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REACTIONS OF CYCLIC ANHYDRIDES XVI.

A NOVEL APPROACH TO ANGULAR OXYGENATED PYRROLOBENZOXAZINONES¶

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Abstract - o-Carboxymaleanilic acids IIIa-g when treated with sodium acetate-acetic anhydride underwent double cyclisation leading to pyrrolobenzoxazinones Va-g carrying an angular acetate. A one-flask reaction of dimethylmaleic anhydride and phthalic anhydride with anthranilic acid furnished the angular hydroxy benzoxazinones IVh and IVi respectively, which were converted to the corresponding acetates Vh and Vi. The acetates Va, Vc, Vf, Vg and Vi underwent solvolysis to the corresponding methyl ethers (VII) on refluxing with anhydrous methanol.

INTRODUCTION

The synthetic utility of anilic acids for novel heterocyclic synthesis has been amply demonstrated : imides[1], isoimides[2,3], indoles[4], benzimidazoles[5], benzothiazoles[6], quinolines[7-10], quinoxalines[11], benzoxazines[12-14], benzothiazines[6,11,15,16], quinazolines[14], benzazepines[17,18], pyrroloquinazolines[19], pyridazinoquinazolines[14] and isoindoloquinazolines[20]. The general synthetic protocol for these heterocyclic skeletons but the first two involves generation of the appropriate ortho substituted anilic acid followed by intramolecular Michael-type addition or condensation. The present communication describes extension of our studies to new reactions of o-carboxymaleanilic acids (IIIa-g) which generate angular oxygenated pyrrolobenzoxazinones (Va-g). Introduction of oxygen functions in projected synthesis of mitomycins and their analogs is a challenging task[21] of much current interest[21-30] The earlier efforts for introduction of angular oxygen functions in mitomycin congeners utilise (i) intramolecular cyclisation of suitably substituted azocine derivatives[22,23] (ii) photochemical oxidation of 2-hydroxymethyl-N-phenylpyrrole[24] and (iii) Reformatski reaction of methyl 2-bromo-2-(o-succinimidophenyl) acetate[26-29]. This paper describes our alternate approach which is simple in design and yet offers scope for desired synthetic variation and/or elaboration.

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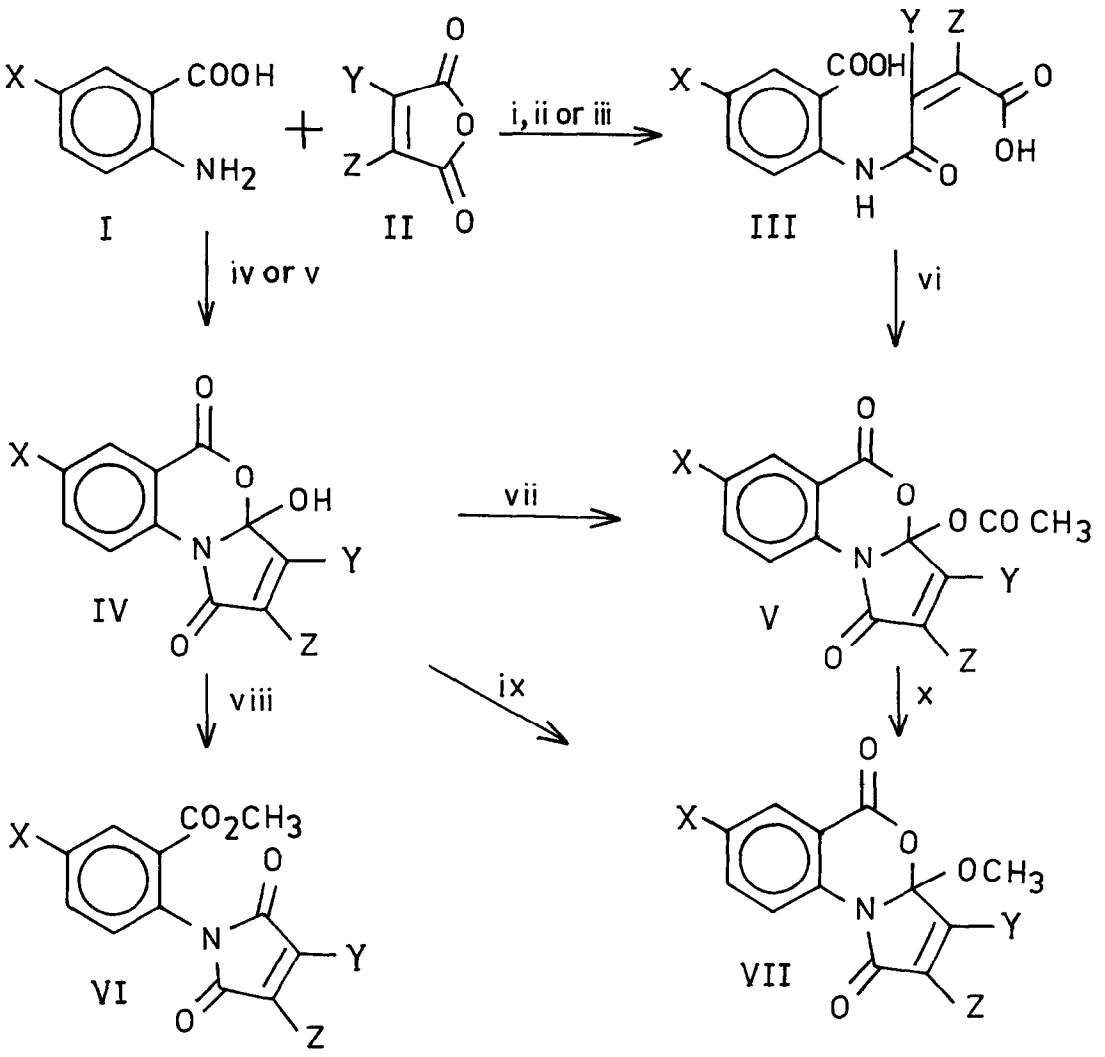
SCHEME 1



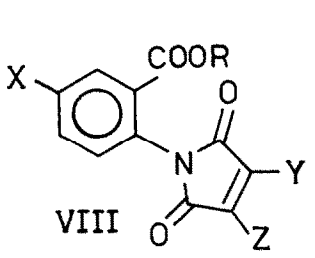
a	X = Y = Z = H	b	X = Cl, Y = Z = H	c	X = Br, Y = Z = H
b	X = I, Y = Z = H	e	X = H, Y = Me, Z = H	f	X = Y = H, Z = Me
g	X = H, Y = Ph, Z = H	h	X = H, Y = Z = Me	i	X = H, YZ = o-C_4H_4

i.	Ether, RT, 20 min (for IIIa-c,e-g)	ii.	AcOH, RT, 20 min (for IIId)
iii.	C_6H_6:Dioxan (6:1), RT, 30 min (for IIIi)	iv.	Water, reflux, 3 hr (for IVh)
v.	Tetralin, reflux, 2 hr (for IVi)	vi.	NaOAc/Ac_2O, RT, 8 hr (for Va-g,i)
vii.	NaOAc/Ac_2O, 90°, 4 hr (for Vh,i)	viii.	MeOH/H^+, reflux, 3 hr (for VIh,i)
ix.	CH_2N_2, ether, RT, 30 min (for VIIi)	x.	MeOH, reflux, 2 hr (for VIIa,c,f,g,i)

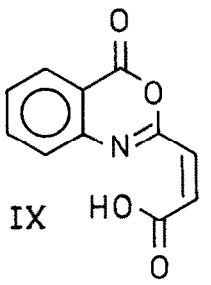
RESULTS AND DISCUSSION

We prepared a series of o-carboxymaleanilic acids by reacting the appropriate anthranilic acid with maleic anhydride (MA), methylmaleic anhydride (MMA) or phenylmaleic anhydride (PMA). The resulting acids III offer multiple pathways for intramolecular dehydration to imides, isomides or benzoxazinones. When IIIa-d were treated with sodium acetate-acetic anhydride at room temperature for 8 hr (Scheme 1), none of these expected products was obtained; instead, they were transformed to tricyclic pyrrolobenzoxazinones Va-d incorporating an angular acetate function. The structural assignment for Va-d follows from the characteristic ir, pmr and cmr spectral features : 1795 cm^{-1} (six-membered lactone), 1755 cm^{-1} (acetate carbonyl), 1730 cm^{-1} (γ-lactam); δ 2.04 (acetate methyl singlet), δ 6.48 and δ 7.73 (vinylic proton doublets) and proton-coupled cmr absorption at δ 21.23 (quartet reducing to a singlet at δ 21.07 on proton decoupling). The mixture of isomeric maleanilic acids IIIe and IIIf (obtained from MMA and anthranilic acid) on similar treatment with sodium acetate-acetic anhydride furnished a mixture of Ve and Vf. The reaction of IIIg (obtained from PMA and anthranilic acid) with this reagent furnished Vg. The angular acetates in pyrrolobenzoxazinones Va,c,f,g and i on refluxing with anhydrous methanol for 2 hr underwent solvolysis demonstrating the labile nature of angular acetate function (absence of acetate carbonyl in ir and shift of 3H-singlet from δ 2.04 to δ 3.28 in going from Va to VIIa). The assignment of the vinylic protons of the α,β-unsaturated systems in Va-d and VIIa,c which appear as well-separated pmr doublets ($H\alpha$ and $H\beta$) can be made by comparing the position of their absorptions to those of the vinylic protons present in α,β-unsaturated lactams and butenolides. In lactams, $H\alpha$ and $H\beta$ protons appear[33a] at δ 6.51 and δ 7.63 respectively. Thus in Va-d, the signal at δ 6.44 (± 0.04) is assigned to $H\alpha$ and the one at δ 7.69 (± 0.04) to $H\beta$. The identity of $H\beta$ in these compounds whose signal is submerged with those of aromatic protons is revealed by INDOR : irradiation of Vc at δ 6.45 affects the absorption at δ 7.69. With the unsymmetrical derivatives, the assignment of the position of Me or Ph in V and VII as well as the regioisomeric ratio of Ve : Vf is corroborated by these observations[34].

Formation of V from III might proceed through imide VIIIa or benzoxazinone IX intermediates although neither of these could be intercepted even under mild conditions. A recent report[35] claiming isolation of VIIIa from the corresponding o-carboxymaleanilic acid prompted us to verify the same. Repetition of the earlier experiments and spectral study of the product established[30] that the structure VIIIa for the product is erroneous. Yet another unwary assignment[36] has been made for the product obtained from o-carboxyphthalanilic acid and sodium acetate-acetic anhydride. Repetition of this work gave the reported product with m.p. 120° but spectral features of this product conform to structure Vi rather than VIIIb. In yet another effort to isolate the elusive o-carboxy-N-phenylmaleimide, we studied the reaction of dimethylmaleic anhydride (DMMA) with anthranilic acid. Reactions of disubstituted MA's with primary amines are known[37-39] to have a great propensity to form the corresponding imides. However, only an angular



VIII



IX

VIIIa X = Y = Z = R = H

VIIIb X = H, YZ = o-C_4H_4, R = COMe

VIIIc X = H, Y = Z = Me, R = H

VIIId X = H, YZ = o-C_4H_4, R = H

tricyclic system IVh (not VIIIc) resulted from this reaction : the presence of a lactonol moiety (3265 cm^{-1} and 1785 cm^{-1}) and an exchangeable singlet (at δ5.34). Likewise, the reaction of phthalic anhydride with anthranilic acid in boiling tetralin furnished only the ring tautomer IVi, contrary to earlier claims[36,40] of formation of VIIId and its derivative. Furthermore, lactonols IVh and IVi on treatment with sodium acetate-acetic anhydride underwent smooth acylation to Vh and Vi.

In summary, we have established that i) o-carboxymaleanilic acids on treatment with sodium acetate-acetic anhydride undergo double cyclisation leading to pyrrolobenzoxazinones carrying an angular oxygen function ii) in attempts to obtain o-carboxy-N-phenyldimethylmaleimide (VIIIc) and o-carboxy-N-phenylphthalimide (VIIId) only the lactonols IVh and IVi were obtained and iii) the angular acetates in all these compounds were smoothly converted to the corresponding methyl ethers. In our ongoing work, we hope to generate mitosanes exploiting this methodology.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra in nujol recorded on a Perkin-Elmer R-37 spectrometer ($\bar{\nu}$ in cm^{-1}), pmr spectra are in $CDCl_3$ or DMSO-d_6 on Perkin-Elmer R-32 spectrometer using TMS as an internal standard (chemical shifts in δ ppm). The elemental analyses observed were within the limits of accuracy (± 0.3%). The compounds IIIa-g gave satisfactory neutralisation equivalents.

o-Carboxymaleanilic acids (III) : In a typical experiment, a mixture of powdered MA (0.98 g; 0.01 m) and anthranilic acid (1.37 g; 0.01 m) in anhydrous ether was stirred at room temperature for 20 minutes. The product that separated from reaction mixture was filtered, washed with ether (2 x 10 ml) and recrystallised from methanol; yield, quantitative. Acids IIIb,c,e-g were prepared similarly by using the appropriate amine [5-chloroanthranilic acid[41] and 5-bromoanthranilic acid[41]] and anhydride [MA, MMA[42] and PMA[43]]. The acid IIId could be more conveniently prepared from 5-iodoanthranilic acid[44] and MA in glacial acetic acid.

IIIa : 192°, IIIb : 189°, IIIc : 190°, IIId : 185°, IIIe/f (mixture) : 120°, IIIg : 140° and IIIh : 172°.

2,3-Dimethyl-3a-hydroxy-5H-pyrrolo(1,2-a)(3,1) benzoxazin-1,5(3aH)-dione (IVh) : A mixture of equimolar amounts of DMMA[37] (1.26 g; 0.01 m) and anthranilic acid (1.37 g; 0.01 m) was gently refluxed in water (15 ml) for 3 hr. The reaction mixture was kept at room temperature for 1 hr. The crystalline product that separated out gradually was filtered and crystallised from ethanol.

IVh : 187° (95%), Ir : 3270, 1785, 1735, 1695, 1600.
Pmr : 2.01(6H), 5.34(bs,1H), 7.14-8.14(m,4H).

5a-Hydroxy-7H-isoindolo(1,2-a)(3,1)benzoxazin-1,7(5aH)-dione (IVi): A mixture of phthalic anhydride (5.92 g; 0.04 m) and anthranilic acid (5.48 g; 0.04 m) was refluxed for 2 hr in tetralin (30 ml) using a water separator. The reaction mixture was allowed to cool to room temperature and the crystalline product was filtered, washed with n-hexane (15 x 2 ml) and recrystallised from ethanol.

IVi : 215° (95%), Ir : 3160, 1770, 1700. Pmr : 3.33(bs,1H), 7.30-8.30(m,8H).

3a-Acetoxy-5H-pyrrolo(1,2-a)(3,1)benzoxazin-1,5(3aH)-dione (Va) : In a typical experiment, o-carboxymaleanilic acid (IIIa, 2.35 g; 0.01 m) was mixed with anhydrous sodium acetate (0.5 g) and acetic anhydride (15 ml). The resulting slurry was kept at room temperature for 8 hrs. The reaction mixture was then poured into water (75 ml). The crystalline product that separated out was filtered, washed with water and recrystallised from benzene. Compounds Vb-g and Vi were prepared similarly.

Va : 160° (77%), Ir : 1795, 1755, 1730. Pmr : 2.04(s,3H), 6.48(d,1H,J=6Hz), 7.37(dt,1H, J=2,8Hz), 7.73(d,1H,J=6Hz), 7.77(dt,1H,J=2,8Hz), 8.04(dd,1H,J=2,8Hz), 8.14(dd,1H, J=2,8Hz). Cmr (ppm); proton coupled : 21.23(q), 116.35(d), 122.21(d), 126.24(s), 128.51(d), 133.52(d), 138.94(s), 139.65(d), 146.49(s), 165.30(s), 167.30(d), 194.03(s), 197.88(s). Proton decoupled : 21.07, 107.00, 113.19, 119.51, 125.31, 129.64, 130.46, 136.19, 142.46, 164.75, 167.39, 194.03, 197.88.

Vb : 170° (75%), Pmr : 2.02(s,3H), 6.45(d,1H,J=6Hz), 7.67(dd,1H,J=3,9Hz), 7.68(d,1H, J=6Hz), 7.94(d,1H,J=9Hz), 8.06(d,1H,J=3Hz).

Vc : 182° (75%), Pmr : 2.04(s,3H), 6.45(d,1H,J=6Hz), 7.69(d,1H,J=6Hz), 7.85(m,2H), 8.20(d,1H,J=3Hz).

Vd : 143° (79 %), Pmr : 2.01(s,3H), 6.40(d,1H,J=6Hz), 7.67(d,1H,J=6Hz), 7.71(d,1H, J=9Hz), 7.97(dd,1H,J=2,9Hz), 8.35(d,1H,J=2Hz).

Ve/f (mixture) : 142° (72%), Pmr : 1.97(s,3H), 2.04(d,3H,J=2Hz), 6.48(q,0.13H,J=2Hz), 7.30(q,0.87H,J=2Hz), 7.30(dt,1H,J=2,8Hz), 7.70(dt,1H,J=2,8Hz), 7.98(dd,1H,J=2,8Hz), 8.07(dd,1H,J=2,8Hz).

Vg : 165° (92%), Pmr : 1.87(s,3H), 6.70(s,1H), 7.20-8.20(9H).

Vi : 120° (90%), Ir : 1775, 1750, 1710.

2,3-Dimethyl-3a-acetoxy-5H-pyrrolo(1,2-a)(3,1)benzoxazin-1,5(3aH)-dione (Vh) : The lactonol (2.0 g) was heated with acetic anhydride (10 ml) and sodium acetate (0.2 g) for 4 hr in boiling water-bath. The reaction mixture on aqueous work-up gave the product which was filtered, washed with ice-cold water and crystallised from benzene/n-hexane. The work-up has to be completed within the minimum time to avoid hydrolysis of the acetate. Similarly IVi was also acylated to Vi and compared with the sample obtained in the foregoing experiment.

Vh : 161° (78%), Pmr : 1.96(s,3H), 1.99(6H), 7.14-8.14(m,4H).

o-Methoxycarbonyl-N-phenyl-3,4-dimethylmaleimide (VIh) : The lactonol IVh (0.2 g) was refluxed in methanol (10 ml) for 3 hr with catalytic amount of sulphuric acid (2-3 drops). After aqueous work-up, the product was crystallised from methanol. Similarly VIi was obtained from IVi.

VIh : 91° (60%), Ir : 1790, 1740, 1720. Pmr : 2.10(s,6H), 3.80(s,3H), 7.10-7.80(m,3H), 8.05(dd,1H,J=2,8Hz).

VIi : 154° (85%), Ir : 1780, 1730, 1710. Pmr : 3.70(s,3H), 7.20-8.20(m,8H).

3a-Methoxy-5H-pyrrolo(1,2-a)(3,1)benzoxazin-1,5(3aH)-diones (VIIa) : In a typical experiment, pyrrolobenzoxazinone Va (0.5 g) was gently refluxed in anhydrous methanol (15 ml) for 2 hr. From the cooled reaction mixture, the product that separated was filtered, washed with methanol and recrystallised from the same solvent. Compounds Viia,c,g,i were also prepared similarly. The sole methanolysis product isolable from the mixture of Ve/f on refluxing with methanol was VIIf.

VIIa : 126° (95%), Ir : 1770, 1680, 1605. Pmr : 3.28(s,3H), 6.38(d,1H,J=6Hz), 7.16(d,1H,J=6Hz), 7.25(dt,1H,J=2,8Hz), 7.62(dt,1H,J=2,8Hz), 7.87(dd,1H,J=2,8 Hz), 8.03(dd,1H,J=2,8Hz).

VIIc : 120° (90%), Pmr : 3.30(s,3H), 6.46(d,1H,J=6Hz), 7.20(d,1H,J=6Hz), 7.80(m,2H), 8.25(d,1H,J=2Hz).

VIIf : 115° (90%), Pmr : 2.10(d,3H,J=2Hz), 3.36(s,3H), 6.93(q,1H,J=2Hz), 7.38(dt,1H, J=2,8Hz), 7.79(dt,1H,J=2,8Hz), 8.02(dd,1H,J=2,8Hz), 8.18(dd,1H,J=2,8Hz).

VIIg : 124° (90%), Pmr : 3.40(s,3H), 7.32(s,1H), 7.40-8.25(m,9H).

VIIi : 144° (90%), Pmr : 3.10(s,3H), 7.20-8.30(m,8H).

5a-Methoxy-7H-isoindolo(1,2-a)(3,1)benzoxazin-1,7(5aH)-dione (VIIi) : The lactonol IVi (2.67 g; 0.01 m) was stirred with an equimolar quantity of diazomethane (0.42 g; 0.01 m) in ether (10 ml) at room temperature for 30 min. The ether layer was concentrated and the product obtained was filtered and recrystallised from methanol. The product was identical to that obtained via Vi ⟶ VIIi.

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REFERENCES AND FOOTNOTES

1. Searle,N.E. U.S.Pat. **1948**, 2,444,536., Chem.Abstr. **1948**, 42, 7340.
2. Sauers,C.K.; Cotter, R.J. J.Org.Chem. **1961**, 26, 6-10.
3. Boyd,G.V.; Monteil,R.L. J.Chem.Soc., Perkin I **1978**, 1338-1350.
4. Mori,M.; Ban,Y. Tetrahedron Lett. **1976**, 1807-1810.
5. Dash,B.; Dora,E.K.; Panda,C.S. Indian J.Chem. **1982**, 21B, 697-698.
6. Balasubramaniyan,V.; Balasubramaniyan,P.; Shaikh,A.S.; Argade,N.P. Indian J.Chem. **1989**, 28B, 0000.
7. Shanmugam,P. Proc.Indian Acad.Sci. **1960**, 51, 75.
8. Shanmugam,P.; Thiruvengadam.T.K.; Palaniappan,R. Z.Naturforsch. **1973**, 28B, 551-553.
9. Ramesh,M.; Arisvaran.V.; Rajendran.S.P.; Shanmugam,P. Tetrahedron Lett. **1982**, 23, 967-970.
10. Patel,M.V.; Balasubramaniyan,P.; Balasubramaniyan,V. Indian J.Chem. **1979**, 18B, 245-247.
11. Balasubramaniyan,P.; Patel,M.V.; Wagh,S.B.; Balasubramaniyan,V. Current Science **1982**, 51, 279-280.
12. Patel,M.V.; Balasubramaniyan,P.; Balasubramaniyan,V. Indian J.Chem. **1979**, 18B, 367-368.
13. Balasubramaniyan,V.; Argade,N.P. Indian J.Chem. **1987**, 26B, 476-477.
14. Balasubramaniyan,V.; Argade,N.P. Indian J.Chem. **1988**, 27B, 0000.
15. a) Wagh,S.B.; Shaikh,A.S.; Balasubramaniyan,V. Indian J.Chem. **1983**, 22B, 868-871.
    b) Shridhar,D.R.; Ram,B.; Rao,K.S.; Jain,M.L. Indian J.Chem. **1985**, 24B, 992-994.
16. Balasubramaniyan,V.; Balasubramaniyan,P.; Shaikh,A.S. Tetrahedron **1986**, 2731-2738.
17. Cooke, R.G.; Haynes,H.F. Aust.J.Chem. **1958**, 11, 225-229.
18. Geissman,T.A.; Cho,A.K. J.Org.Chem. **1959**, 24, 41.
19. "Chemistry of Isatoic Anhydrides", Sherwin Williams Chemicals, Cleveland, USA, 1971, p 1A, 2A and 12G.
20. Kurihara,M. J.Org.Chem. **1969**, 34, 2123-2125.
21. Danishefsky,S.; Berman,E.M.; Ciufolini,M.; Etheredge,S.J.; Segmuller,B.E. J.Am.Chem.Soc. **1985**, 107, 3891-3898 and references cited therein.
22. Fukuyama,T.; Nakatsubo,F.; Cocuzza,A.J.; Kishi,Y. Tetrahedron Lett. **1977**, 18, 4295-5298.
23. Kishi,Y. J.Nat.Prod. **1979**, 42, 549-568.
24. a) Basha, F.Z.; Franck,R.W. J.Org.Chem. **1978**, 43, 3415-3417.
    b) Kametani,T.; Ohsawa,T.; Takahashi,K.; Ihara,M.; Fukumoto,K. Heterocycles **1976**, 4, 1637.

25. Franck,R.W., Prog.Chem.Org.Nat.Prod. **1979**, 38, 1-45.
26. Flitsch,W.; Russkamp,P. Liebigs Ann.Chem. **1985**, 1398-1412.
27. Flitsch,W.; Russkamp,P.; Langer,W. Liebigs Ann.Chem. **1985**, 1413-1421.
28. Flitsch,W.; Russkamp,P. Liebigs Ann.Chem. **1985**, 1422-1436.
29. Dartmann,M.; Flitsch,W.; Kerbs,B.; Russkamp,P. Liebigs Ann.Chem, **1985**, 1437-1447.
30. Balasubramaniyan,V.; Argade,N.P. Tetrahedron Lett. **1986**, 26, 2487-2488.
31. The reaction of MMA with amines in general is not regioselective[32a]; a mixture of isomeric maleanilic acids IIIe/f is obtained. However, the reaction of PMA with amines is regioselective [32b]; only IIIg is formed from PMA and anthranilic acid.
32. a) Mehta,N.B.; Phillips,A.P.; Florence,F.L.; Brooks,R.E. J.Org.Chem. **1960**, 25, 1012-1015.
    b) Bayder,A.E.; Boyd,G.V. J.Chem.Soc., Chem.Commun. **1976**, 718-719.
33. a) Wijnberg,J.B.P.A.; Boer,J.J.J.de.; Speckamp,W.N. Recl.Trav.Chim.Pays-Bas **1978**, 97, 227-231.
    b) Knight,D.W.; Pattenden,G. J.Chem.Soc., Perkin I **1979**, 62-69.
    c) Silverstein,R.M.; Bassler,G.C.; Morrill,T.C. "Spectrometric Identification of Organic Compounds"; John Wiley : New York, 4th Edition, 1981, p 230.
34. We are therefore constrained to reverse the assignment of the position of phenyl made by us earlier[30].
35. Augustin,M.; Muller,W. J.Prakt.Chem. **1985**, 327, 789-798.
36. Butula,I.; Otting,W. Monatsh.Chem. **1968**, 99, 1320-1335.
37. Baumann,M.E.; Bosshard,H. Helv.Chim.Acta **1978**, 61, 2751-2753.
38. Ried,W.; Isenbruck,G. Chem.Ber. **1972**, 105, 337-352.
39. Ried,W.; Isenbruck,G. Chem.Ber. **1972**, 105, 353-354.
40. Gabriel,S. Ber.detsch. Chem.Ges. **1878**, 11, 2261.
41. 5-Chloroanthranilic acid and 5-bromoanthranilic acid were obtained by hydrolysis of corresponding isatoic anhydrides[19].
42. Shriner,R.L.; Ford,S.G.; Roll,L.J. Org.Syn.Coll.Vol II, **1943**, 140-142 and 368-370.
43. a) Miller,C.A.; Long,L.M. J.Am.Chem.Soc. **1951**, 73, 4895-4898.
    b) Hill,R.K. J.Org.Chem. **1961**, 26, 4745-4746.
44. Wallingford,V.H.; Krueger,P.A. Org.Syn.Coll.Vol II, **1943**, 349-351.