Reactions of cyclic anhydrides: Part XVII—Synthesis of pyrrolobenzimidazoles and benzimidazolylacrylic acids

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Reactions of o-phenylenediamines (4) with disubstituted maleic anhydrides (5) afford N-(o-aminophenyl)maleimides (6). Intramolecular dehydration cyclization of 6 furnishes pyrrolobenzimidazoles (7) which are further converted into benzimidazolylacrylic acids (10) and their derivatives (11-13).

In earlier publications, we have reported the formation of 2-oxoquinoxalines by intramolecular cyclization of o-aminomalonic acid esters, generated by in situ reduction of the corresponding o-nitro esters. Our earlier efforts to obtain benzimidazolylacrylic acids (1) were not successful. Details of literature methods are not readily accessible. Further the importance of 1 and its derivatives can not be overlooked, since they provide an elegant entry into azamitosane skeleton. In view of the demonstrated antineoplastic activity of mitomycin C (2), intense efforts at its partial and/or total synthesis have been made. However, the formation of the isosteric azamitosane system (3) has not received much attention.

This paper describes our efforts to reach the azamitosane congeners in pyrrolobenzimidazoles (7; conveniently prepared from maleic acids). Also reported is an elegant method to obtain benzimidazolylacrylic acids (10), a system with established bioactivity. Further we have also attempted to study the reactions of o-phenylenediamines (4) with cyclic anhydrides more exhaustively.

Scheme 1 summarises the course of reactions of o-phenylenediamines with dimethylmaleic anhydride (5A) and methoxyphenylmaleic anhydride (5B) to afford N-(o-aminophenyl)maleimides (6a-h) in good yields. Their structures were fully settled by IR and PMR data. The aminoimides 6a-h underwent facile dehydration cyclization on heating in acetic acid to the corresponding pyrrolobenzimidazoles (7a-h) in quantitative yields. Our yields in this reaction are vastly better than that (7%) reported earlier. Compounds 7a-h were also conveniently prepared in one-pot reaction by heating the corresponding o-phenylenediamine with maleic anhydrides (5) in 1:1 mole ratio in acetic acid. Structures of 7a-h were based on IR and PMR data in comparison to those of 6. As expected, the equivalence of the methyl group resonance at δ 2.0 in symmetrical 6a-d (Table 1) was disturbed in the unsymmetrical 7a-d. The assignment of methyl signals in 7a-d was made on the basis of the shift of methyl group resonance in related 6a-h: the methyl present on α-carbon which is conjugated with the rest of the molecule was expected to appear downfield.

The choice between the isomeric structures 7 and 8 for the product obtained by the condensation of amino function with carbonyls in unsymmetrical imides (6e-h) could be rationalised by the higher reactivity of carbonyl α (not conjugated with OCH3; see structure 6). Chemical proof to this view was provided by treating 7e-h with conc H2SO4, when the sole product formed turned out to be 2-phenylacetylbenzimidazole (15). The latter can be visualised to arise from 7e-h through initial demethylation followed by decarboxylation of the intermediate (14). The regiochemical preference noticed in the conversion 6→7 parallels the behaviour observed by us and others during intramolecular cyclization involving reactions of nucleophiles with several oxo and oxoaryl maleic anhydrides.

The high reactivity of the tertiary amide system in 7a-d is interesting (Scheme 1). Mere contact with water caused rapid hydrolysis of 7a-d to the corresponding 10a-d. Equally facile was nucleophilic ring opening in 7a-d on treatment with piperidine, morpholine, dimethylamine, aromatic amines, methoxide and methanol in the presence of acid. However
the methoxy analogs 7e-h displayed somewhat subdued reactivity: they did undergo hydrolysis but only under basic conditions; with secondary amines, the reaction failed and with other reagents, stronger reaction conditions were required.

Experimental Procedure

Melting points reported are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer R-37 spectrophotometer (ν max in cm⁻¹) and PMR spectra in CDCl₃ on WH-90 FT or Varion XL-100 spectrometer, using TMS as an internal standard (chemical shifts in δ, ppm). The required dimethylmaleic anhydride and methoxyphthalic anhydride were prepared by reported methods. The substituted o-phenylenediamines were prepared by standard procedures.

N-(o-aminophenyl)maleimides (6a-h) : General procedure

In a typical experiment, a mixture of o-phenylenediamine (1.08 g, 0.01 mole) and dimethylmaleic anhydride (1.26 g, 0.01 mole) taken in ethanol (30 ml) was heated on a water bath for 30 min, cooled to 50-60° and diluted with cold water till the solution became turbid. From the reaction mixture, solid that separated out was filtered, washed with cold water and recrystallized from aq. ethanol, m.p. 154°; yield 90%.

Similarly the other derivatives were also prepared; for 6d and 6h, the solvent was 1:1 DMF-ethanol (Table 1).
Table 1—Physical and spectral data of compounds 6, 7 and 10-13

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Elemental analyses were obtained within ± 0.3% of the theoretical values. 10a-h gave satisfactory neutralisation equivalents. All compounds were obtained in 80-95% yields. Solvent for recrystallization: aq. ethanol (6M, 19°ii, and 1la-ta); ethyl alcohol + acetone (6d); ethanol (6e-h); pet ether (7a); n-hexane (7e-s); benzene (7d, 13b); acetone (7e-h); benzene + n-hexane (12a-e); chloroform + benzene (12d, 13d); chloroform + pet ether (13a). 6a: IR 3382, 3295, 1765, 1700, 1622; PMR: 6 2.0 (s, 6H), 3.66 (bs, 2H, D₂O exchangeable), 6.64-7.2 (m, 4H). 6e: IR 3394, 3306, 1778, 1700, 1622; PMR: 6 3.7 (bs, 2H, D₂O exchangeable), 4.3 (s, 3H), 7.35-7.9 (m, 9H). 7a: IR 1760, 1743, 1630; PMR: 6 1.99 (s, 3H), 2.19 (s, 3H), 7.20 (m, 2H), 7.55 (m, 2H). 7e: IR 1752, 1618, 1600; PMR: 6 4.55 (s, 3H), 7.23 (m, 5H), 7.6 (m, 2H), 7.55 (m, 2H). 11a: IR 3510, 3340, 1850, 1600, 1665; PMR: 6 2.08 (s, 3H), 2.35 (s, 3H), 2.85 (s, 3H), 3.0 (s, 3H), 7.19-7.82 (m, 4H). 10a: IR 1603; PMR: 6 2.08 (s, 3H), 2.35 (s, 3H), 2.85 (s, 3H), 3.0 (s, 3H), 7.19-7.82 (m, 4H), 10.45 (bs, 1H, D₂O exchangeable).

3-Methoxy-2-phenyl-1H-pyrrol[1,2-a]benzimidazole-1-one (7e-h)

Experimental procedure was similar to that adopted for 7a-d, except that after distillation of the product, the solvent was taken in acetic acid or ethanol and filtered (Table 1).

β-(2-Benzimidazolyl)-α,β-dimethylacrylic acids (10a-d)

Compounds 7a-d (0.01 mole) were added to aq. NaOH (2N, 15 ml), stirred for 30 min at room temperature and acidified with acetic acid (pH 6), to obtain the corresponding acids, which were filtered and recrystallized (Table 1).

β-(2-Benzimidazolyl)-β-methoxy-α-phenylacrylic acids (10e-h)

Compounds 7e-h (500 mg) were dissolved in boiling ethanol (20 ml) and to this was added slowly a solution of KOH (0.5 g in 10 ml water). The reaction mixture was refluxed until the pink solution was decolourised (2-3 hr), concentrated to about 10-15 ml, cooled to room temperature and carefully neutralised to pH 7 with 2N HCl. Further dilution with water led to turbidity and eventually to a solid which was filtered off from the cooled solution and recrystallized (Table 1).

Methyl β-(2-benzimidazolyl)acrylates (11a-s)

Compounds 7a-h (1 g) were refluxed in dry methanol (25 ml) containing 5 drops of conc H₂SO₄ for 3-4 hr. The solvent was evaporated and the residue treated with a saturated solution of bicarbonate. The solid separated was filtered and recrystallized (Table 1).

Reaction of 7a-d with secondary amines

A solution of the secondary amine (0.01 mole) in chloroform (10 ml) was added to a solution of pyrrolobenzimidazole (0.01 mole) in chloroform (20 ml). The yellowish reaction mixture was stirred at room temperature till it became colourless. Evaporation of the solvent and trituration of the residue with pet ether or n-hexane caused separation of the ring-opened solid product (10-12, Table 1).

2-Phenylacetyl benzimidazole (15a-c)

Compounds 7e-g (500 mg) were refluxed in conc HCl (25 ml) for 15 min with stirring and diluted with water (10 ml). The reflux was continued till solution became clear. The reaction mixture was cooled and the solid product that separated was filtered. The solid (hydroiodide salt) was stirred with saturated aq. sodium bicarbonate (20 ml) for 30 min to liberate the base which was then filtered and recrystallized.

15a: (55%), m.p. 163-64° (lit m.p. 165° benzene + n-hexane); IR: 3290, 1672.
15c: (65%), m.p. 153-54° (benzene + n-hexane); IR: 3280, 1675; PMR: 6 4.59 (s, 2H), 7.2-7.91 (m, 8H), 10.48 (bs, 1H, D₂O exchangeable).
15c: (77%), m.p. 159-60° (benzene + n-hexane);
IR: 3290, 1682; PMR: 2.48 (s, 3H), 4.57 (s, 2H), 7.11-7.97 (m, 8H), 10.4 (bs, 1H, D₂O exchangeable).

Acknowledgement

We thank the CSIR, New Delhi for financial assistance and Prof M S Wadia of University of Poona for elemental and spectral data.

References

Synthesis of azamitosane congeners†:

3a-Acetoxy-4-acetyl-3a, 4-dihydro-1H-pyrrolo[1,2-a]benzimidazol-1-ones

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Intramolecular cyclization of N-(o-acetamidophenyl)maleimides (2a-h) with acetic anhydride-sodium acetate furnishes 3a-acetoxy-4-acetyl-3a, 4-dihydro-1H-pyrrolo[1,2-a]benzimidazol-1-ones (3a-h), incorporating an angular acetoxy function.

Recently we have reported1 a new synthesis of pyrrolobenzimidazoles involving intramolecular cyclization of free amino function in N-(o-aminophenyl)maleimides (la-h). Herein we describe the conversion of la-h to the corresponding 3a-h, which are azamitosane congeners carrying the otherwise elusive angular oxygen function in their molecular framework.

N-(o-Aminophenyl)maleimides1 (la-h) were converted into the corresponding acetyl derivatives (2a-h), which when refluxed in acetic anhydride in the presence of sodium acetate for 2-3 hr resulted in formation of 3a-acetoxy-4-acetyl-3a, 4-dihydro-1H-pyrrolo[1,2-a]benzimidazol-1-ones (3a-h) as the sole products in excellent yields. Compounds 3a-h can also be prepared in a one-pot reaction by refluxing 1a-h in acetic anhydride-sodium acetate. The former two-step procedure appears preferable by virtue of better yield and purity of the final product.

The structures of 3a-h were settled by elemental analyses, IR and PMR data (see Experimental). The IR and PMR signals, characteristic of amide hydroxyl and the angular acetoxy group, in the spectra of the compounds were used to assign the angular oxygen function in each of these congeners.

A distinction in the reactivity of angular acetoxy function in 3e-h and the earlier reported2-11 carbon analog 5 is worth noting. While 5 neatly undergoes exchange of acetoxy with alkoxy group on refluxing in alkane, 3 suffers decomposition to the starting 2 under comparable conditions. Our attempts to effect similar ring closure of 2 with unsubstituted o-acetamidomaleimides (2, R = R' = H) to obtain azamitosane congeners have not yet been successful.

Experimental

Melting points reported are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer R-37 spectrophotometer. (Vmax in cm⁻¹) and PMR spectra in CDCl₃ on WH-90 FT or Varian XL-100 spectrometer using TMS as an internal standard (chemical shifts in ppm). The required dimethylmaleic anhydride12 and methoxyphenylmaleic anhydride6a were prepared by reported methods. The substituted amines such as 4-nitro-o-phenylenediamine12, 4-methyl-o-nitroaniline14 and 4-chloro-o-nitroaniline16 were prepared by reported procedures. The latter two compounds were reduced to the diamine using W-2 Raney nickel.

4-Chloro-o-phenylenediamine

4-Chloro-o-nitroaniline16 (5 g) in ethyl acetate (100 ml) was hydrogenated over W-2 Raney nickel (about 1.5 g) at 40 psi. When hydrogen uptake was complete (2 hr), the catalyst was filtered, the filtrate concentrated and the residue recrystallized from n-hexane, m.p. 75° (lit.17 76°).

Similarly 4-methyl-o-phenylenediamine was prepared and recrystallized from n-hexane m.p. 87° (lit.17 88°).

N-(o-Acetamidophenyl)maleimides (2a-h):

General procedure

In a typical experiment, N-(o-aminophenyl)maleimide1 (1a, 2g) was added to acetic anhydride (10 ml) and the clear solution was kept aside at room temper-
Table 1 — Physical and spectral data of compounds 2 and 3

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Elemental analysis were within 0.3% of theoretical values. Yields were in the range of 70-90%. Solvent for recrystallization: Ethanol (2a, 2c-d, 2f-h), ethyl acetate-I-pet ether (2b, 2e, 3a-b, 3e), benzene + n-hexane (3c-h).

nature for 2 hr, poured into water (30 ml), the solid separated was filtered and crystallized from appropriate solvent (see Table 1). However, refluxing for 1 hr was necessary to obtain 3d and 3h.

2a: IR 3247, 1706, 1664; PMR: 2.08 (apparent singlet, 9H), 7.17-7.68 (m, 4H); 2b: IR 3314, 1714, 1683; 2c: IR 3340, 1775, 1700, 1685; 2d: IR 3337, 1705, 1670; 2e: IR 3211, 3160, 1718, 1661; PMR: 2.08 (s, 3H), 4.34 (s, 3H), 7.22-7.68 (m, 7H), 7.85-8.08 (m, 3H); 2f: IR 3211, 1716, 1665.

3a: Acetoxy-4-acetyl-3a, 4-dihydro-1H-pyrrolo[1, 2-albenzimidazol-1-ones (3a-h)

The foregoing maleimides (500 mg) were gently refluxed in acetic anhydride (10 ml) containing anhydrous sodium acetate (200 mg) for 2-3 hr. Excess acetic anhydride was distilled off to half the volume, which was then cooled and poured into cold water. The pasty product slowly solidified and was further purified by recrystallization. Alternately, the product could be extracted with chloroform. Evaporation of the dried chloroform extract left a residue which on trituration with light petroleum or n-hexane afforded a solid. For isolation of 3e-h, the chloroform extract was loaded on a column of silica gel and eluted with benzene or chloroform (Table 1).

3a: IR 1728, 1711, 1684; PMR: 1.90 (apparent singlet, 6H), 2.20 (apparent singlet, 6H), 7.12-7.47 (m, 4H); 3b: IR 1722, 1711, 1683; PMR: 1.96 (apparent singlet, 6H), 2.22 (apparent singlet, 6H) 2.37 (s, 3H), 7.0-7.25 (m, 3H); 3c: IR 1728, 1706; 3e: IR 1728, 1718; PMR: 2.28 (apparent singlet, 6H), 4.21 (s, 3H), 7.18-7.56 (m, 7H), 7.68-7.87 (m, 2H); 3f: IR 1728, 1711; 3g: IR 1730, 1703, 1640; PMR: 2.28 (apparent singlet, 6H), 4.25 (s, 3H), 7.17-7.60 (m, 6H), 7.74-8.00 (m, 2H).

Acknowledgement

We thank the CSIR, New Delhi for financial assistance and Prof. M S Wadia of University of Poona for elemental and spectral data.

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