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# STEREOCHEMISTRY OF FRIEDEL-CRAFTS ADDITION OF PHTHALYLASPARTIC ANHYDRIDE TO BENZENE

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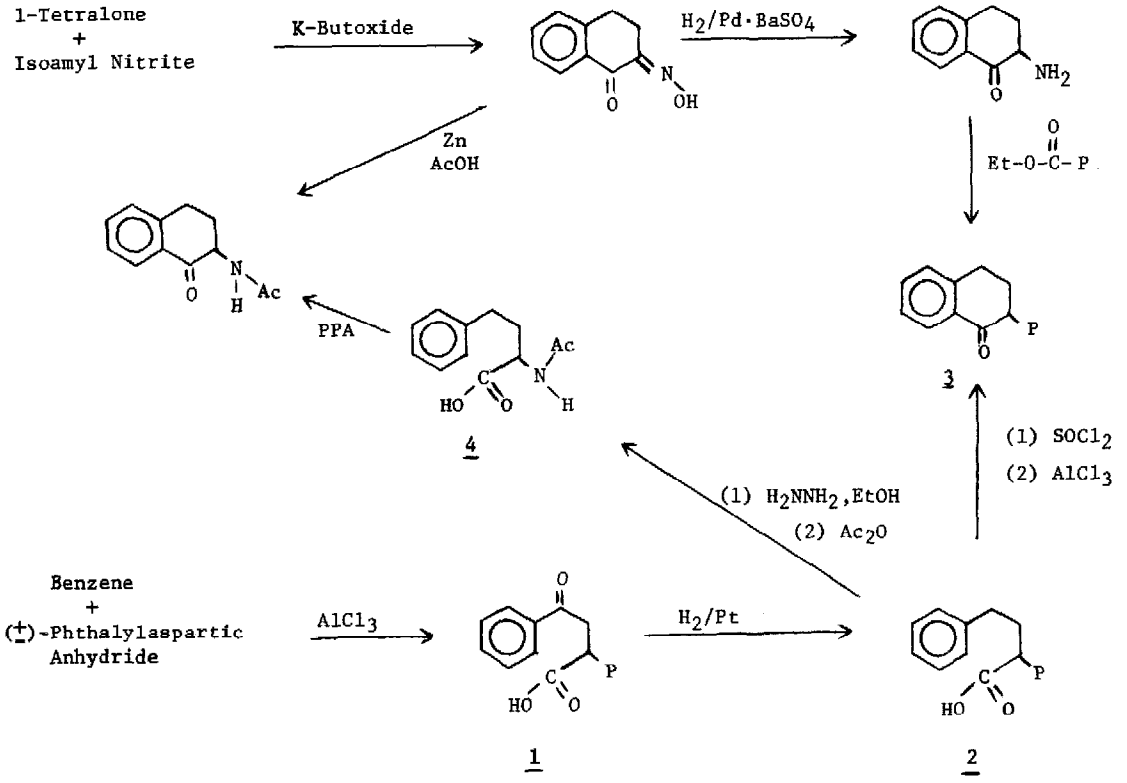
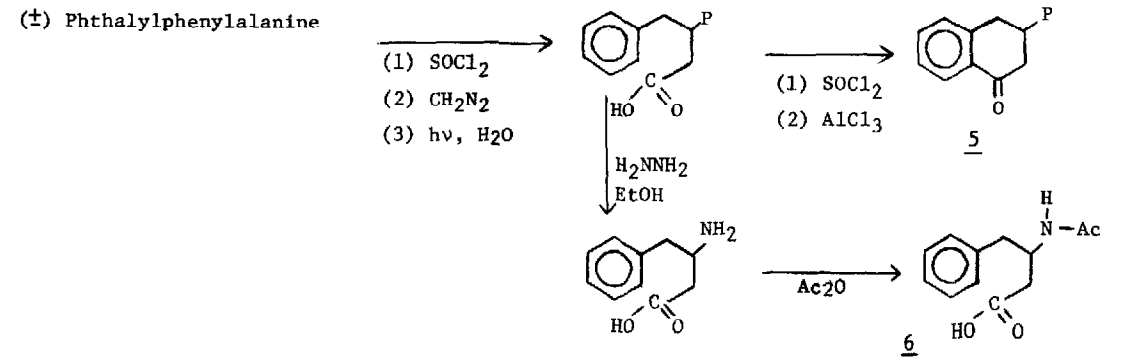
It has been reported that N-phthalimidoaspartic anhydride will react with benzene in the presence of $AlCl_3$ to give 3-benzoyl-3-phthalimidopropionic acid, which upon reduction and cyclization yields 3-phthalimido-1-tetralone.[1,2] This reaction sequence is of interest for two reasons. First, the opening of the anhydride ring in the manner indicated would not be anticipated on mechanistic grounds, since it would appear that the phthalimido group would oppose development of positive charge at the neighboring carbon. Second, this route is of synthetic interest because it constitutes a facile route to otherwise difficultly obtainable 3-aminotetralones.

Since studies in our laboratories required both 2- and 3-aminotetralones as synthetic intermediates, we had occasion to carry out the reaction sequence indicated in Scheme 1, which incorporates the reported synthesis of 3-phthalimido-1-tetralone. However, we found that the same product was obtained from both starting points as evidenced by identical nmr and ir spectra of the products. Compound 4 could also be cyclized to 2-acetamidotetralone which was identical in structure to the Zn-acetic acid reduction product of 2-(hydroxyimino)-tetralone.[3,4] These data indicated that the anhydride ring opening in Scheme 1 occurred in the more readily anticipated direction to give 3-benzoyl-2-phthalimidopropionic acid (1), which upon subsequent reduction and cyclization yielded 2-phthalimidotetralone (3). To fully verify this point and to provide an unequivocal synthesis of 3-phthalimido-1-tetralone (5), we have

Scheme 1. Preparation of 2-phthalimidotetralone (P = phthalimido; Ac = acetyl).




Scheme 2. Preparation of 3-phthalimidotetralone (P = phthalimido; Ac = acetyl).



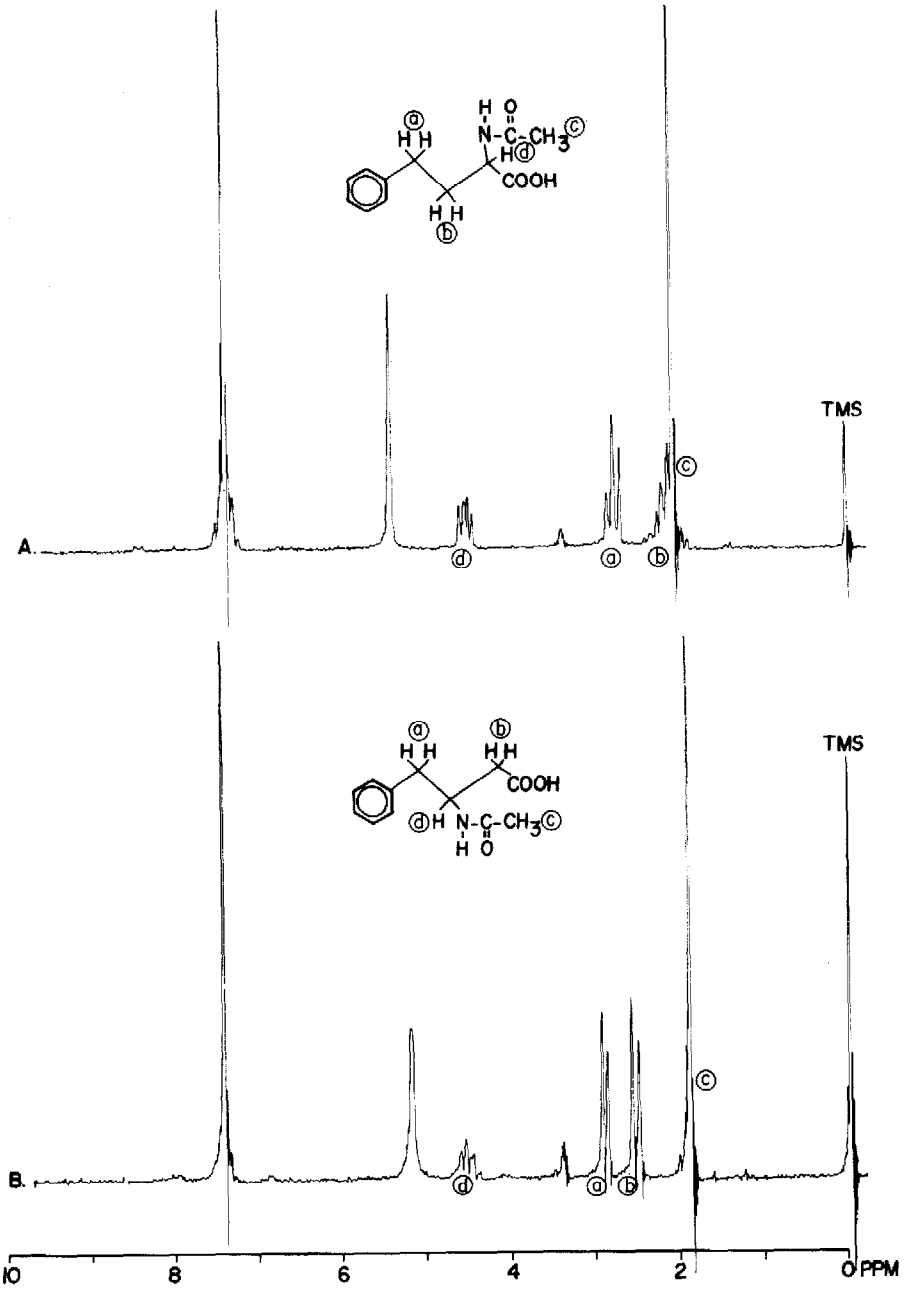



Figure 1. NMR Spectra of 4-phenyl-2-acetamidobutyric acid (A) and 4-phenyl-3-acetamidobutyric acid (B).

carried out the reaction sequence indicated in Scheme 2.[5] Differing physical and spectral properties of products (5 and 6) obtained from the latter sequence, compared to the reportedly identical products (3 and 4) acquired from Scheme 1 indicated that the two pathways did not yield identical compounds.

The reported structural assignment for 3 was based primarily on interpretation of the nmr spectra of the initial acid (1), obtained from benzene and N-phthalimidoaspartic acid, and its reduction product 2.[2] The nmr spectra of 3 (m.p. 180°) and 5 (m.p. 182-184°) are very similar, differing mainly in the chemical shift values of the C-2 methylene of the 3-phthalimido compound and the C-3 methylene protons of the 2-phthalimido compound, these peaks appearing as complex multiplets at δ 2.6-3.4 and δ 2.5-2.9 respectively. Spectral differentiation of the two positional isomers is clearly illustrated in the nmr spectra (Figure 1) of 2-acetamido-4-phenylbutyric acid (4; m.p. 148-150°) and 3-acetamido-4-phenylbutyric acid (6; m.p. 144-145°). The methylene protons attached to C-2 and C-4 are split by the proton on C-3 of the 3-acetamido isomer and appear as doublets at δ 2.44 and 2.86 respectively. In contrast the C-4 protons of the 2-acetamido compound are split into a triplet (δ 2.5) by the adjacent protons on C-3.

These combined physical, synthetic and spectral data offer conclusive proof that Friedel Crafts addition of N-phthalimidoaspartic anhydride to benzene does not afford 3-benzoyl-3-phthalimidopropionic acid as originally reported but rather the mechanistically predicted 3-benzoyl-2-phthalimidopropionic acid.

ACKNOWLEDGEMENT

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REFERENCES

1. F. Zymalkowski and E. Dornhege, Tetrahedron Lett., 5743 (1968).

2. F. Zymalkowski and E. Dornhege, Liebigs Ann. Chem., 728, 144 (1969).

3. F. Zymalkowski and H. J. Rimek, Arch. Pharm., 294, 581 (1961).

4. R. I. Thrift, J. Chem. Soc. (C), 1967, 288.

5. 3-Amino-4-phenylbutyric acid, reported in Scheme 2, has been previously prepared by N. C. Chaturvedi, W. K. Park, R. R. Smeby and F. M. Bumpas, J. Med. Chem., 13, 177 (1970).