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Some 1,3-Dipolar Adducts from Benzodiazepine. I. Condensation of Nitrilimines with 2-Methyl-4-phenyl-1,5-benzodiazepines

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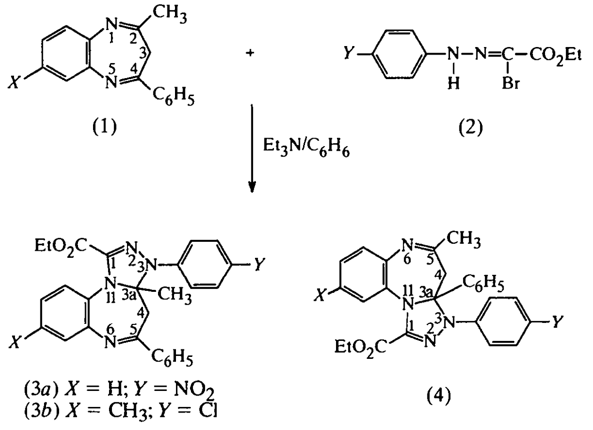
Abstract

The condensation reaction of *N-p*-nitrophenyl-*C*-ethoxycarbonyl nitrilimine or *N-p*-chlorophenyl-*C*-ethoxycarbonyl nitrilimine with 7-*X*-2-methyl-4-phenyl-1,5-benzodiazepine (*X* = H or CH_3) is regio- and periselective. The 1,3-dipolar cycloaddition occurs in a unique way on the N1═C2 double bond of the 1,5-benzodiazepine and leads to ethyl 3a-methyl-3-(4-nitrophenyl)-5-phenyl-3a,4-dihydro-3*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine-1-carboxylate, $C_{26}H_{23}N_5O_4$, (3*a*), or ethyl 3-(4-chlorophenyl)-3a,8-dimethyl-5-phenyl-3a,4-dihydro-3*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine-1-carboxylate, $C_{27}H_{25}ClN_4O_2$, (3*b*).

Comment

In recent publications (Hasnaoui *et al.*, 1991; El Messaoudi *et al.*, 1992, 1994; Baouid *et al.*, 1996), we have emphasized the noteworthy regio- and periselectivity of 1,3-dipolar cycloadditions on 1,2(1,4)-diazepines and 1,5-benzodiazepine. Developing our work concerning the synthesis of bi- and triheterocyclic systems from seven-membered nitrogen heterocycles, we describe here the cycloaddition of nitrilimines to 1,5-benzodiazepines.



According to the scheme above, the condensation reaction of the 2-methyl-4-phenyl-1,5-benzodiazepines, (1) (*X* = H or CH_3) (Barltrop *et al.*, 1959), with *N-p*-nitro(or chloro)phenyl-*C*-ethoxycarbonyl nitrilimine, prepared *in situ* by the action of triethylamine on ethyl α-bromo-α-[*p*-nitro(or chloro)phenylhydrazono]-acetate, (2) (Huisgen & Koch, 1955; Sharp & Hamilton, 1946), produces the monocyclo adducts (3) or (4). The structures were assigned by X-ray crystallography analysis, which showed that these adducts are (3*a*) and (3*b*): the N1═C2 double bond of the benzodiazepine is the site of the addition. The reaction is periselective, as only the N1═C2 double bond of (1) is affected. The N atom of the dipole is linked to the C atom of the N1═C2 dipolarophile, making the reaction regioselective.

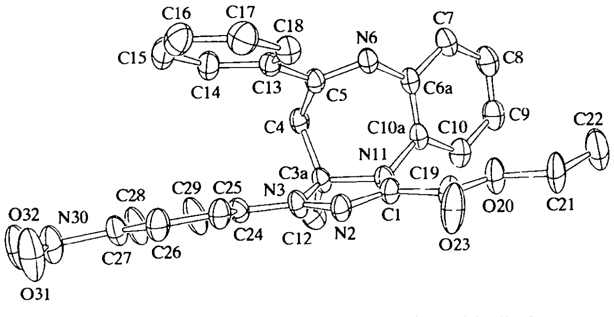


Fig. 1. The molecular structure of compound (3*a*) with displacement ellipsoids at the 50% probability level.

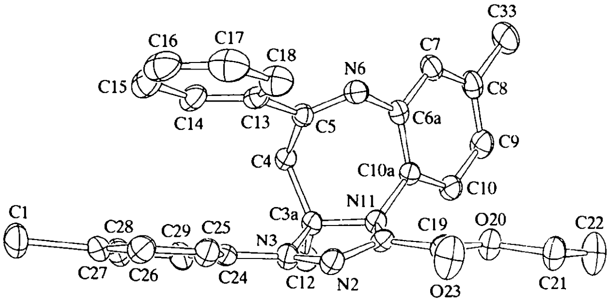


Fig. 2. The molecular structure of compound (3*b*) with displacement ellipsoids at the 50% probability level.

The core of each molecule is composed of a seven-membered ring to which a phenyl ring is attached and a five- and six-membered ring are fused. The seven-membered ring consists of a triangle plane (*p*1) formed by C4—C3a—N11 linking the plane (*p*2) formed by C4—C5—N6—C6a [r.m.s. deviations: 0.009 and 0.012 Å for (3*a*) and (3*b*), respectively] and the plane (*p*3) of N6—C6a—C10a—N11 [r.m.s. deviations: 0.001 and 0.013 Å for (3*a*) and (3*b*), respectively]; the dihedral angle between *p*1 and *p*2 is 63.8 (1)° in (3*a*) and 62.6 (2)° in (3*b*), and that between *p*2 and *p*3 is 50.0 (1)° in (3*a*) and 50.1 (2)° in (3*b*). The fused benzo ring [r.m.s. deviations: 0.008 and 0.003 Å for (3*a*) and (3*b*), respectively] is in the plane *p*3; the dihedral angles are 4 (1) and 1 (2)° for (3*a*) and (3*b*), respectively. With respect to the unsubstituted phenyl group [r.m.s. deviations: 0.005 and 0.007 Å for (3*a*) and (3*b*), respectively], the plane *p*2, containing the C5=N6 double bond, makes a dihedral angle of 30.6 (2)° in (3*a*) and 28.3 (1)° in (3*b*). The triazolo ring C1—N2—N3—C3a—N11 [*p*4; r.m.s. deviations: 0.035 and 0.047 Å for (3*a*) and (3*b*), respectively] contains the C1=N2 double bond and has two planar substituents: the ethoxycarbonyl group [*p*5; r.m.s. deviations: 0.020 and 0.026 Å for (3*a*) and (3*b*), respectively] and the substituted phenyl group [*p*6; r.m.s. deviations: 0.004 and 0.003 Å for (3*a*) and (3*b*), respectively]. In (3*a*), *p*4 and *p*5 are almost coplanar [dihedral angle 2 (1)°], while in (3*b*), *p*4 and *p*5 form a dihedral angle of 20.8 (4)°. The phenyl plane *p*6 is inclined at angles of 15.3 (2) and 27.7 (3)° [for (3*a*) and (3*b*), respectively] to *p*4. The nitro group in (3*a*) forms a dihedral angle of 5.8 (9)° with its phenyl ring.

Experimental

To a solution of 1.17 g (5 mmol) of (1) (X = H) and 0.85 g (2.8 mmol) of (2) (Y = NO_2) in dry benzene (15 ml) was slowly added dropwise under stirring and at a temperature lower than 278 K, a solution of 0.5 ml (3.6 mmol) of triethylamine dissolved in dry benzene (3 ml). The mixture was stirred at 283 K for 20 h, then washed with water and the organic layers concentrated. The crude product was dissolved in methanol and compound (3*a*) precipitated in 82% yield (m.p. 476–478 K). Compound (3*b*) was prepared using the same procedure: 1.24 g (5 mmol) of (1) (X = CH_3) and 1.37 g (4.7 mmol) of (2) (Y = Cl) in dry benzene (15 ml); 1.2 ml of triethylamine dissolved in dry benzene (5 ml); 75% yield (m.p. 479–480 K). Crystals of both (3*a*) and (3*b*) suitable for X-ray analysis were prepared by slow solvent evaporation from ethanol solutions at room temperature.

Compound (3*a*)

Crystal data

$C_{26}H_{23}N_5O_4$
M_r = 469.50
Monoclinic
$C2/c$
a = 22.711 (6) Å
b = 15.498 (5) Å
c = 14.642 (4) Å
β = 117.97 (2)°
V = 4551 (5) Å^3
Z = 8
D_x = 1.37 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 22 reflections
θ = 11–17°
μ = 0.089 mm^{-1}
T = 294 K
Prism
0.50 × 0.35 × 0.25 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
4343 measured reflections
4006 independent reflections
2591 reflections with $I > 1.5\sigma(I)$

R_{int} = 0.052
θ_{max} = 25°
$h = -26 \rightarrow 23$
$k = 0 \rightarrow 18$
$l = 0 \rightarrow 17$
3 standard reflections
frequency: 120 min
intensity decay: 4.2%

Refinement

Refinement on F
R = 0.055
wR = 0.066
S = 1.783
2591 reflections
317 parameters
H atoms not refined
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0025F_o^4]$
$(\Delta/\sigma)_{max}$ = 0.003

$\Delta\rho_{max}$ = 0.150 e Å^{-3}
$\Delta\rho_{min}$ = 0.104 e Å^{-3}
Extinction correction: isotropic (Zachariasen, 1963)
Extinction coefficient: 0.31 × 10^{-6}
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 1. *Selected geometric parameters (Å, °) for (3a)*

N2—N3	1.387 (2)	N11—C3a	1.493 (3)
N2—C1	1.277 (4)	N11—C10a	1.434 (4)
N3—C3a	1.490 (3)	C3a—C4	1.530 (4)
N6—C5	1.291 (3)	C4—C5	1.501 (4)
N6—C6a	1.412 (4)	C6a—C10a	1.394 (4)
N11—C1	1.383 (3)		
N3—N2—C1	105.9 (2)	N3—C3a—N11	97.9 (1)
N2—N3—C3a	112.7 (2)	N3—C3a—C4	111.7 (2)
C5—N6—C6a	119.3 (2)	N11—C3a—C4	110.1 (2)
C1—N11—C3a	107.3 (2)	C3a—C4—C5	111.0 (2)
C1—N11—C10a	122.0 (2)	N6—C5—C4	121.7 (2)
C3a—N11—C10a	117.8 (2)	N6—C6a—C10a	122.2 (3)
N2—C1—N11	115.3 (2)	N11—C10a—C6a	119.6 (3)

Compound (3*b*)

Crystal data

$C_{27}H_{25}ClN_4O_2$
$M_r = 472.98$
Monoclinic
$P2_1/c$
$a = 12.985\ (1)$ Å
$b = 14.036\ (2)$ Å
$c = 13.314\ (3)$ Å
$\beta = 102.7\ (3)°$
$V = 2368\ (4)$ Å^3
$Z = 4$
$D_x = 1.33$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 11–16°$
$\mu = 0.190$ mm^{-1}
$T = 294$ K
Prism
$0.60 \times 0.50 \times 0.30$ mm
Yellow

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
5058 measured reflections
4847 independent reflections
2659 reflections with $I > 2.5\sigma(I)$

$R_{\rm int} = 0.026$
$\theta_{\rm max} = 26°$
$h = -15 \rightarrow 15$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 16$
3 standard reflections
frequency: 120 min
intensity decay: 0.2%

Refinement

Refinement on F
$R = 0.049$
$wR = 0.065$
$S = 1.877$
2659 reflections
308 parameters
H atoms not refined
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0025F_o^4]$
$(\Delta/\sigma)_{\rm max} = 0.006$

$\Delta\rho_{\rm max} = 0.331$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.301$ e Å^{-3}
Extinction correction: isotropic (Zachariasen, 1963)
Extinction coefficient: 0.48×10^{-6}
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 2. *Selected geometric parameters (Å, °) for (3b)*

N2—N3	1.387 (4)	N11—C3a	1.481 (4)
N2—C1	1.275 (4)	N11—C10a	1.448 (4)
N3—C3a	1.501 (4)	C3a—C4	1.542 (4)
N6—C5	1.281 (4)	C4—C5	1.510 (4)
N6—C6a	1.409 (4)	C6a—C10a	1.384 (4)
N11—C1	1.387 (4)		
N3—N2—C1	107.2 (2)	N3—C3a—N11	98.7 (2)
N2—N3—C3a	110.8 (2)	N3—C3a—C4	113.0 (2)
C5—N6—C6a	118.9 (3)	N11—C3a—C4	111.6 (2)
C1—N11—C3a	107.3 (2)	C3a—C4—C5	111.2 (2)
C1—N11—C10a	122.9 (3)	N6—C5—C4	121.7 (3)
C3a—N11—C10a	117.1 (2)	N6—C6a—C10a	123.2 (3)
N2—C1—N11	114.6 (3)	N11—C10a—C6a	120.0 (3)

For both compounds, data collection: *CAD*-4 *Operations Manual* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Operations Manual*; data reduction: *BEGIN* in *SDP-Plus* (Frenz, 1985); program(s) used to solve structures: *MULTAN*80 (Main *et al.*, 1980); program(s) used to refine structures: *LSFM* in *SDP-Plus*; molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *CIF VAX* in *MolEN* (Fair, 1990).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1173). Services for accessing these data are described at the back of the journal.

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17α-(4-Chlorobenzoyloxy)-3-methoxy-13α-gona-1,3,5(10)-triene†

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Abstract

The hydroboration of 3-methoxy-18-norestra-1,3,5(10),-13(18)-tetraene in an anti-Markovnikov sense leads to the formation of two diastereomeric alcohols which have been separated by high-performance liquid chromatography or fractional crystallization of their 17-*p*-chlorobenzoates. The assignment of the absolute configuration of the title compound, $C_{25}H_{27}ClO_3$, has been carried out by X-ray analysis.

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† IUPAC name: 3-methoxy-13α-gona-1,3,5(10)-trien-17α-yl 4-chlorobenzoate.