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THE HIGH PRESSURE MEDIATED REACTION OF Π-EXCESSIVE HETEROCYCLES WITH MALEIC ANHYDRIDE DERIVATIVES: A SYNTHETIC APPROACH TO CANTHARIDIN ANALOGUES

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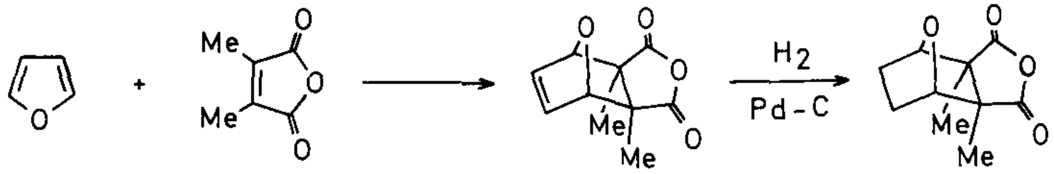
Abstract — High pressure mediated Diels-Alder reactions of 3,4-dimethoxyfuran with cyclohexene-1,2-dicarboxylic anhydrides and cyclopentene-1,2-dicarboxylic anhydride followed by catalytic hydrogenation produced 11-oxatricyclo[6.2.1.$0^{2,7}$]undecane-*endo*-2,7-dicarboxylic anhydrides and 10-oxatricyclo[5.2.1.$0^{2,6}$]decane-*endo*-2,6-dicarboxylic anhydride albeit in low yields. Reactions of N-methylpyrrole and pyrrole with dichloromaleic anhydride at high pressure resulted in Friedel-Crafts type of acylation.

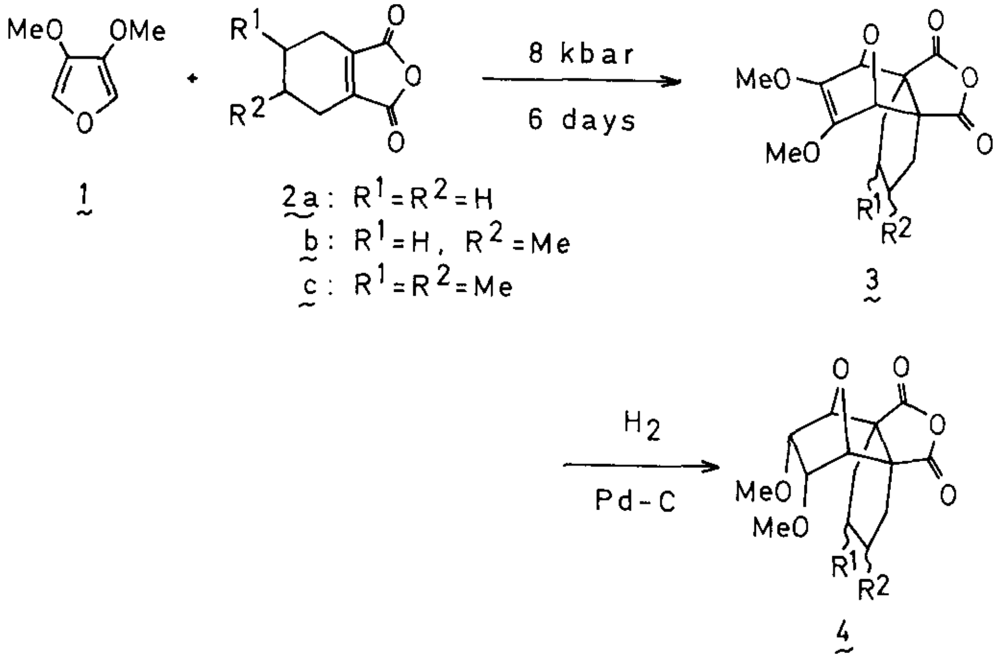
Cantharidin is a powerful vesicant that can be isolated from dried beetles (*Cantharis vesicatoria* or "Spanish fly").[1] The first stereospecific synthesis of cantharidin was achieved in 16 steps from furan in 1953.[2] A simple synthesis of cantharidin would consist of the cycloaddition of furan to dimethylmaleic anhydride followed by hydrogenation. Unfortunately, dimethylmaleic anhydride does not add to furan even at pressures upto 60 kbar.[3] This difficulty has been overcome by employing 2,5-dihydrothiophene-3,4-dicarboxylic anhydride as a dienophile that



serves as a dimethylmaleic anhydride equivalent.[4] An appropriate modification of the furan, e.g. 3,4-dimethoxyfuran[5] and isobenzofuran,[6] permit use of dimethylmaleic anhydride to construct the cantharidin framework by the Diels-Alder strategy.

We now report the high pressure reaction of some representative π-excessive heterocycles with maleic anhydride derivatives that would lead to new kinds of cantharidin analogues.

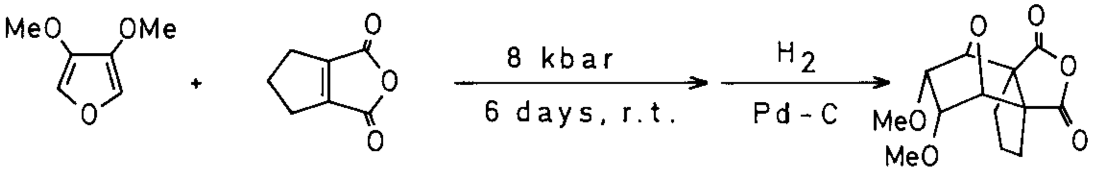
Diels-Alder reaction of 3,4-dimethoxyfuran (1)[7] with cyclohexene-1,2-dicarboxylic anhydride (2a) at 8 kbar and room temperature for 6 days produced a propellane type of the exo adduct (3a)[8,9] in 18 % yield. The adduct 3a is very labile, reverting to the starting compounds at room temperature and normal pressure even in the solid phase. Hydrogenation of 3a in the presence of 5 % Pd/C at 5 bar in an ethyl acetate solution gave a single stereoisomer 4a[10] in 80 % yield.



Comparison of the ^{1}H-NMR spectra of 4a with those of the analogous compounds[5] reveals that the initial Diels-Alder adduct has the proposed structure 3a and that hydrogenation has taken place from the *exo* face to give 4a exclusively.

Reaction of 1 with 4-methylcyclohexene-1,2-dicarboxylic anhydride (2b) and 4,5-dimethylcyclohexene-1,2-dicarboxylic anhydride (2c) under similar condition followed by catalytic hydrogenation (without isolation of 3b and 3c) produced 9,10-dimethoxy-4-methyl-11-oxatricyclo[6.2.1.$0^{2,7}$]undecane-*endo*-2,7-dicarboxylic anhydride (4b)[11] and the 4,5-dimethyl adduct (4c)[12] only in 10 % and 4 % yield respectively. These products 4b and 4c indicate, in contrast with those of 4a, a pretty complex pattern of ^{1}H- and ^{13}C-NMR spectra presumably because of the presence of the two stereoisomers with respect to the methyl group(s). The more reduced yields in these cases might reflect a more steric hindrance by the methyl group(s) in the transition state of the Diels-Alder reaction.

Cyclopentene-1,2-dicarboxylic anhydride (5), having more strained double bond, underwent cycloaddition with 1 at 8 kbar and room temperature followed by hydrogenation, giving a propellane type of the cantharidine analogue (6)[13] in 26 % yield.



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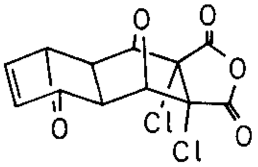
Dichloromaleic anhydride (7) must be more reactive than dimethylmaleic anhydride because of the electron withdrawing property of chlorine that is almost of the same size as methyl group. Indeed, furan reacts with (7) at 5 kbar and 50 °C giving the 2:1 adduct (8),[14] whereas 7 with 1 produces the product (9) via the 1:1 adduct followed by rearrangement with elimination of hydrogen chloride.[15]



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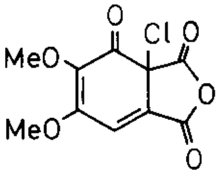

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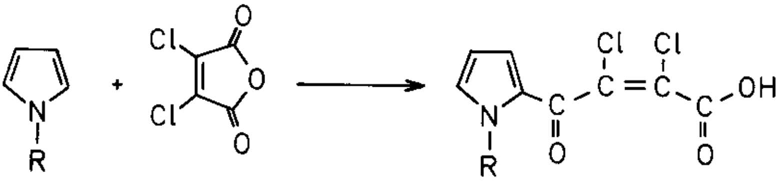
Reaction of N-methylpyrrole (10; R=Me) with 7 at 8 kbar and 35 °C for 5 days afforded a 36 % yield of 1:1 adduct, the structure of which, however, immediately proved to be (11)[16] based upon mass, ^{1}H- and ^{13}C-NMR analyses, probably arising from Friedel-Crafts type acylation of 10 (R=Me) by 7. A completely analogous product was obtained from pyrrole and 7 in 12 % yield. This result is not unexpected since the extreme readiness of the pyrrole system to undergo substitution at C-2 is well known.



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9. (**3a**): too labile to take the melting point; i.r.(KBr) 2930(OMe), 1835, 1775 (C=O) cm^{-1}; ^{1}H-NMR(CDCl$_3$) 1.10-2.40(m, 8H, -C$\underline{H}_2$- ×4), 3.78(s, 6H, OC$\underline{H}_3$ ×2), 4.88(s, 2H, $\underline{H}$-1, 8); ^{13}C-NMR(CDCl$_3$) 17.8(t, C-4, 5), 23.2(t, C-3, 6), 57.7(s, C-2, 7), 58.8(q, O$\underline{C}$H$_3$), 84.1(d, C-1, 8), 139.0(s, C-9, 10), 174.7(s, C=O).
10. (**4a**): mp 121-122 °C; i.r.(KBr) 2925(OMe), 1840, 1775($\underline{C}$=O) cm^{-1}; ^{1}H-NMR(CDCl$_3$) 0.91-2.80(m, 8H, -C$\underline{H}_2$- ×4), 3.46 (s, 6H, OC$\underline{H}_3$ ×2), 3.94(dd, J=3.3, 2.4 Hz, 2H, $\underline{H}$-9, 10), 4.77(dd, J=3.1, 2.1 Hz, 2H, $\underline{H}$-1, 8); ^{13}C-NMR(CDCl$_3$) 17.3(t, C-4, 5), 19.4(t, C-3, 6), 57.9(s, C-2, 7), 59.1(q, O$\underline{C}$H$_3$), 78.5(d, C-9, 10), 82.6(d, C-1, 8), 175.8(s, $\underline{C}$=O).
11. (**4b**): mp 73-74 °C; i.r.(KBr) 2920, 2880(OMe), 1845, 1780(C=O) cm^{-1}; ^{1}H-NMR

($CDCl_3$) 0.84-1.00(m, 3H, $C\underline{H}_3$), 1.23-2.83(m, 7H, $\underline{H}$-3, 4, 5, 6), 3.45(s, 6H, $OC\underline{H}_3$ ×2), 3.86-3.94(m, 2H, $\underline{H}$-9, 10), 4.63-4.80(m, 2H, $\underline{H}$-1, 8).

12. (**4c**): mp 91-93 °C; i.r.(KBr) 1840, 1775(C=O) cm^{-1}; ^1H-NMR($CDCl_3$) 0.67-1.06 (m, 6H, $C\underline{H}_3$), 1.55-3.35(m, 6H, $\underline{H}$-3, 4, 5, 6), 3.45(s, 6H, $OC\underline{H}_3$), 3.85-4.02 (m, 2H, $\underline{H}$-9, 10), 4.65-4.77(m, 2H, $\underline{H}$-1, 8).
13. (**6**): mp 99-100 °C; i.r.(KBr) 2980, 2930(OMe), 1845, 1780(C=O) cm^{-1}; ^1H-NMR ($CDCl_3$) 1.61-3.07(m, 6H, $-C\underline{H}_2-$ ×3), 3.41(s, 6H, $OC\underline{H}_3$ ×2), 3.97(dd, J=3.2, 2.2 Hz, 2H, $\underline{H}$-8, 9), 4.57(dd, J=3.4, 2.3 Hz, 2H, $\underline{H}$-1, 7); ^{13}C-NMR($CDCl_3$) 27.4, 31.0(each t, C-3, 4, 5), 59.2(q, $O\underline{C}H_3$), 68.6(s, C-2, 6), 77.1(d, C-8, 9), 78.4 (d, C-1, 7), 175.4(s, $\underline{C}$=O).
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16. (**11**; R=Me): mp 157-160 °C; MS(m/z) 248(M^+), 108(M^+-CCl=CClCOOH); i.r.(KBr) 3050(OH), 1738(C=O) cm^{-1}; ^1H-NMR(DMSO) 3.90(s, 3H, $C\underline{H}_3$), 6.10(dd, J=4.2, 2.7 Hz, 1H, $\underline{H}$-4), 6.70(dd, J=4.2, 1.3 Hz, 1H, $\underline{H}$-3), 7.09(m, 1H, $\underline{H}$-5); ^{13}C-NMR (DMSO) 36.5(q, $\underline{C}H_3$), 109.3(d, C-4), 122.0(d, C-3), 127.5(s, C-3'), 134.1(d, C-5), 138.9(s, C-2'), 160.9(s, C-2), 175.6(s, C=O).

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