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Synthetic Studies of 4-Oxo- and 4-Imino-3,4-dihydro-1,3-oxazoles*[1]

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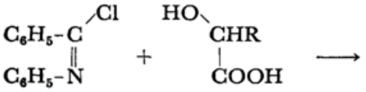
For the purpose of synthesizing new mesoionic compounds of oxazole ring system having oxo group at 4 position, reaction of *N*-phenylbenzimidoyl chloride with glycolic acid was examined. Only an unexpected rearranged product was obtained. The reaction of *N*-phenylbenzimidoyl chloride with glycolonitrile successfully afforded the intermediate, which was treated with hydrogen chloride or with picric acid or with acetyl perchlorate to give 4-imino-3,4-dihydro-1,3-oxazole derivatives. Condensation of *N*-phenylbenzimidoyl chloride with mandelonitrile followed by treatment with acetyl perchlorate gave 4-imino-3,4-dihydro-1,3-oxazole derivative.

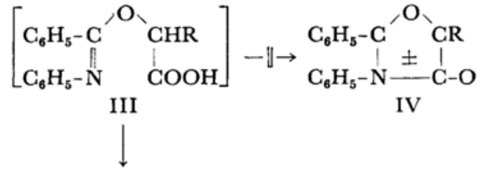
Of the possible mesoionic oxazoles, only 5-oxo-[1,2] and 5-imino-3,5-dihydro-1,3-oxazoles[3] have been reported. Though they are unstable in comparison with mesoionic thiazoles, some reactions were reported.[4] In the present study, we undertook the synthesis of 4-oxo- and 4-imino-3,4-dihydro-1,3-oxazoles because their structural relationship to 4-oxo- and 4-imino-3,4,-dihydrothiazoles[5] is of considerable interest.

As a possible route towards a synthesis of 4-oxo-3,4-dihydro-1,3-oxazole (IV), we tried the reaction of *N*-phenylbenzimidoyl chloride (I) with glycolic acid (IIa) anticipating the formation of an intermediate III. When this reaction was carried out in an ether solution in presence of triethylamine, the reaction product was benzoyloxyacetanilide (Va), its structure being deduced from its elementary analysis and infrared spectrum. Treatment of I with lactic acid (IIb) or mandelic acid (IIc) under the same conditions gave also rearranged products, Vb and Vc respectively.



I II

IIa: $R=H$
IIb: $R=CH_3$
IIc: $R=C_6H_5$

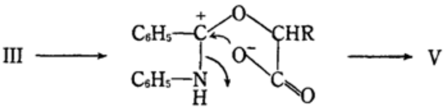


III IV

$C_6H_5COOCHRCONHC_6H_5$
V

Va: $R=H$
Vb: $R=CH_3$
Vc: $R=C_6H_5$

The reaction of *N*-phenyl-*p*-methoxybenzimidoyl chloride with IIa also afforded the rearranged product. Attempts to obtain III and IV under various conditions were unsuccessful. For the formation of V the C=N bond in I must be cleaved. The same type of rearrangement has been reported for the reaction of thiobenzanilide with bromoacetic acid in boiling benzene.[5] The formation of V may proceed through the intermediate III which is not stable enough to be isolated, presumably due to the enhanced electrophilic character of imidate carbon atom as compared with thioanalog. The rearrangement occurred even in the presence of less equimolar triethylamine. As a possible mechanism, it seems that the reaction is initiated by a nucleophilic attack of carboxyl oxygen toward imidate carbon atom as shown below.



As a first step in the formation of 4-imino-3,4-dihydro-1,3-oxazole (VIII), I was condensed with glycolonitrile (VIa) in the presence of sodium hydride in THF to yield VIIa. Relatively unstable intermediate without purification gave undetectable brownish oil.

[*1] Studies of mesoionic compounds. XXXII.

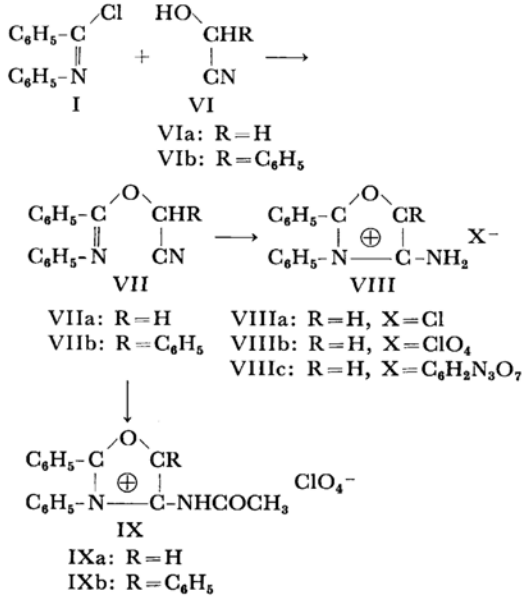
1) R. Huisgen, H. Gotthardt, H. O. Bayer and F. C. Schaefer, *Angew. Chem.*, **76**, 185 (1964).

2) M. Ohta and T. Mase, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **89**, 714 (1968).

3) S. Sato and M. Ohta, This Bulletin, **41**, 2218 (1968).

4) R. Huisgen, E. Funke, F. C. Schaefer, H. Gotthardt and E. Brunn, *Tetrahedron Letters*, **1967**, 1809.

5) M. Ohta, H. Chosho, C. Shin and K. Ichimura, *Nippon Kagaku Zasshi, (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **85**, 440 (1964).



I VI

VIa: R=H

VIb: R=C_6H_5

VII VIII

VIIa: R=H

VIIb: R=C_6H_5

VIIIa: R=H, X=Cl

VIIIb: R=H, X=ClO_4

VIIIc: R=H, X=$C_6H_2N_3O_7$

IX

IXa: R=H

IXb: R=C_6H_5

Treatment of this intermediate with hydrogen chloride in benzene gave the expected product, 4-imino-2,3-diphenyl-3,4-dihydro-1,3-oxazole hydrochloride (VIIIa). The infrared spectrum was consistent with that expected for VIIIa, but the elementary analysis indicated that the solid contained a small amount of dihydrochloride. The hydrochloride VIIIa, which was unstable and decomposed gradually into an unknown brownish compound, was converted to stable perchlorate (VIIIb) by treatment with silver perchlorate. The perchlorate showed a characteristic band at 308 mμ (ε, 9200) in its ultraviolet spectrum suggestive of its heteroaromatic system. On treating VIIa with picric acid, ring formation took place to produce the picrate (VIIIc) as yellow needles. *N*-Acetyl derivative IXa was obtained by treatment of VIIa with perchloric acid in acetic anhydride. Condensation of I with mandelonitrile followed by addition of acetyl perchlorate, without isolation of the intermediate (VIIb) because of its unstability, gave 5-phenyl derivative of *N*-acetyl perchlorate (IXb). These ring formations seem to proceed as a result of interaction of two polar groups, by a mechanism similar to that of sydnone imine salts.[6] The treatment of IXa and IXb with sodium bicarbonate afforded benzanilide, sodium perchlorate and an unidentified compound, and did not give free bases, probably because it has a high unstability unlike *N*-acylthiazone-imines.[7] The ring formation of VIIa with acetyl chloride, benzenesulfonyl chloride, oxalyl chloride and malonyl chloride was unsuccessful.

The structure of these products were established by infrared spectra, which showed strong bands at 3150—3350 cm^{-1} resulting from N–H stretching vibration, and at 1630—1680 cm^{-1} resulting from oxazole ring. They are very similar to those of 4-thiazone-imines. *N*-Substituted carbonyl group showed absorption band at relatively high frequency, 1690—1705 cm^{-1}, probably due to the effect of positive charge of the ring.

Some 4-imino-3,4-dihydro-1,3-oxazole salts showed absorption maxima in their ultraviolet spectra at about 300 mμ just as 4-thiazone-imine salts.

Experimental

All melting points were determined on a micro hot stage, and are not corrected. Infrared spectra were taken on KBr tablets.

Benzoyloxyacetanilide (Va). To a solution of 0.8 g of glycolic acid (IIa) and 2.0 g of triethylamine in 30 m*l* of dry ether, 2.2 g of *N*-phenylbenzimidoyl chloride (I) was added. The precipitates which separated out gradually were allowed to stand overnight, filtered and washed repeatedly with water. Recrystallization of the solid from benzene gave 2.2 g of white needles; mp 152—153°C. IR: 3295, 1725, 1670 cm^{-1}.

Found: C, 70.33; H, 4.78; N, 5.49%. Calcd for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.13; N, 5.49%.

Benzoyloxymethylacetanilide (Vb). To a solution of 4.3 g of I and 1.8 g of lactic acid in 30 m*l* of dry ether, 6.0 g of triethylamine was added dropwise and the solution was stirred for an hour at room temperature. The precipitates which separated out were collected by filtration, washed with water, recrystallized from benzene to give 4.3 g of white needles; mp 154—155°C. IR: 3260, 1725, 1670 cm^{-1}.

Found: C, 71.15; H, 5.90; N, 5.46%. Calcd for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.61; N, 5.20%.

Benzoyloxyphenylacetanilide (Vc). A solution of 2.3 g of I in 10 m*l* of dry ether was added to a solution of 1.5 g of mandelic acid and 1.2 g of triethylamine in 30 m*l* of dry acetonitrile under cooling with water. The precipitates separated out gradually. After stirring for an hour, the precipitates were filtered off and the filtrate was concentrated under vacuum. Then the crystalline product was collected and washed repeatedly with ether. The product was recrystallized from benzene to give 2.8 g of white needles; mp 170.5—171.5°C. IR: 3220, 1723, 1663 cm^{-1}.

Found: C, 76.24; H, 5.41; N, 4.07%. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23%.

***p*-Methoxybenzoyloxyacetanilide.** A solution of 0.8 g of IIa and 2.0 g of triethylamine and 2.5 g of *N*-phenyl-*p*-methoxybenzimidoyl chloride was allowed to stand overnight at room temperature. Precipitates which separated out gradually were collected and washed with water repeatedly. The solid was reprecipitated from benzene solution with ligroin to give 1.5 g of white needles; mp 104—105°C. IR: 3280, 1728, 1673 cm^{-1}.

Found: C, 67.05; H, 5.26; N, 5.56%. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91%.

***o*-Cyanomethyl-*N*-phenylbenzimidate (VIIa).** To a solution of 2.8 g of I and 2.8 g of glycolonitrile (VIa) in 30 m*l* of THF, a suspension of 4.8 g of sodium

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[6] P. Brookes and J. Walker, *J. Chem. Soc.*, **1957**, 4409.

[7] H. Chosho, K. Ichimura and M. Ohta, This Bulletin, **37**, 1670 (1964).

hydride in THF was added dropwise under cooling with an ice-salt bath, resulting in a violent evolution of hydrogen gas. After stirring for an hour, the solid was filtered off and the filtrate was concentrated under vacuum without heating. The resulting oily product was washed a few times with *n*-hexane, which was cooled with dry ice in acetone, in order to crystallize the product. Recrystallization of the product from the minimum amount of *n*-hexane gave 2.2 g of white needles; mp 61—62°C. IR: 1680 cm^{-1}.

Found: C, 76.06; H, 4.95; N, 11.76%. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86%.

4-Imino-2,3-diphenyl-3,4-dihydro-1,3-oxazole hydrochloride (VIIIa). To a solution of 0.7 g of VIIa in 15 m*l* of benzene, 10 m*l* of benzene containing 0.2 g of gaseous hydrogen chloride was added and an exothermic reaction took place. The precipitates which separated out were collected and recrystallized from chloroform to give 0.27 g of VIIIa; mp 116—122°C. IR: 1680, 1650 cm^{-1}. The elementary analysis of the product was slightly inconsistent with that expected for VIIIa, probably because of a small amount of dihydrochloride.

4-Imino-2,3-diphenyl-3,4-dihydro-1,3-oxazole perchlorate (VIIIb). To a solution of 0.27 g of VIIIa in 15 m*l* of dry acetonitrile, was added dropwise a solution of 0.20 g of silver perchlorate in chloroform-ethanol. The precipitated silver chloride was filtered off and the filtrate was concentrated under vacuum to give a white solid. Reprecipitation from chloroform solution with ether gave 0.16 g of white needles; mp 160—166°C. $\lambda_{\max}^{CH_3CN}$ 298 mμ (ε, 13600).

Found: C, 53.50; H, 3.89; N, 8.32%. Calcd for $C_{15}H_{13}N_2O_5Cl$: C, 53.49; H, 3.86; N, 8.32%.

4-Imino-2,3-diphenyl-3,4-dihydro-1,3-oxazole picrate (VIIIc). A benzene solution of VIIa was treated with a solution of picric acid in benzene to yield picrate which was recrystallized from isopropyl alcohol to give yellow needles; mp 108—109°C. IR: 3320, 3150, 1660, 1628 cm^{-1}.

Found: C, 53.86; H, 2.94; N, 15.15%. Calcd for $C_{21}H_{15}N_5O_8$: C, 54.20; H, 3.25; N, 15.05%.

***N*-Acetyl-4-imino-2,3-diphenyl-3,4-dihydro-1,3-oxazole perchlorate (IXa).** To a solution of 1.6 g of VIIa in 40 m*l* of acetic anhydride, 2 g of 70% aqueous perchloric acid was added dropwise with stirring and cooling with ice-salt bath. After 10 min ether was poured into the solution to give white precipitates, which were reprecipitated from chloroform solution with ether to give 1.1 g of white needles; mp 178—178.5°C. IR: 3260, 3215, 1690, 1640 cm^{-1}. $\lambda_{\max}^{CH_3CN}$ 308 mμ (ε, 9200), 244 mμ (ε, 9200).

Found: C, 53.23; H, 3.97; N, 7.02%. Calcd for $C_{17}H_{15}N_2O_6Cl$: C, 53.62; H, 3.99; N, 7.40%.

***N*-Acetyl-4-imino-2,3,5-triphenyl-3,4-dihydro-1,3-oxazole Perchlorate (IXb).** To a solution of 5.4 g of I and 3.3 g of mandelonitrile (VIIb) in 20 m*l* of benzene, 5 g of triethylamine was added dropwise. After stirring for 2 hr at room temperature, precipitates which separated out were filtered off and the filtrate was concentrated under vacuum, until no triethylamine was detected. The concentrated solution was diluted with 30 m*l* of acetic anhydride, to which 7 g of 70% aqueous perchloric acid was added under cooling with ice-salt bath. Precipitates, which gradually separated out, were collected and recrystallized from ethanol to give 2.6 g of white needles; mp 228.5—230°C. IR: 3215, 3170, 1705, 1670 cm^{-1}.

Found: C, 60.48; H, 4.54: N, 5.97%. Calcd for $C_{23}H_{19}N_2O_6Cl$: C, 60.73; H, 4.18; N, 6.16%. $\lambda_{\max}^{CH_3CN}$ 312 mμ (ε, 17600), 251 mμ (ε, 21900).