# Reaction of Some Unsaturated Carboxylic Acids with O-Phenylenediamine in Acid Medium-II

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**Summary:** $\alpha,\beta$-Unsaturated carbocylic acids, e.g. crotonic, methyl-crotonic, methacrylic and acrylic acid when separately treated with unsubstituted o-phenylenediamine under Philip's reaction conditions gave benzodiazepinone (1,3-5) as expected. However, when crotonic acid was treated with 4-nitro-o-phenylenedimine under similar conditions, benzimidazole (6) was the product, with 4-chloro it gave a mixture of benzimidazole (8) and of regioisomeric benzodiazepinones (9a,b), with 4-methyl only one regioisomeric benzodiazepinone (10) was the product. Methacrylic acid gave only one regioisomer of benzodiazepinone (7) with 4-nitro-o-phenylenediamine, whereas vinylacetic acid when separately treated with 4-nitro-,4-chloro-, 4-methyl- as well as unsubstituted o-phenylenediamine led to the formation of corresponding benzimidazole (6,8,11 and 2). All the products (1, 11) were identified and their structure was confirmed with the help of elemental and spectroscopic analyses. These results indicate that not only the structure of unsaturated carboxylic acid, but also the substituent present in the ring of o-phenylenediamine influence the mechanism of Philip's reaction.

Search for new medicinal agents has led to the synthesis of several benzimidazoles and benzodiazepinones. Condensation of o-phenylenediamine with carbocylic acids in 4N HCl gives benzimidazoles [1]. When $\alpha,\beta$-unsaturated carbocylic acids are used, benzodiazepinones [2] are formed under similar conditions. Thus 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (1) is easily prepared by the reaction of unsubstituted o-phenylenediamine with crotonic acid. On this basis, 4-nitro-o- phenylenediamine was condensed with crotonic acid in 4N HCl to obtain 7/8-nitro-4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2 -one. This compound could serve as starting material after resolution for the preparation of a series of configurationally similar 7/8 substituted benzodiazepinones and CD spectral studies could lead to useful results. However, the reaction gave 5-nitro-2,3-propen-2-benzimidazole (6) and the desired benzodiazepinone had to be synthesized by the nitration [3] of (1). This observation pointed to the influence of the substituents present in the 4-poisiton of o-phenylenediamine on the mechanism of Philip's reaction. It was therefore considered worthwhile to perform some more condensation reactions using o-phenylenediamine having different substituents in 4-position in order to establish this influence. Present paper describes the results of these experiments. In the first paper of the series [2c] reaction of crotonic and vinylacetic acids separately with unsubstituted o-phenylenediamine leading to the formation of 1 and 2 has been described.

To begin with, unsubstituted o-phenylenediamine was reacted with different unsaturated carboxylic acids in 4N hydrochloric acid. It was found that $\alpha,\beta$−unsaturated acids, e.g. crotonic, methyl crotonic, methacrylic and acrylic acids led to the formation of respective benzodiazepinones (1,3-5, Table-1) while vinylacetic acid in its reaction separately with 4-nitro-,4-chloro-, 4-methyl- and unsubstituted o-phenylene- diamine was consistent, i.e., it gave respective benzimidazoles (6,8,11 and 2 [2c] Table-1). However, crotonic acid reacted with 4-nitro-o-phenylenediamine to give benzimidazole (6, Table-1) as already stated, with 4-chloro- o-phenylenediamine it gave a mixture of benzimidazole and of regioisomeric benzodiazepinones (8 and 9a, 9b, Table 1) and only one regioisomer of the expected benzodiazepinones (10, Table 1) with 4-methyl-o-phenylenediamine. Methacrylic acid gave one regioisomer of benzodiazepinone (7, Table-1) in its reaction with 4-nitro-o-phenylenediamine. Percentage yield, physical properties and mass spectral fragmentation pattern

Table-1

| Compound No. | Name of Compound | M.P./Solvent for Recrystallisation | $R_fX10^2$ | % Yield | Mass Spectral Fragmentation |
|---|---|---|---|---|---|
| (1) | 4-Methyl-1,3,4,5-tetrahydro-5-benzodiazepin-2-one | 184-186°C/$CHCl_3$ | 40[a)] | 72 | 176,161,144,133, 119 (base peak) 108,92. |
| (2) | 2,3-Propene-2-benzimidazole | 158-60°C/EtOAc | 91[b)] | 50 | 158,143,132,118 |
| (3) | 4,4-Dimethyl-1,2,4,5-tetrahydro-2H-1, t-benzodiazepin-2-one | 253°C/$CHCl_3$ | 15[b)] | 10 | 190,175,150,133 (base peak, 119,106,92. |
| (4) | 3-Methyl-1,3,4,5-tetrahydro-2H-1, 5-benzodiazpin-2-one | 196°C/$CHCl_3$ | 16[b)] | 45 | 176,160,150,134,119 (base peak), 107,92. |
| (5) | 1,3,4,5-Tetrahydro-2H-1, 5-benzodiazepin-2-one | 119-120°C/$CCl_4$ | 18[b)] | 40 | 162,147,133,119 (base peak), 107,92. |
| (6) | 5-Nitro-2,3-propene-2-benzimidazole | 196-198°/Acetone | 82[a)] | 50 | 203,177,157(bac peak) 142,132,119,107. |
| (7) | 3-Methyl,8-nitro-1,3,4,5-tetrahydro-2H-1, 5-benzodiazepin-2-one | 235°C/Acetone | 77[a)] | 5 | 221,204,193,164(base |
| (8) | 5-Chloro-2,3-propene-2-benzimidazole | 196-198°C/C | 42[a)] | 30 | 192(base peak),166, 155,131,103,90. |
| (9) | 7&8-Chloro-4-methyl-1,3,4,5-2H-tetrahydro-1,5-benzodiazepin-2-one | 1,162-170°C/ | 48[a)] | 20 | 210,195,167,153(base peak),142,119,90. |
| (10) | 4,7/8-Dimethyl-1,3,4,5-tetrahydro-2H-1, 5-benzodiazepin-2-one | 186-188°C/EtOAC | 52 | 13 | 190,175,147,134,133 (base peak)122,106,92 |
| (11) | 5-Methyl 2,3-propene-2-benzimidazole | 187°C/MeOH/$H_2O$ | 53 | 15 | 172 (base peak),157, 146,131,116,104. |

a) $CHCl_3$ : MeOH (9:1)
Acetone : Pet.ether (4:1)

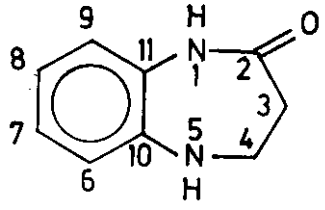
of different prodcuts (1 -11) are shown in Table-1. Tables 2a and 2b show $^1H$ n.m.r peak assignments to (1 - 11).

As described above, only reaction of two acids, namely crotonic and vinyl acetic acids have been investigated with the whole series of 4-nitro, 4-chloro-, 4-methyl and unsubstituted o-phenyl enediamines. Vinyl acetic acid which is not an $\alpha,\beta-$unsaturated acid gave respective benzimidazole (6,8,11) and (2) as expected. Reaction of crotonic acid, on the other had turned out to be sensitive to the influence of substituents present in the aromatic ring of o-phenylenediamine.

Electron attracting group such as nitro-led to the formation of benzimidizole (6) only, whereas $CH_3$ - group, which is electron donating gives one regioisomer of benzodiazepinone (10). Behaviour of chloro-substituent is intermediate, and it leads to the formation of a mixture of benzimidazole (8) and regioisomeric benzodiazepinones (9a, b). It is interesting to note that methyl subsituated o-phenylenediamine gives only one regio-siomer of the benzodiazepinone instead of two possible isomers (Table-2a). Another point of interest is that the structure of $\alpha,\beta-$unsaturated acid also influences the mechanism of this reaction. Methacrylic acid gives one regioisomerically pure benzodiazepionone (7) in contrast to crotonic acid which gives nitro-substituted benzimidazole (6) under similar conditions (Table-1 and 2a).

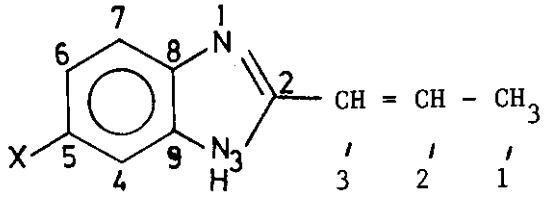
Separation of (8) from the mixture of (9a,b) could be effected with the help of silica-gel medium pressure column chromatography. All attemps to separate (9a) and (9b) failed. However, in $^1H$ n.m.r. spectrum of(9), two sets of peaks were visible (Table 2a) and peak assignments could be made because one of the isomers formed in larger amounts than the other and was designated as (9a) and the other one which was present only in half the amount was nominated as( 9b).

Table-2(a): $^1$H Chemical shifts of compound 1,3-5,7,9a,b,10 in ppm



| Compound No. | Solvent | 1NH | 3CH$_2$ | 3CH | 3CH$_3$ | 4CH$_2$ | 4CH | 3CH$_3$ | 5NH | 6H | 7H | 8H | 9H | 8CH$_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) | CDCl$_3$ | 8.2 | 2.14/2.61 | - | - | - | 3.99 | 1.30 | 3.50 | 6.72 | | | 7.0) | - |
| (3) | DMSO-d$_6$ | ? | 2.21 | - | - | - | - | 1.25 | ? | (6.86 | | | .90) | - |
| (4) | CDCl$_3$ | ? | - | 2.83 | 1.19 | 3.37/3.60 | - | | ? | (6.70 | | | 6.96) | - |
| (5) | CDCl$_3$ | 8.2 | 2.73 | - | - | 3.36 | - | - | ? | (6.68 | | | 7.06 ) | - |
| (7) | CDCl$_3$ | ? | - | 2.75 | 1.03 | 3.35 | - | - | ? | 7.04 | - | 7.43 | 7.64 | - |
| (9a) | DMSO-d$_6$ | 9.57 | 2.23/2.44 | - | - | - | 3.80 | 1.15 | 5.50 | 6.80 | 6.68 | - | 6.88 | - |
| (9b) | DMSO-d$_6$ | 9.35 | 2.23/2.44 | - | - | - | 3.39 | 1.16 | 5.63 | 6.88 | - | 6.88 | 6.81 | - |
| (10) | DMSO-d$_6$ | 9.37 | 2.47/2.11 | - | - | - | 3.35 | 1.15 | 4.96 | 6.77 | - | 6.77 | 6.68 | 2.15 |

Table-II(b): 1H Chemical shifts of compounds 6,8,11 and 2 in ppm




| Compound No. | Solvent | 1'CH$_3$ | 2'CH | 3'CH | 4H | 5H | 6H | 7H | 5CH$_3$ |
|---|---|---|---|---|---|---|---|---|---|
| 6 | CDCl$_3$ | 1.96dd | 6.96 dq | 6.52 d | 8.35 | - | 8.06 | 7.62 | - |
| 8 | DMSO | 1.97 | 6.49 | 6.85 | 7.57 | - | 7.51 | 7.45 | |
| 11 | CDCl$_3$ | 1.91 | 6.36 | 6.67 | 7.0 | - | 7.32 | 7.32 | 2.44 |
| 2[2c] | CDCl$_3$ | 1.92 | 6.81 | 6.54 | 7.5 | 7.22 | 7.22 | 7.5 | - |

Structure assignment to regioisomeric (9a) and (9b) has been made on the basis of comparison of their $^1$H n.m.r. spectra with that of 7-chloro-4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one prepared from another route [3]. This compound exhibited one doublet at $\delta$ 6.91, one dd at $\delta$ 6.86 and one doublet at $\delta$ 6.82 ppm assigned to 6H, 8Hand 9H respectively when its n.m.r. spectrum was measured in acetone-d$_6$. This pattern is closer to that of (9b) rather than to that of 9a where aromatic dd appears at a much higher field than the two aromatic doublets. On the same basis (7) and (10) also seem to have nitro- and methyl groups at positions 7 respectively (Table 2a). There is however, a need of systematic work on the preparation, separation and structure assignment to 7/8- substituted (regioisomeric)-methyl-substituted-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones.

It is clear from the foregoing that not only the structure of unsaturated acid but also the substituents present in the benzene ring of o-

phenylenediamine influence the mechanism of Philip's reaction.

## Experimental

Preparation of compounds **1 - 2** was carried out by refluxing a mixture of one mole of respective unsaturated carboxylic acid with one mole of o-phenylenediamine in 4N HCl for 8 hours and the products were isolated by subsequent neutralization of the reaction mixture with $Na_2CO_3$ and filtration and/or extraction with proper organic solvent ($CHCl_3$, EtOAc). Reaction products were subjected to thin-layer chromatography on silica-gel and separation and purification of the compounds was done using silica-gel columns.

Mass spectra of the synthesized compound (**1 - 11**) and elemental analyses were carried out in HEJ Research Institute of Chemistry, University of Karachi, Karachi-32, Pakistan. $^1H$ n.m.r spectra of (**1-7**) and (**11**) were recorded on 100 MHz Jeol n.m.r. spectrometer.

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## References

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