CYCLOADDITIONS OF C-BENZOYL-N-PHENYLNITRONE WITH FUROCONDENSED DERIVATIVES*

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Single regioisomeric cycloadduct *IIa* was formed in a 35% yield upon cycloaddition of the title nitrone *Ia* with benzofuran. The 1,3-dipolar cycloaddition proceeded with derivatives of 4-R--furo[3,2-*b*]pyrrole *V* or *VI* to the furan ring to form only one regioisomer *VIIa* or *VIIIa* in a high yield (93—95%). Dehydrogenation of the latter with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone led to the nitrone *X* or *XII*. Also C,N-diphenylnitrone reacted with furopyrroles to afford the cycloadduct *VIIIb*. Exlusively *endo*-cycloadducts originated; their transition state was stabilized by secondary orbital interactions.

Our preceding papers dealt with 1,3-dipolar cycloadditions of C-benzoyl-N-phenylnitrone with furan derivatives[1-4]. As found[2], 2 methyl- and 2-ethylfuran afforded 1,3-addition products besides 1,3-cycloaddition products. This paper concerns the cycloaddition to benzofuran, 5-ethoxycarbonyl-4*H*-furo[3,2-*b*]-pyrrole (*V*) and its N-ethyl derivative *VI*. Nitrilimines[5] and nitriloxides[6,7] were reported to react with benzofuran *via* a 1,3-dipolar cycloaddition. Like reactions with derivatives of furopyrrole have so far not been published.

Benzofuran reacts with nitrone *Ia* slowly; a five-fold excess of benzofuran in toluene furnished the monoadduct *IIa* after 40 days in a 26% yield (Scheme 1). The same adduct was obtained in a 35% yield in a 40 h-reaction at 55°C in addition to diketoamide *IV* (14%), which originated by a rearrangement of the starting nitrone *Ia* (ref.[1]). The structure of *IIa* was ascribed on the basis of electron impact mass spectrum (the presence of M^+ at m/z 343) and analysis of the ^{1}H-NMR spectrum (values in ppm on δ scale). Thus, the singlet of the 3-H isoxazolidine proton resonated at 5·78, whilst both bridged protons, forming an AB system of two significant doublets, have — due to their quite equivalent shielding by oxygen heteroatoms — similar chemical shifts, (5·91 and 6·09). The more down field signal was assigned the 3a-H proton with respect to the coupling constant $J_{3,3a}$ = 0·5 Hz with the isoxazolidine

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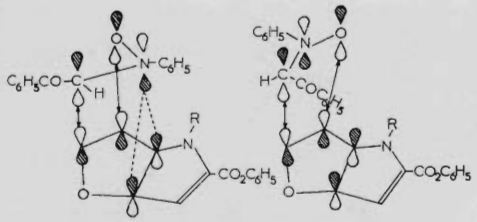
3-H proton, which was seen at high resolution measurement. Compound *IIa* is a cycloadduct and not the 1,3-addition product, as backed by chemical shifts of bridged proton signals with those of 2-H and 3-H of benzofuran, which are downfield shifted (7·51 and 6·63). This shift can be rationalized by the loss of the ring current effect in the cycloadduct *IIa*. Four aromatic protons of the benzofuran moiety resonate jointly with those of phenyls as a complex multiplet at the appropriate region of the spectrum. The doublet-doublet at 6·38 does not couple with the bridged protons, as evidenced by the INDOR technique. It applies to one of the benzofuran moiety proton; the coupling constant $J = 8{\cdot}5$ Hz is indicative of benzofuran derivatives.

The regioisomer *IIb* should, however, reveal one proton due to a shielding of two oxygen heteroatoms as a doublet in lower field at about 7, and the second bridged proton at about 5, as diagnostic of 4-H proton in isoxazolidine derivatives[8]. The cycloadduct *IIb* was not found in the reaction mixture. Benzenenitriloxides afford



„*endo*" XIII „*exo*" XIV

both regioisomeric cycloadducts of types *IIa* and *IIb* (ref.[6,7]), nitrilimines gave only adducts of type *IIa* (ref.[5]) in agreement with the known LU(dipole) control of cycloaddition of nitrilimines[9]. The perturbation interaction diagram, constructed of *IP* and *EA* values of C-benzoyl-N-phenylnitrone[4] $IP = 849{\cdot}06$ kJ mol^{-1} and $EA = 84{\cdot}90$ kJ mol^{-1} and benzofuran $IP = 835{\cdot}55$ kJ mol^{-1}, ref.[10] and $EA =$ $= -10{\cdot}61$ kJ mol^{-1}, ref.[6] shows that dominant is the limit interaction LUMO(*Ia*) – – HOMO(benzofuran). The greatest atom-orbital coefficients in HOMO and LUMO in benzofuran are at the α-C atom[6], and therefore, the mentioned interaction leads to the regioisomer *IIa*. The second interaction leading to regioisomer *IIb* did not come into account, since the difference ΔE is greater than 1 eV. Although nitrone *Ia* behaves as an electrophile with benzofuran, the 1,3-addition substitution product *III* was not identified in the mixture. Formation of the by-product of reaction of diketoamide *IV* indicates, similarly as with furan, a small dipolarophillic reactivity.

Substance *V* was selected as another model of furocondensed derivatives capable for investigation of dipolarophilic activity. A very low value $IP = 752{\cdot}57$ kJ mol^{-1} (ref.[4]) was found from the charge-transfer complexes with tetracyanoethylene. Employing the equation published in[4] ($EA = IP - \pi - \pi^* - \Delta$), $EA = -100{\cdot}34$

kJ mol^{-1}. Energy of the $\pi-\pi^*$ electronic transition of *V* in hexane is 402·34 kJ mol^{-1} with a value of constant Δ = 450·58 kJ mol^{-1} taken from the series[4] of furan derivatives. The dominant limit interaction from the perturbation interaction diagram is LU(*Ia*)–HO(*V*), and consequently and increased reactivity in comparison with benzofuran (*IP* = 835·55 kJ mol^{-1}), or furan (*IP* = 850·02 kJ mol^{-1}) could be anticipated on the basis of the decrease of the difference between limit orbitals HOMO(*V*) and LUMO(*Ia*). Compound *VIIa* was obtained in a 95% yield from reaction between the equimolar mixture of nitrone *Ia* and furopyrrole *V* in benzene for 21 days at room temperature. The structure was determined from spectroscopic data. Results of elemental analysis together with the presence of the peak M^+ at *m/z* 404 indicate the formation of a 1 : 1 adduct. Molecule of compound *V* possesses three possible reaction centres for addition of nitrone *Ia*, namely the NH and multiple bonds at furan and pyrrole rings. Addition to NH bond can be excluded, since the IR spectrum of compound *VIIa* contains vibration of NH groups at 3 437 cm^{-1}. This is the first example of a 1,3-dipolar cycloaddition of heterocycles, where cycloaddition was not accompanied with an addition of NH bond to 1,3-dipole. Cycloaddition of C-acetyl-N-phenylnitrilimine[11,12] with either pyrrole or indole did not result in isolation of a cycloadduct with a preserved NH bond; only the 1 : 2 adduct was isolated. Of extraordinary interest, in connection with this finding, was the rationalization of "loxoselectivity"[13], *i.e.* which of both halves of the molecule is more reactive considering 1,3-cycloaddition. Since the reaction is governed by interaction LU(*Ia*)–HO(*V*), *i.e.* the nitrone *Ia* behaves as an electrophile, one can easily anticipate a higher electron density at the double bond of the furan moiety than at that of pyrrole *V*, where an electron accepting substituent is attached. Steric effects of the attached group hinder, together with electronic effects, the access to the nitrone *Ia*. Reaction of *Ia* with 2-substituted derivatives of furan proceeded exclusively *via* cycloaddition to an unsubstituted double bond[2,3]. Moreover, preservation of NH group in *VIa* excluded cycloaddition to pyrrole moiety; here, an NH-indoline grouping would originate, which is, however, very reactive for a further addition of *Ia* to the NH bond. Should a cycloaddition to pyrrole ring occur, the ^{1}H-NMR spectrum had to contain the AM system of furan protons; derivative *V* had the chemical shift values at 6·43 (3-H) and 7·50 (2-H) with a coupling constant *J* = = 2·4 Hz. The ^{1}H-NMR spectrum of *VIIa* revealed an AB system of two bridged proton doublets 3a-H and 7a-H at 5·78 and 6·42, $J_{3a,7a}$ = 6·0 Hz confirming the *cis*-stereospecificity of the concerted cycloaddition of *Ia* to *V*. The loss of ring current effect on the value of chemical shift of bridged protons indicates a cycloaddition and not 1,3-addition. The detailed structure *VII* can be derived on the basis of a finding that isoxazolidine proton 3-H absorbs as a singlet at 5·61. The zero value of coupling constant $J_{3,3a}$ evidences the *anti*-arrangement of bridged protons 3a-H, 7a-H with that of isoxazolidine 3-H proton. The formation of this *endo*-adduct, similarly as with benzofuran or furan derivatives[1–3] can be explained by a subsequent second-

ary orbital interactions between the π-bond of heterocycle (HOMO) in an "*endo*" transition state *XIII* in comparison with an "*exo*" transition state in *XIV*.

Due to a contraction of the heterocyclic system, the singlet associated with the 6-H proton of the pyrrole moiety of *V* was shifted from 6·81 to higher fields, 5-H is at 6·16 similarly as with benzofuran, the appearance of two AB doublets of bridged protons in the ^{1}H-NMR spectrum excludes the other regioselective structure *IX*. The opposite regioisomer head-to-head originating from cycloaddition of benzenenitriloxide with furan is associated with the occurrence of a doublet of proton at 4·81 in the neighbourhood of which no heteroatom is present. In *VIIa*, it resonates at 5·78, what means that it is deshielded by an oxygen atom. Cycloaddition of *Ia* to *VI* (R = C_2H_5) was observed to have the same regiospecificity. The cycloadduct *VIIIa* obtained in a 93% yield has the AB system of bridged protons at 5·88 and 6·41. Protons 5-H and 3-H absorb in deuteriochloroform as a two-proton singlet at 5·82. nevertheless in deuterioacetone they appear as distinct singlets at 6·18 (5-H) and 5·66 (3-H). The UV spectrum displayed a maximum at 245 nm (the isoxazolidine moiety), whilst the last maximum at 307 nm did not show, as anticipated, any noticeable bathochromic shift when compared with the starting *V* and *VI*. Reaction of the cycloadduct *VIIIa* with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at room temperature did not afford the furopyrrolisoxazolidine derivative, but similarly as with cycloadducts *Ia* with furan derivatives[3], a nitrone derivative *X*. The 3-H proton signal was shifted down field due to deshielding of nitrone oxygen to 8·47 and addition of a shift reagent made this shift even more significant, as diagnostic of protons adjacent to nitrone oxygens[14]. Addition of ^2H_2O, or heating to 60°C is of no effect to the position of this signal. The re-establishment of the heterocyclic system was evidenced by the downfield shift of 6-H singlet signal to 6·65. The chemical shift value of 2-substituted furopyrrole 6-H proton is very close (6·68). The UV absorption maximum of *X* (381 nm) also confirmed the formation of a 2-substituted furo[3,2-*b*]pyrrole system with a nitrone grouping by its bathochromic shift towards *VI*. The same result was achieved when dehydrogenating *V* to the nitrone *XII*. The appearance of $M^{+\cdot}-16$ fragments, typical of nitrones, is in favour of the proposed structures *X* and *XII*. The furo[3,2-*b*]pyrrole system is much more reactive than furan derivatives in reaction with nitrones. Compound *VI* reacted in a 20% yield with C,N-diphenylnitrone (*Ib*) at 60°C to give the cycloadduct *VIIIb*; furan derivatives did not react with this nitrone even at 140°C either (ref.[1]).

It is quite surprising that 2-(4-bromophenyl)-5-ethoxycarbonyl-4*H*-furo[3,2-*b*]-pyrrole (*XI*) did not react with the highly-reactive nitrone *Ia* either at a long lasting standing at room temperature, or at 60°C. The unreacted *XI* was every time almost quantitatively recovered together with the by-products of nitrone *Ia*, the formation of which has already been reported[1]. Cycloaddition did not likely proceed to the furan ring due to steric hindrance. The 1,3-dipolar cycloaddition of nitrone *Ia* to 2-R-substituted furan derivatives (R = CH_3, C_2H_5, CH_2OH, CH_2OCOCH_3,

CH_2SH) proceeded every time at the substituted double bond. The double bond of the pyrrole ring is, on the other hand, not reactive due to steric hindrance and electronic effects.

EXPERIMENTAL

Melting points are not corrected. The IR spectra of chloroform solutions were measured with a UR-20 (Zeiss, Jena) spectrophotometer, UV spectra with a UV-VIS (Zeiss, Jena) apparatus in methanol. The ^{1}H-NMR spectra were recorded with a Tesla BS 487C spectrometer operating at 80 MHz using tetramethylsilane as an internal reference. Electron impact mass spectra were measured with a MS 902 S (AEI, Manchester) instrument at 70 eV. Furo[3,2-*b*]pyrrole derivatives *V*, *VI*, *XI* were prepared according to[15–17]. Reaction mixtures were separated by chromatography on silica gel with chloroform–heptane 8 : 2.

Cycloaddition of *Ia* to Benzofuran

A mixture of *Ia* (3 g, 13·3 mmol), benzofuran (5 g, 42 mmol) and benzene (20 ml) were heated at 55°C for 40 h and at 25°C for 10 days in a nitrogen atmosphere. The vacuum-concentrated mixture was chromatographically separated into two products: monocycloadduct *IIa* (1·6 g, 35%), m.p. 141–143°C, (dichloromethane–light petroleum). For $C_{22}H_{17}NO_3$ (343·4) calculated: 76·95% C, 4·99% H, 4·08% N; found: 76·81% C, 5·04% H, 4·37% N. ^{1}H-NMR spectrum ($CDCl_3$): 6·92–8·14 (m, 14 H, aromatic protons); 6·09 (d, $J_{3a,8a}$ = 6·5 Hz, 1 H, 8a-H); 5·91 (d, $J_{3a,8a}$ = 6·5 Hz, 1 H, 3a-H); 5·78 (s, 1 H, 3-H). UV spectrum λ_{max}, nm (log ε): 245 (4·17), 283 (3·56). IR spectrum, cm^{-1}: ν(C=O) 1 692. Mass spectrum, *m/z* (%): $M^{+\cdot}$ 343 (9), 248 (45), 222 (21), 221 (57), 220 (50), 135 (15), 131 (14), 122 (21), 118 (28), 105 (63), 104 (32), 93 (19), 77 (100), 51 (35), 39 (15). Diketoamide *IV* (0·4 g, 14%) m.p. 55–57°C. IR spectrum. cm^{-1}: ν(N—H) 3 450. Mass spectrum, *m/z*: $M^{+\cdot}$ 225 ($C_{16}H_{11}NO_2$), 121, 120, 105 (C_6H_6—C≡O)$^+$, 92 ($C_6H_5NH)^+$, 91 ($C_6H_5N)^+$, 77 (C_6H_5).

Cycloaddition of *Ia* to *V*

A mixture of *Ia* (1·1 g, 4·88 mmol), *V* (0·9 g, 5·02 mmol) and toluene (50 ml) was left to stand at 20°C for 2y days. Concentration under diminished pressure, trituration with light petroleum and crystallization from benzene–light petroleum afforded monocycloadduct *VIIa* (1·85 g, 95%), m.p. 161–163°C, For $C_{23}H_{20}N_2O_5$ (404·4) calculated: 68·30% C, 4·99% H, 6·93% N; found: 68·43% C, 4·82% H, 6·96% N. ^{1}H-NMR spectrum (CD_3COCD_3): 6·95–8·08 (m, 10 H, aromatic protons); 6·42 (d, $J_{3a,7a}$ = 6·0 Hz, 1 H, 3a-H): 6·16 (s, 1 H, 5-H), 5·78 (d, $J_{3a,8a}$ = = 6·0 Hz, 1 H, 7a-H); 5·61 (s, 1 H, 3-H); 4·15 (q, J = 7·8 Hz, 2 H, CH_2); 1·17 (t, J = 7·8 Hz, 3 H, CH_3). UV spectrum, λ_{max}, nm (log ε): 242 (4·50), 303 (4·20). IR spectrum, cm^{-1}: ε(C=O) 1 692 and 1 710, ε(NH) 3 437.

Cycloaddition of *Ia* to *VI*

Compound *Ia* (1 g, 4·4 mmol) was allowed to react with *VI* (0·9 g, 5·0 mmol) under the same conditions to furnish monocycloadduct *VIIIa* (1·8 g, 93%), m.p. 124–126°C (benzene–hexane). For $C_{25}H_{24}N_2O_5$ (432·5) calculated: 69·43% C, 5·59% H, 6·48% N; found: 69·38% C, 5·50% H, 6·53% N. ^{1}H-NMR spectrum (CD_3COCD_3): 6·66–8·07 (m, 10 H, aromatic protons), 6·41 (d, $J_{3a,7a}$ = 6·0 Hz, 1 H, 3a-H), 6·18 (s, 1 H, 5-H), 5·88 (d, $J_{3a,7a}$ = 6·0 Hz, 7a-H), 5·66 (s, 1 H,

3-H); 3·96—4·75 (m, 4 H, CH_2); 1·07—1·47 (m, 6 H, CH_3). UV spectrum, λ_{max}, nm (log ε): 245 (4·50), 307 (4·19). IR spectrum, cm^{-1}: ν(C=O) 1 699. ;Mass spectrum, *m/z* (%): 432 (2), 327 (4), 209 (18), 207 (58), 179 (18), 164 (14), 162 (21), 135 (14), 134 (12), 133 (16), 105 (38), 104 (74), 93 (38), 91 (22), 77 (100).

Nitrone X (0·35 g, 87%), m.p. 218—220°C was obtained by dehydrogenation of *VIIIa* (0·4 g, 0·9 mmol) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0·35 g, 1·5 mmol) in benzene (20 ml) at 25°C (8 h) and crystallization from chloroform. For $C_{25}H_{22}N_2O_5$ (430·4) calculated: 69·75% C, 5·15% H, 6·51% N; found: 69·99% C, 5·12% H, 6·49% N. ^{1}H-NMR spectrum ($CDCl_3$): 8·47 (s, 1 H, 3-H), 7·22—7·87 (m, 1: H, aromatic protons); 6·65 (s, 1 H, 6-H), 4·16—4·55 (m, 4 H, CH_2), 1·24—1·55 (m, 6 H, CH_3). UV spectrum λ_{max}, nm (log ε): 265 (4·17) and 381 (4·52). IR spectrum, cm^{-1}: ν(C=O) 1 698. Mass spectrum, *m/z* (%): $M^{+\bullet}$ 430 (16), 414 (19), 309 (100), 234 (51), 105 (48), 77 (54).

Nitrone XII (0·15 g, 75%), m.p. 215—216°C was obtained under the same conditions as nitrone *X* by dehydrogenation of *VIIa* (0·2 g, 0·5 mmol) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0·3 g, 1·3 mmol). For $C_{23}H_{18}N_2O_5$ (402·4) calculated: 68·65% C, 4·51% H, 6·96% N; found: 68·72% C, 4·72% H, 7·05% N. ^{1}H-NMR spectrum (CDC_3OCD_3): 8·22 (s, 1 H, 3-H); 7·28—7·87 (m, 10 H, aromatic protons); 6·56 (s, 1 H, 6-H); 4·25 (q, J = 7·0 Hz, 2 H, —OCH_2—); 1·23 (t, J = 7·0 Hz, 3 H, CH_3). UV spectrum, λ_{max}, nm (log ε): 267 (4·29), 382 (4·57). IR spectrum, cm^{-1}: ν(C=O) 1 695 and ν(NH) 3 452.

Cycloaddition of *Ib* to *VI*

A mixture of nitrone *Ib* (1 g, 5 mmol), *VI* (0·9 g, 5 mmol) and benzene (20 ml) was kept at 60°C for 40 h. The monocycloadduct *VIIIb* (0·38 g, 20%), m.p. 135—136°C was obtained after concentration under diminished pressure and chromatography on a silica gel column (eluent cyclohexane–ethyl acetate 4 : 1). For $C_{24}H_{24}N_2O_4$ (404·5) calculated: 71·27% C, 5·98% H, 6·92% N; found: 71·25% C, 5·86% H, 6·97% N. ^{1}H-NMR spectrum ($CDCl_3$): 6·81—7·52 (m, 10 H, aromatic protons); 5·82—6·10 (m, 3 H, 3a-H), 7a-H, 5-H); 5·21 (s, 1 H, 3-H); 4·11—4·60 (m, 4 H, 2 × CH_2); 1·21—1·59 (m, 6 H, 2 × CH_3).

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