincidence in absorption spectrum with that previously reported¹⁴ and from the characteristic transformation into a yellow substance of the hydrated composition $C_{18}H_{14}O_3N_4$ upon heating in glacial acetic acid¹³.

The reaction between aromatic aldehydes, glyoxal and amidines, studied by Ekeley *et al.* in a series of papers was a subject of discussion for many years, until it was eventually shown¹⁵ that the reaction products possessed the imidazolone-structures (V). It was further suggested that (I) was intermediately formed from benzamidine and glyoxal and then in turn condensed with the aldehydes. The above preparation of 2-phenyl-5(4)-imidazolone (I) and its established reactivity towards aromatic aldehydes lend strong support to this assumption.

That the reaction between a benziminoester and glycine ethyl ester is by no means a simple reaction appeared from an experiment, in which a chromatographic purification of the crude reaction product was attempted. Using aluminium oxide as an adsorbent and chloroform with progressively increasing amounts of ethanol as the eluting solvent, a great number of differently coloured bands were noticed. Besides a small amount of 2-phenyl-5(4)-imidazolone, a considerable quantity of a secondary product, $C_{25}H_{21}O_2N_5$, was isolated. It appeared as intensely yellow needles, m.p. 128–130°, soluble in acid and yielding a picrate in ethanolic solution. No reaction was noticed with benzaldehyde, and addition of ferric chloride produced only a weak, greenish colouration. The above empirical formula was confirmed through analysis of a well-crystallising, yellow mono-acetyl derivative. The composition suggests that the compound is a result of reaction between two molecules of α -amino ester and three molecules of iminoester, with the elimination of five molecules of ethanol. Therefore, the intermediate formation of some dimeric structure (*cf.* the preceding papers of this series), followed by further combina-

tion with an additional molecule of iminoester, seems an attractive possibility. Owing to the complex nature of the product, no satisfactory structural expression has yet been established. It should be noted in this connection that Zeh³ demonstrated reaction to take place between substituted 2-phenyl-5(4)-imidazolones and iminoesters to give products where the latter have combined with glycine ester in the ratio 2 : 1.

EXPERIMENTAL *

Ethyl benzimidate. The ester was liberated from its hydrochloride by means of sodium bicarbonate, as described by Glickman and Cope¹⁶ for the analogous ethyl acetimidate. B.p. 85–86° at 2.9 mm.

2-Phenyl-5(4)-imidazolone (I). Glycine ethyl ester (7.9 g) and ethyl benzimidate (11.4 g) were dissolved in anhydrous ether. The solution was covered with nitrogen and kept at room temperature for 19 hours. The crystalline, light-brown solid (2.3 g) formed was isolated by filtration in a nitrogen atmosphere and thoroughly washed with ether. It was rapidly crystallised from anhydrous benzene, care being taken to exclude oxygen. The product was finally sublimed at a bath-temperature of 140° and 0.5 mm, when it appeared as colourless crystals, m.p. 165–167° (dec.), rapidly turning yellow on exposure to air.

C ₉ H ₉ ON ₂ (160.2)	Calc.	C 67.48	H 5.03	N 17.50
	Found	» 67.35	» 4.89	» 17.72

The mother liquor on further keeping deposited a mixture of a higher melting brown compound and an intensely red substance. In addition, the crude product contained additional amounts of (I), which could be isolated upon extraction with benzene.

Experiments conducted under no special precautions resulted in the production of a more impure product, contaminated with large amounts of the red pigment.

2-Phenyl-4(5)-benzylidene-5(4)-imidazolone (V, R = C₆H₅). Pure (I) (0.5 g) was dissolved in glacial acetic acid (5 ml) and benzaldehyde (0.5 ml) and a drop of morpholine added. The mixture was briefly heated, whereupon the separation of an orange solid (0.6 g) started. The product recrystallised from amyl acetate as small, golden needles. M.p. 278–279°.

C ₁₆ H ₁₅ ON ₂ (248.3)	Calc.	C 77.38	H 4.84	N 11.28
	Found	» 77.41	» 4.80	» 11.45

No depression of the m.p. was noticed on admixture with a specimen prepared by cyclodehydration of *a*-benzamidocinnamamide⁷.

2-Phenyl-4(5)-furfurylidene-5(4)-imidazolone (VI). This was prepared from (I) (0.5 g) and furfural (0.4 ml) in a similar way. The product separated from amyl acetate in greenish-yellow needles. M.p. 268–269° (dec.).

C ₁₄ H ₁₀ O ₂ N ₂ (238.2)	Calc.	C 70.57	H 4.23	N 11.76
	Found	» 70.89	» 4.09	» 11.56

2-Phenyl-4(5)-1'-naphthylidene-5(4)-imidazolone (V, R = 1-C₁₀H₇). (I) (0.5 g), 1-naphthaldehyde (0.65 ml) and a few drops of morpholine were briefly heated in glacial acetic acid (5 ml). The red, crude material (0.82 g) recrystallised from amyl acetate in thin, golden needles. M.p. 273–274°.

C ₂₀ H ₁₄ ON ₂ (298.3)	Calc.	C 80.54	H 4.73	N 9.40
	Found	» 80.58	» 4.74	» 9.36

2-Phenyl-4(5)-3'-oxindolylidene-5(4)-imidazolone (VII). When a hot solution of isatin (450 mg) in acetic acid (4 ml) was mixed with a solution of (I) (450 mg) in acetic acid (4 ml), a dark-purple, crystalline solid separated at once. The product was soluble in NaOH and could be reprecipitated unchanged on addition of acid. It was recrystallised

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

from a large volume of amyl acetate and appeared as a dark-red, crystalline powder which melted above 300°.

$C_{17}H_{11}O_2N_3$ (289.3) Calc. C 70.57 H 3.82 N 14.52
Found » 70.82 » 3.70 » 14.55

2-Phenyl-4(5)-1'-carboxyethylidene-5(4)-imidazolone (VIII). A solution of (I) (200 mg), pyruvic acid (0.25 ml of a 53 % solution) and a few drops of morpholine in acetic acid (2 ml), rapidly deposited the crystalline, dark-violet condensation product. This recrystallised from amyl acetate in dense, pointed prisms which melted completely above 300°.

$C_{15}H_{10}O_3N_2$ (230.2) Calc. C 62.63 H 4.38 N 12.18
Found » 62.90 » 4.52 » 12.18

The formation of "glyoxaline red" (X). When a solution of (I) in glacial acetic acid was treated with a stream of oxygen, the solution rapidly turned cherry-red. After some hours it was concentrated *in vacuo* to half its volume, when a dark-red, crystalline solid separated. It was filtered off and thoroughly washed with ethanol and ether. Then it was dissolved in NaOH and reprecipitated on addition of acid; this operation was repeated several times. The appearance of the product did not change during these treatments. The m.p. was found to be higher than 300°.

The ultra-violet absorption spectrum of a saturated solution in dioxane agreed well with the one previously reported¹⁴.

When heated to boiling in anhydrous acetic acid a colour-shift to yellow took place, and the yellow reaction product gave analytical figures agreeing with the composition, $C_{15}H_{14}O_2N_4$, previously stated.

$C_{15}H_{14}O_2N_4$ (334.3) Calc. C 64.68 H 4.22 N 16.76
Found » 64.90 » 4.01 » 17.04

Chromatography of a crude reaction product from the interaction of ethyl benzimidate and glycine ethyl ester. The yellow reaction product (9.1 g), resulting from a condensation between ethyl benzimidate and glycine ester, was dissolved in 250 ml of chloroform. A trace of insoluble material was removed by filtration, and the solution poured on to a column (200 × 40 mm), packed with active aluminium oxide.

After development with fresh chloroform, eight different bands were noticed. The elution proceeded as shown in Table 1.

Table 1. Elution of adsorbed material.

Fraction No.	Eluting solvent	ml	mg	Appearance
1-6	CHCl ₃	300	120	brown oil
7	»	250	450	yellow crystals
8	CHCl ₃ /EtOH 10/1	200	1 950	brownish crystals
9	»	30	600	red crystals
10	»	100	400	red crystals
11	»	100	220	red oil
12	CHCl ₃ /EtOH 10/2	300	290	dark-red oil
13	»	100	80	red oil

The remaining material was very firmly bound to the adsorbent and could not be effectively eluted, even with pure ethanol.

The crystalline material from fraction 7 was repeatedly recrystallised from methanol. It separated in clusters of thin, yellow needles, m.p. 128–130° (dec.).

$C_{25}H_{21}O_2N_5$ (423.5) Calc. C 70.91 H 5.00 N 16.54
Found » 70.69 » 5.23 » 16.60

The compound was soluble in acid and gave a crystalline picrate, m.p. 260–261°, in ethanol solution.

When the yellow crystals were briefly heated with acetic anhydride, a mono-acetyl derivative crystallised on cooling. It separated in hair-fine, yellow needles from ethanol, m.p. 280–281°.

$C_{27}H_{23}O_3N_5$ (465.5)	Calc.	C	69.65	H	4.98	N	15.05
	Found	»	69.53	»	4.73	»	14.96

Treatment of fraction 8 with cold benzene removed ca. 400 mg of 2-phenyl-5(4)-imidazolone (I), while the residue after purification proved identical with the yellow compound from fraction 7.

The fractions 9 and 10 consisted of 2-phenyl-5(4)-imidazolone, contaminated with the red pigment discussed above. Rather surprisingly, acetylation afforded a yellow product, identical with the mono-acetyl derivative mentioned above.

SUMMARY

The previously unknown and rather unstable 2-phenyl-5(4)-imidazolone (I) has been prepared by condensation of ethyl benzimidate with glycine ethyl ester. Its reactivity towards aromatic aldehydes, furfural, isatin and pyruvic acid has been demonstrated.

Its close relationship to "glyoxaline red" has been established.

The complex nature of the condensation between benziminoesters and glycine ester has been studied and discussed.

Microanalyses were performed in this laboratory by Mr. A. Grossmann.

REFERENCES

1. Finger, H. *J. prakt. Chem.* [2] **76** (1907) 93.
2. Finger, H., and Zeh, W. *J. prakt. Chem.* [2] **82** (1910) 50.
3. Zeh, W. *Über die Condensation von Imidoäthern mit Amidoestern*, Thesis, Darmstadt 1909.
4. Karrer, P., and Gränacher, C. *Helv. Chim. Acta* **7** (1924) 763.
5. Kjær, A. *Acta Chem. Scand.* **3** (1949) 647.
6. Kjær, A. *Acta Chem. Scand.* **7** (1953) 1024.
7. Erlenmeyer jr., E. *Ber.* **33** (1900) 2036.
8. Kjær, A. *Acta Chem. Scand.* **7** (1953) 900.
9. Cornforth, J. W., and Huang, H. T. *J. Chem. Soc.* **1948** 731.
10. Ekeley, J. B., and Ronzio, A. R. *J. Am. Chem. Soc.* **57** (1935) 1353.
11. Erlenmeyer jr., E., and Stadlin, W. *Ann.* **337** (1904) 283.
12. Sumpter, W. S. *Chem. Revs.* **34** (1944) 393.
13. Ruhemann, S., and Stapleton, H. E. *J. Chem. Soc.* **77** (1900) 804.
14. Ekeley, J. B., and Ronzio, A. R. *J. Am. Chem. Soc.* **59** (1937) 1313.
15. Williams, D. L., Symonds, F. L., Ekeley, J. B., and Ronzio, A. R. *J. Am. Chem. Soc.* **67** (1945) 1157.
16. Glickman, S. A., and Cope, A. C. *J. Am. Chem. Soc.* **67** (1945) 1017.

Received June 9, 1953.