ACTA CHEMICA SCANDINAVICA 7 (1953) 1024—1029

Reactions between Imino Esters and α-Amino Acid Esters

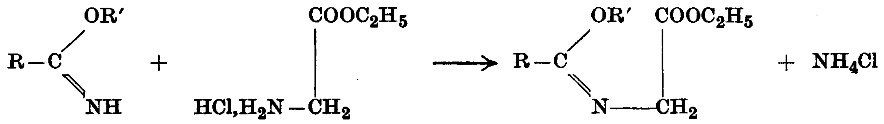
II. The Reaction of N-Substituted Imino Esters with Amines

ANDERS KJÆR

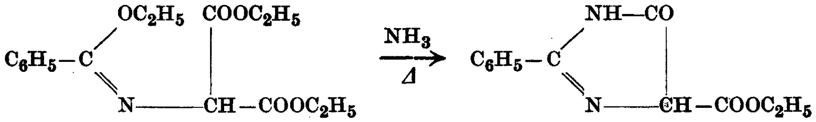
Chemical Laboratory, University of Copenhagen, Denmark

The preceding paper described an example of the preparation of 5(4)-imidazolones by condensation of iminoesters and α-amino acid esters. Although this preparative method promised to be of extensive application, several cases were noted where diminished reactivity (*e.g.* in case of tertiary α-amino acid esters, *cf.* Ref. 1), complications due to dimerisation (*cf.* the preceding paper), and the production of undesired coloured by-products, made an alternative route desirable.

In 1914 Schmidt [2] made the interesting observation that if an imino ester as the free base in an organic solvent was shaken with an aqueous solution of the hydrochloride of glycine ethyl ester, a substituted iminoester was formed according to the following scheme.



It was not until the penicillin programme that the synthetic potentialities of this reaction were recognised, when it was found that ethyl α-ethoxybenzylideneaminomalonate (I) upon treatment with ammonia and subsequent heating was transformed into 2-phenyl-4(5)-carbethoxy-5(4)-imidazolone (II) [3].

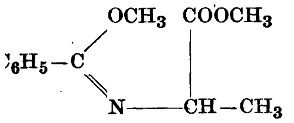


I II

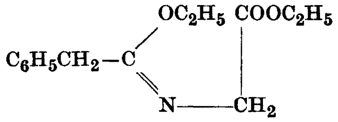
This represents the only example to be found in the literature of ammonolysis of Schmidt-esters, although the latter have been utilised for other synthetic purposes, *e.g.* in the elegant oxazole-syntheses of Cornforth and Cornforth [4].

After the conclusion of the present work a paper by Miller, Gurin and Wilson [5] appeared in which they reported the preparation of two 4(5)-carboxamido-5(4)-imidazolones in a one-step operation from an iminoester and aminomalonamide hydrochloride.

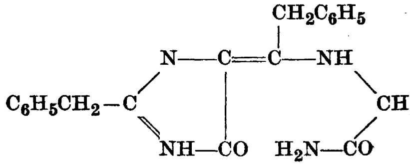
The first attempts to cyclise a substituted iminoester were made with methyl α-methoxybenzylideneaminopropionate (III), readily prepared from methyl benzimidate and DL-alanine methyl ester hydrochloride by the ordinary Schmidt-reaction. When (III) was kept at room temperature in ethanol, saturated with ammonia, no reaction was observed.



III



IV

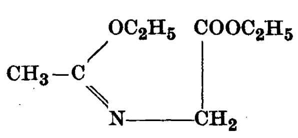


V

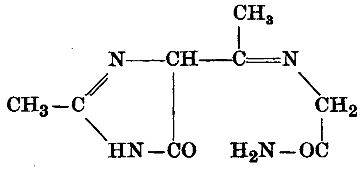
The application of higher temperature led to an intractable dark reaction mixture. Recalling the otherwise established anormal reactivity of benziminoester derivatives (*cf.* the following paper), it was thought that esters containing a benzyl grouping might provide a more attractive starting material.

Ethyl phenylacetimidate was condensed with the hydrochloride of glycine ethyl ester to give ethyl α-ethoxyphenylethylideneaminoacetate (IV) as a distillable base. When the latter was kept at 0° with ethanolic ammonia, the solution rapidly turned brown and after a few days deposited a colourless, crystalline powder, m.p. 214—218° (dec.). Quite unexpected, the product proved to be identical with the dimeride (V), discussed in the preceding communication. The appearance of this compound in the present reaction may be considered as resulting from dimerisation of primarily formed 2-benzyl-5(4)-imidazolone under the influence of excess ammonia. This suggestion was further supported by the observation that alkali or tertiary amines would bring about dimerisation. When (IV) was treated with excess methylamine in ethanol, extensive browning occurred and no well-defined crystalline material could be isolated.

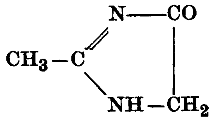
Ethyl α-ethoxyethylideneaminoacetate (VI) was prepared by the Schmidt-reaction with minor modifications [4]. Treatment of (VI) with alcoholic ammonia afforded a crystalline solid $C_8H_{12}O_2N_4$, 2 H_2O, m.p. 240—242° (dec.). In analogy with the result above the structure (VII), or possibly a tautomeride, suggested itself for this compound.



VI



VII

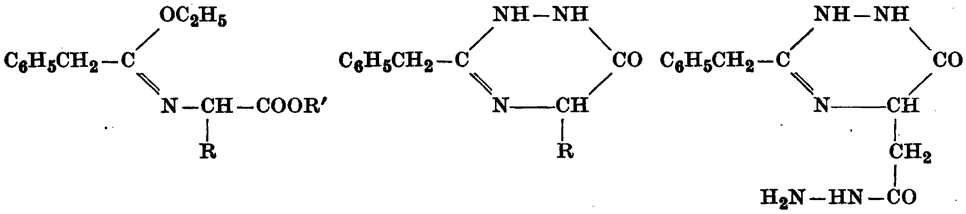


VIII

The dimeric nature of (VII) was deduced from its high melting point, the blue colour produced with ferric chloride and the absorption spectrum which exhibited a high peak at 335 mμ and was formally similar to that of (V), reported in the preceding paper. The auxiliary band at 225 mμ had disappeared but otherwise the absorption curve was so similar to that of (V) that it can be excluded that the benzene ring of the latter is part of the chromophoric system. This fact further strengthens the formula (V) proposed in the preceding paper.

Finger[6] formerly prepared 2-methyl-5(4)-imidazolone (VIII) by condensation of ethyl acetimidate with glycine ester. No indication of dimerisation is found in his paper, except maybe for the isolation of a benzoyl-derivative containing one benzoyl grouping per two imidazolone rings. This benzoylated product is probably a derivative of the dimeride (VII), the latter being spontaneously formed in the alkaline solution employed in the Schotten-Baumann reaction.

In order to study the scope of the above dimerisation reaction, ethyl phenylacetimidate was condensed with the hydrochlorides of DL-alanine methyl ester, ethyl L-glutamate, ethyl L-aspartate and DL-phenylalanine ethyl ester to give the corresponding substituted iminoesters (IX). These were colourless liquids which could be distilled at low pressure. They were best stored at dry ice temperature. The phenylalanine-derivative (IX d) crystallised on keeping, m.p. 30—31°.



a. R = CH_3; R′ = CH_3
b. R = $CH_2CH_2COOC_2H_5$; R′ = C_2H_5
c. R = $CH_2COOC_2H_5$; R′ = C_2H_5
d. R = $CH_2C_6H_5$; R′ = C_2H_5

R = H
R = CH_3
R = $CH_2C_6H_5$

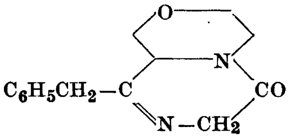
IX X XI

When the esters (IX) were exposed to dry ammonia dissolved in ethanol, the solutions gradually took on colours changing from yellow, through red, to dark brown. Traces of crystalline material were obtained from the solutions but many attempts to isolate sufficient material for a closer investigation were not rewarded. Similar experiments with *n*-butylamine and *cyclo*hexylamine instead of ammonia gave no promising results.

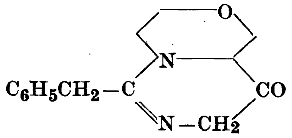
The Schmidt-esters were next studied in their behaviour towards hydrazine. When ethyl α-ethoxyphenylethylideneaminoacetate (IV) was mixed with a molecular proportion of hydrazine hydrate in ethanol, an exothermic reaction took place followed by the separation of a highly crystalline solid, $C_{10}H_{11}ON_3$. Again, (IXa) and (IXd) similarly treated afforded colourless products of the compositions $C_{11}H_{13}ON_3$ and $C_{17}H_{17}ON_3$, respectively. None of the compounds gave any colour with ferric chloride and they proved unreactive in the presence of Fehling's and Tollen's reagents. These facts and the empirical formulæ above support the formulation of the products as 3-benzyl-1,2,4-dihydrotriazinones (X), probably resulting from spontaneous cyclisation of primarily formed amidrazones or hydrazides. When (IXc) was treated with excess hydrazine at slightly increased temperature, a colourless solid, $C_{12}H_{15}O_2N_5$, resulted which smoothly reduced Fehling's solution and gave a crystalline benzylidene-derivative with benzaldehyde. The expression (XI) accounts well for these facts and is suggested as the most probable structure. Condensation of (IXb) with hydrazine did not yield any crystalline reaction product.

A few experiments were made in which the esters, (IV) and (IXa), were treated with phenylhydrazine. Crystalline solids were isolated in poor yields, but analyses of the purified reaction products indicated their complicated composition. No structural suggestions can be given at present.

With morpholine as a model secondary amine, the Schmidt-ester (IV) afforded a crystalline solid $C_{14}H_{15}O_2N_2$. This composition suggests that (IV) and morpholine have combined in the ratio 1 : 1 with the elimination of the elements of two molecules of ethanol. The bicyclic structures (XII) or (XIII) therefore present themselves as possibilities. The tentative character of these postulations should be emphasized, not least because the Dieckmann type of condensation involved seems unprecedented in such systems.



XII



XIII

EXPERIMENTAL *

Methyl α-methoxybenzylideneaminopropionate (III). The heterogenous mixture of methyl benzimidate (9.7 g) in ether (10 ml) and DL-alanine methyl ester hydrochloride (10.1 g) in water (5 ml) was shaken mechanically for 3 hours. The ethereal phase was removed by decantation and the aqueous layer, containing crystalline ammonium chloride, thoroughly washed with small portions of fresh ether. The combined ether solutions were washed with water and dried. The ether was removed and the residue fractionated at 0.7 mm pressure. The first fraction (2.4 g), b.p. 67—68°, consisted of unreacted methyl benzimidate. Then came a mixture (3.0 g), b.p. 69—106°, and finally the Schmidt-ester (4.5 g), b.p. 106—107°. The analytical sample was redistilled and appeared as a colourless oil.

$C_{12}H_{15}O_3N$ (221.3)	Calc.	C	65.11	H	6.83	N	6.33
	Found	»	64.89	»	6.91	»	6.40

No reaction was noticed on keeping the ester in ethanol, saturated with ammonia, for two days at room temperature. Heating at 60° of a similar mixture in a closed vessel gave a viscous, dark brown residue from which no crystalline material could be isolated.

Ethyl α-ethoxyphenylethylideneaminoacetate (IV). This substituted iminoester was prepared from ethyl phenylacetimidate and glycine ethyl ester hydrochloride, essentially as described above. After a small fore-run of unchanged iminoester, the Schmidt-ester distilled as a colourless oil at 125—128° and 0.5 mm. The yield was 70 %, calculated on

---

* The melting points are uncorrected and determined in capillary tubes in an electrically heated block; those below 80° though in a water bath.

unrecovered iminoester. The product remained colourless at dry ice temperature, whereas it rapidly turned yellow at ordinary temperature.

$C_{14}H_{19}O_3N$ (249.3) Calc. C 67.44 H 7.68 N 5.62
Found » 67.64 » 7.76 » 5.86

Ammonolysis of (IV) to (V). When the above ester (10.6 g) was kept at 0° in 96 % ethanol (50 ml), previously saturated at 0° with dry ammonia, the solution rapidly took on yellow and later brown colours. Next day, a crystalline solid had separated, and after 4 days the crystals (2.2 g) were filtered off. The product recrystallised from aqueous pyridine as a colourless crystalline powder, developing a deep-blue colour with ferric chloride in alcohol solution. M.p. 214—218° (dec.). Its identity with the dimeride (V), discussed in the preceding paper, was definitely established on comparison.

The analogous treatment with methylamine afforded no crystalline material.

Dimerisation of 2-benzyl-5(4)-imidazolone to (V). When the monomeride was dissolved in ethanol, containing 2 *N* sodium hydroxide or excess triethylamine, colouration rapidly occurred followed by gradual separation of a colourless product in varying yields. After purification, its identity as the dimeride (V) was secured upon comparison.

Ammonolysis of (VI) to (VII). Ethyl α-ethoxyethylideneaminoacetate (VI)[4], treated with ethanolic ammonia as described above, gave a 30 % yield of the dimeride (VII). This separated as colourless needles from aqueous ethanol, m.p. 240—242° (dec.). The air-dried sample gave analytical results indicating a dihydrate.

$C_8H_{12}O_2N_4$, $2H_2O$ (232.2) Calc. C 41.37 H 6.95 N 24.13
Found » 41.60 » 6.71 » 24.10

The water was lost on drying over P_2O_5 at ordinary temperature for 48 hours.

Calc. for 2 H_2O 15.5 % H_2O
Found 15.2 % »

The dimeride gave qualitative reactions similar to those previously noted for the analogous benzyl-derivative (V).

Methyl α-ethoxyphenylethylideneaminopropionate (IXa). This substituted iminoester was prepared from ethyl phenylacetimidate and DL-alanine methyl ester hydrochloride in the usual way. The ester distilled as a colourless, viscous oil at 90—110° and 0.1 mm. The yield was 42 %, calculated on unrecovered iminoester. The ester was stored at low temperature.

$C_{14}H_{19}O_3N$ (249.3) Calc. C 67.44 H 7.68 N 5.62
Found » 67.54 » 7.58 » 5.72

Diethyl α-(α-ethoxyphenylethylideneamino)glutarate (IXb). This was obtained in a similar way from ethyl phenylacetimidate and diethyl L-glutamate hydrochloride. The ester distilled as a very viscous, colourless oil, b.p. 159° at 0.2 mm. Yield 35 %, calculated on unrecovered ester.

$C_{19}H_{27}O_5N$ (349.4) Calc. C 65.31 H 7.79 N 4.01
Found » 65.54 » 7.68 » 3.85

Diethyl α-ethoxyphenylethylideneaminosuccinate (IXc). Ethyl phenylacetimidate and ethyl L-aspartate hydrochloride, treated in the usual way, gave the Schmidt-ester in 67 % yield, calculated on unrecovered iminoester. B.p. 153—157° at 0.2 mm. The viscous, slightly yellow oil was kept at dry ice temperature.

$C_{18}H_{25}O_5N$ (335.4) Calc. C 64.46 H 7.52 N 4.18
Found » 64.65 » 7.56 » 4.34

Ethyl α-(α-ethoxyphenylethylideneamino)-β-phenylpropionate (IXd). This was prepared from ethyl phenylacetimidate and DL-phenylalanine ethyl ester hydrochloride in the usual way. The yield of distilled, colourless ester was 73 %, calculated on unrecovered iminoester. B.p. 163° at 0.2 mm. The ester crystallised on keeping at low temperature, m.p. 30—31°.

$C_{21}H_{25}O_3N$ (339.4) Calc. C 74.31 H 7.42 N 4.13
Found » 74.59 » 7.45 » 4.13

3-Benzyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine (X, R = H). The substituted iminoester (IV) (603 mg) was dissolved in ethanol (1 ml) and hydrazine hydrate (125 mg) added, when an exothermic reaction occurred. Next day, ether was added and colourless prisms (398 mg) separated on scratching. They recrystallised from ethanol-ether in rhombic plates. M.p. 184—186°.

$C_{10}H_{11}ON_3$ (189.2) Calc. C 63.64 H 5.86 N 22.20
Found » 63.22 » 5.84 » 22.27

3-Benzyl-5-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine (X, R = CH_3). This compound was prepared in 84 % yield from (IXa) and hydrazine in a similar way. It separated in dense, rhombic plates from ethanol, m.p. 189—190°.

$C_{11}H_{13}ON_3$ (203.2)	Calc.	C	65.01	H	6.45	N	20.68
	Found	»	64.70	»	6.78	»	20.88

3,5-Dibenzyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine (X, R = $C_6H_5CH_2$). When (IXd) was treated with hydrazine as above, a 90 % yield of the condensation product was obtained. It crystallised from absolute ethanol in colourless, rhombic plates, m.p. 171°.

$C_{17}H_{17}ON_3$ (279.3)	Calc.	C	73.10	H	6.14	N	15.05
	Found	»	73.38	»	6.24	»	14.91

3-Benzyl-5-carboxhydrazidomethyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine (XI). The ester (IXc) (695 mg) and hydrazine hydrate (609 mg) were dissolved in ethanol (2 ml) and the solution refluxed for 30 minutes. On cooling, the crystalline reaction product separated (464 mg). It recrystallised from hot water in small needles, m.p. 197—198°.

$C_{12}H_{15}O_2N_5$ (261.3)	Calc.	C	55.15	H	5.79	N	26.81
	Found	»	55.08	»	5.76	»	26.78

The compound reduced Fehling's reagent in the cold.

Benzylidene-derivative of (XI). The hydrazone (196 mg) was readily obtained, when a solution of (XI) (212 mg) and benzaldehyde (106 mg) in 50% ethanol (6 ml) was briefly heated. It separated in colourless needles from ethanol. The derivative sintered from *ca.* 140° but did not melt completely until 200° (dec.).

$C_{19}H_{19}O_2N_5$ (349.4)	Calc.	C	65.30	H	5.48	N	20.05
	Found	»	65.04	»	5.75	»	20.02

The reaction product of (IV) and morpholine, (XII) or (XIII)? When (IV) (890 mg) and morpholine (622 mg) were mixed and heated at 100° for 30 minutes, crystallisation sat in spontaneously. The product was repeatedly recrystallised from ethanol, and finally once from chloroform-petroleum ether. It appeared as colourless needles, m.p. 219°, soluble in dilute acid.

$C_{14}H_{16}O_2N_2$ (244.3)	Calc.	C	68.82	H	6.60	N	11.47
	Found	»	69.06	»	6.29	»	11.49

The above composition was supported by a molecular weight determination in phenol giving the values 218, 229 and 241.

SUMMARY

Ammonolysis of the substituted iminoesters, (IV) and (VI), has been shown to give compounds possessing the dimeric structures (V) and (VII).

Several N-substituted iminoesters (IX) have been prepared and their behaviour towards ammonia and hydrazine studied. With the latter they afford crystalline compounds, formulated as benzyldihydrotriazinones, (X) and (XI).

The ester (IV) reacts with morpholine at higher temperature to a crystalline compound, tentatively formulated as (XII) or (XIII).

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

REFERENCES

1. Kjær, A. *Acta Chem. Scand.* **7** (1953) 889.
2. Schmidt, E. *Ber.* **47** (1914) 2545.
3. In *The Chemistry of Penicillin,* Princeton University Press, Princeton, N. J. 1949, p. 727.
4. Cornforth, J. W., and Cornforth, R. H. *J. Chem. Soc.* **1947** 96.
5. Miller, C. S., Gurin, S., and Wilson, D. W. *J. Am. Chem. Soc.* **74** (1952) 2892.
6. Finger, H. *J. prakt. Chem.* [2] **76** (1907) 93.

Received June 9, 1953.