# Acylation of Nitrogen Heterocycles under the Conditions of the Schotten-Baumann Reaction. III. Imidazoles.

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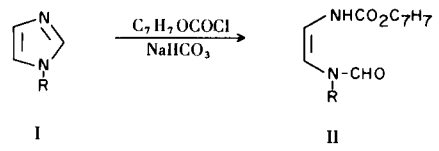
Imidazole and five *N*-monoalkylimidazoles were tested for their ability to undergo ring fission on carbobenzoxylation. Reaction occurred only with imidazoles substituted with strong electron withdrawing groups such as nitrophenyl, dinitrophenyl and monocarbobenzoxy.

Recently we have described the benzoylations and carbobenzoxylations of benzimidazoles (1) and substituted adenines (2) in ethyl acetate-aqueous base. It was found that in the condensed ring systems the imidazole ring was opened on acylation to give Bamberger fission products (II). This investigation has now been extended to the more stable monocyclic imidazole. In contrast to the benzimidazoles, *N*-benzylimidazole, *N*-*p*-methoxyphenylimidazole and *N*-phenylimidazole failed to react with carbobenzoxy chloride in ethyl acetate-aqueous bicarbonate mixture. The starting material was recovered unchanged in the three cases. Only the introduction of strong electron withdrawing groups into the phenyl substituent facilitated the reactions. Thus, *N*-*p*-nitrophenylimidazole (Ia) and *N*-(2,4-dinitrophenyl)imidazole (Ib) reacted with carbobenzoxy chloride to give 11 and 96% yield of the fission products, IIa, IIb, respectively.




I II

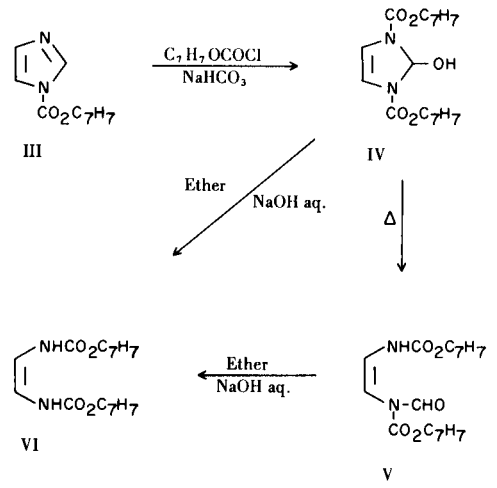
a. R = *p*-$NO_2C_6H_4$-.
b. R = 2,4-$(NO_2)_2C_6H_3$-.

These observations support the explanation suggested in the benzimidazole series (1) to account for the substituent effect on the fission reaction. The monocyclic imidazole system is more stable (resonance energy) than the imidazole ring in the condensed benzimidazole or purine systems and, therefore, a stronger electron withdrawing group is needed to reduce the resonance stability of the imidazole in order to facilitate the Bamberger reaction.

Carbobenzoxylation of the unsubstituted imidazole in a mixture of ether-aqueous bicarbonate with one equivalent of carbobenzoxy chloride afforded *N*-monocarbobenzoxyimidazole (III) (3) in 89% yield. If two equivalents of the acid chloride were used, or if the monoacyl derivative (III) was further acylated with another mole of carbobenzoxychloride, *N*,*N*'-dicarbobenzoxy-2-hydroxyimidazoline (IV) was obtained. (See Scheme I).

The thermally unstable hydroxyimidazoline (IV) opened up in boiling benzene to give *N*,*N*'-dicarbobenzoxy-*N*-formyldiaminoethylene (V), which was converted by the removal of the formyl group with aqueous base, to 1,2-dicarbobenzoxyaminoethylene (VI). Under the same experimental conditions the dicarbobenzoxy-2-hydroxyimidazoline derivative (IV) is directly converted to the 1,2-dicarbobenzoxyaminoethylene (VI).

SCHEME I



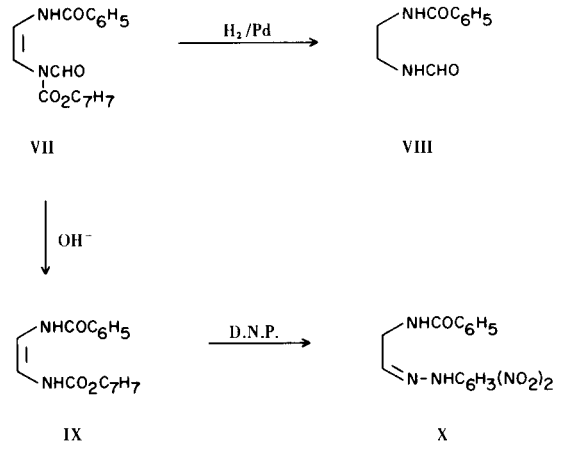

III IV V VI

The structures assigned to the various products are based on their infrared spectra. The 2-hydroxyimidazoline derivative (IV) showed OH absorption at 3660 $cm^{-1}$ and only one CO absorption at 1725 $cm^{-1}$. Its open chain isomer (V) showed NH absorption at 3520 and 1505 $cm^{-1}$ and CO absorptions at 1755 and 1710 $cm^{-1}$ (broad). The 1,2-dicarbobenzoxyaminoethylene (VI) showed NH absorptions at 3430 and 1525 $cm^{-1}$, CO absorption at 1725 $cm^{-1}$ and a strong C=C (*cis*) absorption at 1695 $cm^{-1}$. The *cis* isomer was isomerized in aqueous acetone and in the presence of iodine to the *trans* isomer.

Benzoylation of the monocarbobenzoxyimidazole (III) with benzoyl chloride in ether-aqueous bicarbonate afforded only the ring fission product (VII).

Catalytic hydrogenation converted VII to 1-formamido-2-benzamidoethane (VIII). Mild basic hydrolysis removed the formyl group giving 1-benzamido-2-carbobenzoxyaminoethylene (IX), which gave a 2,4-dinitrophenyl (D.N.P.) derivative identical with the 2,4-dinitrophenyl derivative obtained from benzamidoacetaldehyde diethylacetal (X).

SCHEME II




## EXPERIMENTAL

Melting points are corrected. Infrared spectra were measured in chloroform solutions (unless otherwise indicated).

*N*-Substituted imidazoles.

*N*-Benzylimidazole was prepared from *N*-benzylaminoacetal and thiocyanate according to Jones (4), *N*-phenylimidazole was prepared from phenylisothiocyanate and aminoacetal according to Wohl and Marckwald (5) and *N*-*p*-nitrophenylimidazole was prepared by the nitration of the phenyl derivative according to Forsythe and Pyman (6).

*N*-*p*-Methoxyphenylimidazole.

*N*-*p*-Methoxyphenyl-2-imidazolethione (10 g., m.p. 217-219°) which was prepared from *p*-methoxyphenylisocyanate and aminoacetal was dissolved in dilute nitric acid (20 ml. concentrated acid + 130 ml. water). The solution was refluxed for two hours, concentrated *in vacuo*, and made alkaline with aqueous sodium hydroxide (10%). The oil which separated was extracted with ethyl acetate, the solution was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The solid obtained was crystallized three times from hexane, m.p. 67-68°; yield, 4.3 g. (50%).

*Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.13; H, 5.92; N, 16.18.

*N*-(2,4-Dinitrophenyl)imidazole.

A mixture of 2,4-dinitrochlorobenzene (20.2 g., 0.1 mole) in ether (300 ml.) and imidazole (6.8 g., 0.1 mole) in aqueous sodium bicarbonate (250 ml., 0.4 *N*) was stirred for one week. The brown precipitate was filtered and crystallized from aqueous ethanol. The yield was 8.1 g. (34.6%), m.p. 143-144° (lit. (7) m.p. 144°).

Carbobenzoxylation of *N*-monosubstituted Imidazole- General Procedure.

A mixture of the imidazole derivative (0.005 mole), ether (20 ml.) and aqueous sodium bicarbonate (15 ml., 1 *N*) was cooled in an ice-water bath. To the well stirred suspension there was added dropwise, carbobenzoxy chloride (1.28 g., 0.0075 mole) dissolved in 10 ml. of ether. The solution was stirred for one hour at the ice-bath temperature and an additional hour at room temperature. The ether layer was separated, washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by chromatography. In the case of 1-benzyl, 1-phenyl and 1-*p*-methoxyphenyl imidazole the starting material was recovered together with benzyl alcohol.

Carbobenzoxylation of *N*-*p*-nitrophenylimidazole (IIa).

A mixture of the imidazole derivative (2.85 g., 0.015 mole) in ethyl acetate (120 ml.) and aqueous sodium bicarbonate (45 ml., 1 *N*) was treated with carbobenzoxy chloride (2.80 g., 0.0165 mole) as described above. The mixture obtained after removal of the solvent was chromatographed on silica gel (120 g.). The product was eluted with benzene and crystallized from benzene-hexane. It melted at 117-119°, yield, 560 mg. (10.8%). It showed NH absorptions at 3450 and 1515 $cm^{-1}$, CO absorptions at 1725 and 1690 $cm^{-1}$, and C=C absorption at 1670 $cm^{-1}$ in the infrared.

*Anal.* Calcd. for $C_{17}H_{15}N_3O_5$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.92; H, 4.61; N, 12.29.

Carbobenzoylation of *N*-(2,4-dinitrophenyl)imidazole (IIb).

*N*-(2,4-dinitrophenyl)imidazole was carbobenzoxylated as described above for the mononitro derivative. The dark red product which separated from the reaction mixture was combined with the fraction that dissolved in the ethyl acetate. Crystallization from ethyl acetate afforded a crystalline product in 96% yield, m.p. 155-156°. It showed NH absorptions at 3340 and 1520 $cm^{-1}$, CO absorptions at 1755 and 1710 $cm^{-1}$ and C=C absorption at 1670 $cm^{-1}$ in the infrared.

*Anal.* Calcd. for $C_{17}H_{14}N_4O_7$: C, 52.85; H, 3.65; N, 14.50. Found: C, 52.72; H, 3.73; N, 14.61.

*N*-Carbobenzoxyimidazole (III).

Imidazole (0.75 g., 0.011 mole) was dissolved in a mixture of ether (50 ml.) and aqueous bicarbonate (30 ml., 1 *N*). To the

cooled mixture (ice-water bath) was added dropwise with stirring, carbobenzoxy chloride (1.7 g., 0.01 mole) dissolved in ether (20 ml.). Stirring was continued for an additional hour at room temperature. The ether solution was washed with water, dried over anhydrous sodium sulfate and the ether was evaporated under reduced pressure. The product (3) (1.8 g., 89%) which solidified in the refrigerator, was an oil at room temperature. It decomposes on chromatography on silica gel or alumina columns. It showed a carbonyl absorption at 1780 $cm^{-1}$ in the infrared (chloroform).

1,3-Dicarbobenzoxy-2-hydroxyimidazoline (IV).

*N*-carbobenzoxyimidazole (1.01 g., 0.005 mole) was carbobenzoxylated in a mixture of ether (30 ml.) and aqueous bicarbonate (15 ml., 1 *N*) with carbobenzoxy chloride (0.95 g., 0.006 mole) dissolved in ether (5 ml.) as described above. The residue was dissolved in ether (5 ml.) and was left in the refrigerator overnight. The thermally unstable solid was purified by dissolving it in benzene, and precipitating with hexane. An analytical sample was obtained by crystallization at low temperature from benzene-hexane. It melted at 90-91°, yield, 1.4 g. (79%). It showed OH absorption at 3660 $cm^{-1}$ and a carbonyl absorption at 1725 $cm^{-1}$ in the infrared.

The same product was also obtained in 82% yield by the carbobenzoxylation of imidazole with two equivalents of carbobenzoxy chloride in ether-aqueous bicarbonate.

*Anal.* Calcd. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.22; H, 5.18; N, 8.07.

*N,N'*-Dicarbobenzoxy-*N*-formyl-1,2-diaminoethylene (V).

A solution of 1,3-dicarbobenzoxy-2-hydroxyimidazoline (0.5 g.) in benzene (50 ml.) was refluxed for 3 hours. The solvent was removed *in vacuo* and the residue triturated with hexane. The white solid was filtered and crystallized from benzene-hexane. The yield was 0.3 g. (60%), m.p. 103°. The product showed NH absorptions at 3550 and 1505 $cm^{-1}$ and CO absorptions at 1755 and 1710 $cm^{-1}$ (broad) in the infrared.

*Anal.* Calcd. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.24; H, 5.17; N, 7.80.

*cis*-1,2-Dicarbobenzoxyaminoethylene (VI).

1,3-Dicarbobenzoxy-2-hydroxyimidazoline (0.5 g.) was dissolved in ether (100 ml.), aqueous sodium hydroxide (50 ml., 1 *N*) was added and the mixture was stirred for 2 hours at room temperature. The ether solution was separated, washed with water and dried over sodium sulfate. The oil obtained after removal of the ether, solidified on trituration with hexane. It was filtered and crystallized from ethyl acetate-hexane. The yield was 0.25 g. (54%), m.p. 101-102°. It showed NH absorptions at 3430 and 1525 $cm^{-1}$, CO absorption at 1725 $cm^{-1}$ and C=C absorption at 1695 $cm^{-1}$.

The same product (mixed m.p. and I.R.) was obtained by treating V in either with aqueous sodium hydroxide.

*Anal.* Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C. 66.47; H, 5.57; N, 8.81.

*trans*-1,2-Dicarbobenzoxyaminoethylene.

The *cis* isomer (0.5 g.) was dissolved in acetone (20 ml.) and water (15 ml.). A crystal of iodine was added and the solution was left at room temperature for 48 hours. The solid which separated was filtered and crystallized from acetone. The yield was 0.41 g. (82%), m.p. 214-216°. It showed (potassium bromide) NH absorptions at 3360 and 1550 $cm^{-1}$ and a CO absorption at 1680 $cm^{-1}$ (broad).

*Anal.* Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.15; H, 5.35; N, 8.54.

The two carbobenzoxyaminoethylenes gave a positive reaction with dinitrophenylhydrazine (m.p. 187-188°). The D.N.P. derivative was found to be identical (mixed m.p., I.R.) with a D.N.P. derivative obtained from carbobenzoxyaminoacetaldehyde diethyl acetal.

*N*-Benzoyl-*N'*-carbobenzoxy-*N'*-formyl-1,2-diaminoethylene (VII).

*N*-Carbobenzoxyimidazole (8.08 g., 0.04 mole) was benzoylated in ether (200 ml.)-aqueous bicarbonate (120 ml., 1 *N*) mixture with benzoyl chloride (6.2 g., 0.044 mole) dissolved in ether (30 ml.) as described above for the carbobenzoxylation. The product was triturated with hexane, filtered and crystallized from benzene-hexane. It melted at 89-91°, yield 8.4 g. (65%). It showed NH absorptions at 3430 and 1510 $cm^{-1}$ and CO absorptions at 1760 and 1690 $cm^{-1}$ (broad) in the infrared.

*Anal.* Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.81; H, 4.94; N, 8.85.

1-Benzamido-2-carbobenzoxyaminoethylene (IX).

A suspension of compound VII (3.5 g.) in a mixture of ether (150 ml.) and aqueous sodium hydroxide, (120 ml., 1 *N*) was stirred for 2 hours at room temperature. The ether solution was separated, dried over sodium sulfate and the ether evaporated under reduced pressure. The oily residue was triturated with hexane and was left overnight in the refrigerator. The solid which separated was filtered and crystallized twice from ethyl acetate. The product melted at 112-113°, yield 2 g. (60%). It showed NH absorptions at 3340 and 1515 $cm^{-1}$ and CO absorptions at 1725 and 1670 $cm^{-1}$ in the infrared.

*Anal.* Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 69.00; H, 5.55; N, 9.48.

This compound gave a positive reaction with dinitrophenylhydrazine in methanol (24 hours). The D.N.P. derivative melted at 203-204° (dec.) and was identical (mixed m.p. and I.R.) with a D.N.P. derivative prepared from benzamidoacetaldehyde diethylacetal.

1-Formamido-2-benzamidoethane (VIII).

The fission product (VII) (2 g.) in acetic acid (80 ml.) was catalytically hydrogenated at 4 atmospheres pressure and in the presence of 5% palladium charcoal (0.4 g.). After 7 hours the catalyst was filtered off and the solvent was removed *in vacuo*. The residue was triturated with ethyl acetate, filtered and crystallized from ethyl acetate. The yield was 0.87 g. (83%), m.p. 105-106°. It showed NH absorptions at 3460, 3340 and 1525 $cm^{-1}$ and CO absorption at 1675 $cm^{-1}$ (broad) in the infrared.

*Anal.* Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.54; H, 6.40; N, 14.69.

## REFERENCES

(1) D. Ben-Ishai, E. Babad and Z. Bernstein, *Israel J. Chem.*, 6, 551 (1968).

(2) J. Altman and D. Ben-Ishai, *J. Heterocyclic Chem.*, 5, 679 (1968).

(3) H. A. Staab and A. Mannschreck, *Chem. Ber.*, 95, 1284 (1962).

(4) R. G. Jones, *J. Am. Chem. Soc.*, 71, 383 (1949).

(5) A. Wohl and W. Marckwald, *Ber.*, 22, 568 (1889).

(6) R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 397 (1930).

(7) M. Zahan and H. Pflannmuller, *Biochem. Z.*, 330, 97 (1958).

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