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Unusual Hetarynic Condensation of 3-Bromo-2-ethoxypyridine with Diisopropyl Ketone Enolate in the Presence of a Complex Base

SANDRA IANELLI,^a MARIO NARDELLI,^{a*} DANIELE BELLETTI,^a KARINE PASQUIER^b AND PAUL CAUBÈRE^b

^aDipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica, Università degli Studi di Parma, Centro di Studio per la Strutturistica Diffraattometrica del CNR, Viale delle Scienze 78, I-43100 Parma, Italy, and

^bLaboratoire de Chimie Organique I, UA CNRS No. 457, Université de Nancy I, BP 239, 54506 Vandoeuvre-Les-Nancy CEDEX, France. E-mail: nardelli@ipruniv.cce.unipr.it

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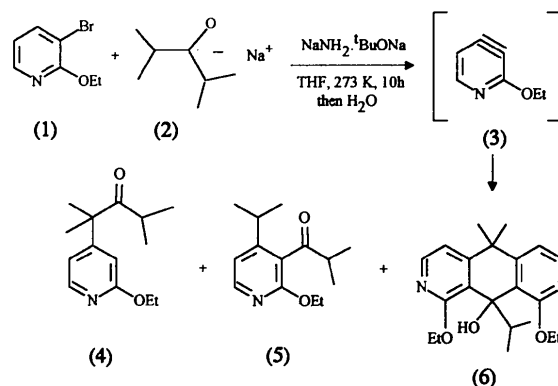
Abstract

The crystal structure analysis of 1,8-diethoxy-9,10-dihydro-9-isopropyl-10,10-dimethyl-2,7-diaza-9-anthrol, C₂₁H₂₈N₂O₃, obtained from the condensation of 3-bromo-2-ethoxypyridine with diisopropyl ketone enolate in the presence of the complex base NaNH₂·tBuONa, shows the tricyclic nature of the compound and allows interpretation of the reaction mechanism. The structure and conformation of the two independent molecules present in the asymmetric unit are compared with molecular modelling results.

Comment

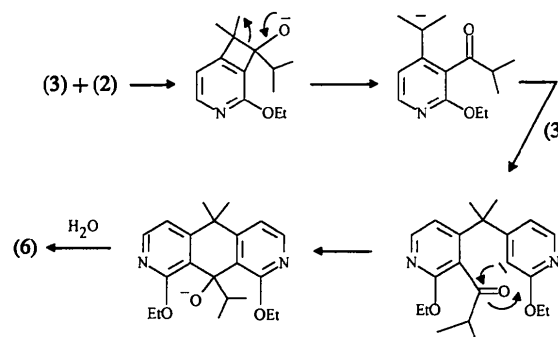
In a preceding short communication (Jamart-Grégoire, Léger & Caubère, 1990), it was established for the first time that ketone enolates are capable of condensation with 3,4-dihydropyridines generated from 3-bromopyridines and appropriate complex bases (Caubère, 1991, 1993) to give pyridinyl ketones and pyridinocyclobutenols. In a continuation of our exploration of this new route to pyridine derivatives, we undertook the study of the chemical behaviour of 3-bromo-2-ethoxypyridine in such reactions and found that during its condensation with isopropyl ketone enolate in the

presence of the complex base NaNH₂·tBuONa, an unusual result was observed (see scheme below).



Taking into account the results obtained from the aryinc condensation of ketone enolates (Caubère, 1974, 1978, 1991, 1993), the formation of compounds (4) and (5) was expected. The formation of compound (6) was also observed, however, and this is rather unusual. Interestingly, we once observed such a reaction during the aryinc condensation of diisopropyl ketone enolate with bromobenzene (Caubère & Guillaumet, 1972).

Compounds (4) and (5) were easily identified from spectroscopic data, but characterization of compound (6) required X-ray analysis. The results show that, as in aryinc chemistry, the alkoxy groups direct the nucleophilic attack in the *meta* position relative to the carbon bearing the O atom. We can thus propose the mechanism given in the scheme below for the formation of compound (6).



One of the two independent molecules is shown in Fig. 1. The geometric parameters were compared with those calculated for the free molecule by the *TRIPOS* molecular-modelling optimization procedure of the *SYBYL* package (Tripos Associates Inc., 1992) using default parameters. From the results of this comparison it was noticed that the largest differences were observed for: (i) bond distances in the isopropyl and ethyl groups, probably caused by the high thermal motion (or disorder) affecting these groups, (ii) bond angles at the junction of the isopropyl substituent on the central

ring and at the junctions of the ethoxy groups, and (iii) torsion angles involving atoms of the central ring and the isopropyl substituent.

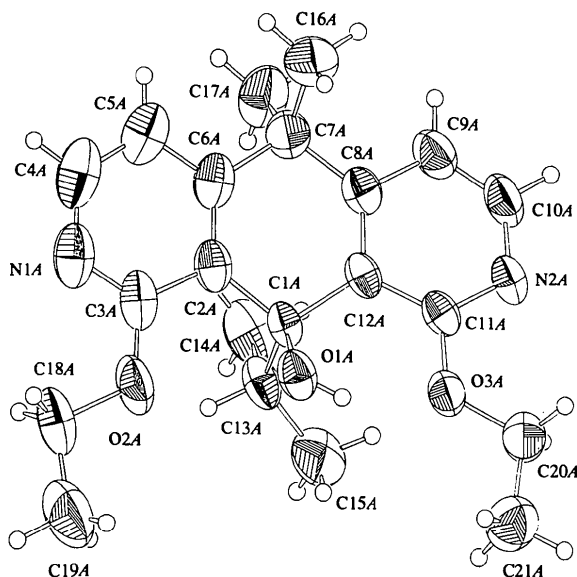


Fig. 1. The structure of molecule A with 50% probability displacement ellipsoids.

Moreover, there were indications that the three-ring system is not rigid and deformations are produced both by intramolecular and packing interactions. A global quantitative evaluation of these deformations is also seen from the following values of the total puckering amplitudes (Cremer & Pople, 1975) of the three rings (calc. is for the calculated model): ring (I) (C2, C3, N1, C4, C5, C6) molecule A 0.021 (7), molecule B 0.047 (7), calc. 0.049 Å; ring (II) (C1, C2, C6, C7, C8, C12) molecule A 0.161 (6), molecule B 0.163 (6), calc. 0.160 Å; ring (III) (C8, C9, C10, N2, C11, C12) molecule A 0.065 (6), molecule B 0.028 (7), calc. 0.127 Å. The three rings are not coplanar, the dihedral angles formed by the weighted least-squares planes through them being (I)/(II) molecule A 5.1 (2), molecule B 9.1 (2), calc. 7.2°; (II)/(III) molecule A 8.9 (2), molecule B 7.5 (2), calc. 9.3°; (I)/(III) molecule A 13.2 (2), molecule B 15.4 (2), calc. 11.2°.

Analysis of the difference-potential-energy profiles, carried out with the ROTENER (Nardelli, 1991a) program, considered the ethoxy and the ethyl groups rotating about the C—O bonds and the isopropyl group about the C—C bond joining it to the ring in the free molecule. These profiles show that: (i) rotation about C3—O2 and C11—O3 does not involve any intramolecular hindrance, so that the orientation of the ethoxy groups is determined by packing van der Waals forces, (ii) rotation of the ethyl groups involves small energy barriers (ca 7–8 kJ mol⁻¹), which indicates that their orientation is also conditioned mainly by intermolecular interactions,

and (iii) the orientation of the isopropyl group is mainly determined by intramolecular steric effects.

In both molecules, the hydroxyl group is involved in an intramolecular O1—H···O3 hydrogen-bonding interaction (Table 2) which determines the orientation of the group, so packing is only due to van der Waals interactions.

Experimental

To 8 equivalents of NaNH₂ in tetrahydrofuran [5 ml for every 10 mmol of (1)], a solution of ^tBuOH in tetrahydrofuran (5 ml for every 10 mmol) was added at 318 K. The reaction medium was then stirred for 2 h at 318 K. To the complex base thus prepared was added slowly a solution of 2 equivalents of diisopropyl ketone in tetrahydrofuran (5 ml for every 10 mmol) at 308 K and the reaction medium stirred for a further 2 h at the same temperature. The bromo derivative (1) (1 equivalent) was then added slowly at 273 K to the reaction mixture, which was stirred until gas-phase chromatography indicated that no compound (1) remained. After hydrolysis on ice and extraction with CH₂Cl₂, the organic phase was dried over MgSO₄ and the solvents removed under vacuum. The reaction products were isolated by flash chromatography and crystals for analysis were obtained from CH₂Cl₂ solution.

Crystal data

C₂₁H₂₈N₂O₃

M_r = 356.46

Triclinic

P $\bar{1}$

a = 10.580 (1) Å

b = 13.784 (3) Å

c = 15.218 (3) Å

α = 66.59 (1)°

β = 86.91 (3)°

γ = 75.93 (1)°

V = 1973.3 (6) Å³

Z = 4

D_x = 1.200 Mg m⁻³

D_m not measured

Mo *K*α radiation

λ = 0.71073 Å

Cell parameters from 25 reflections

θ = 8–12°

μ = 0.080 mm⁻¹

T = 293 (2) K

Prism

0.32 × 0.26 × 0.22 mm

Colourless

Data collection

Siemens-AED three-circle diffractometer

$\theta/2\theta$ scans

Absorption correction:

none

6662 measured reflections

6662 independent reflections

1432 observed reflections

[*I* > 2σ(*I*)]

θ_{\max} = 25.03°

h = -12 → 12

k = -16 → 15

l = 0 → 18

1 standard reflection

monitored every 50

reflections

intensity decay: none

Refinement

Refinement on *F*²

R(*F*) = 0.0527

wR(*F*²) = 0.0643

S = 1.524

6655 reflections

484 parameters

H atoms riding

$\Delta\rho_{\max}$ = 0.25 e Å⁻³

$\Delta\rho_{\min}$ = -0.24 e Å⁻³

Extinction correction:

SHELXL93 (Sheldrick, 1993)

Extinction coefficient:

0.0086 (4)

$$w = 1/[\sigma^2(F_o^2) + (0.0044P)^2]$$

where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = -0.001$

Atomic scattering factors
 from *International Tables*
 for *Crystallography* (1992,
 Vol. C)

N2A—C10A	1.340 (9)	N2B—C10B	1.328 (9)
N2A—C11A	1.323 (11)	N2B—C11B	1.338 (11)
C1A—C2A	1.516 (11)	C1B—C2B	1.534 (8)
C1A—C12A	1.532 (11)	C1B—C12B	1.527 (10)
C1A—C13A	1.578 (9)	C1B—C13B	1.571 (9)
C2A—C3A	1.441 (12)	C2B—C3B	1.422 (10)
C11A—C12A	1.409 (11)	C11B—C12B	1.418 (10)
C3A—O2A—C18A	117.2 (6)	C3B—O2B—C18B	116.7 (5)
C11A—O3A—C20A	118.6 (5)	C11B—O3B—C20B	117.2 (5)
C3A—N1A—C4A	116.2 (8)	C3B—N1B—C4B	116.6 (6)
C10A—N2A—C11A	115.8 (6)	C10B—N2B—C11B	115.0 (6)
C2A—C1A—C12A	110.9 (6)	C2B—C1B—C12B	111.0 (5)
C1A—C2A—C6A	125.2 (7)	C1B—C2B—C6B	123.8 (5)
C3A—C2A—C6A	113.9 (7)	C3B—C2B—C6B	115.4 (6)
N1A—C3A—C2A	126.7 (7)	N1B—C3B—C2B	125.7 (6)
N1A—C4A—C5A	123.5 (8)	N1B—C4B—C5B	123.5 (7)
C4A—C5A—C6A	119.8 (7)	C4B—C5B—C6B	118.6 (6)
C2A—C6A—C5A	119.8 (7)	C2B—C6B—C5B	120.0 (6)
C2A—C6A—C7A	121.6 (7)	C2B—C6B—C7B	122.3 (6)
C6A—C7A—C8A	113.8 (6)	C6B—C7B—C8B	114.0 (5)
C7A—C8A—C12A	123.5 (6)	C7B—C8B—C12B	122.4 (6)
C8A—C9A—C10A	119.1 (6)	C8B—C9B—C10B	119.0 (6)
N2A—C10A—C9A	123.8 (7)	N2B—C10B—C9B	125.4 (7)
N2A—C11A—C12A	125.8 (6)	N2B—C11B—C12B	125.9 (6)
C8A—C12A—C11A	116.5 (6)	C8B—C12B—C11B	115.9 (6)
C1A—C12A—C8A	122.7 (6)	C1B—C12B—C8B	124.1 (6)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2)

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	U_{eq}
O1A	-0.1288 (4)	0.3534 (3)	-0.2328 (3)	0.0596 (12)
O2A	-0.2082 (5)	0.3079 (4)	-0.3696 (3)	0.080 (2)
O3A	-0.0098 (4)	0.4610 (3)	-0.1671 (3)	0.0558 (12)
N1A	-0.4316 (7)	0.3494 (5)	-0.3893 (4)	0.081 (2)
N2A	-0.1282 (5)	0.6098 (5)	-0.1442 (4)	0.061 (2)
C1A	-0.1989 (6)	0.4601 (5)	-0.2918 (4)	0.049 (2)
C2A	-0.3262 (7)	0.4485 (5)	-0.3228 (4)	0.052 (2)
C3A	-0.3276 (8)	0.3692 (6)	-0.3619 (5)	0.068 (2)
C4A	-0.5459 (8)	0.4107 (7)	-0.3817 (5)	0.090 (3)
C5A	-0.5593 (7)	0.4919 (5)	-0.3483 (4)	0.070 (2)
C6A	-0.4492 (7)	0.5106 (6)	-0.3178 (4)	0.062 (2)
C7A	-0.4668 (6)	0.6012 (5)	-0.2831 (5)	0.061 (2)
C8A	-0.3428 (6)	0.6060 (5)	-0.2421 (4)	0.051 (2)
C9A	-0.3511 (6)	0.6836 (5)	-0.2025 (4)	0.064 (2)
C10A	-0.2422 (8)	0.6836 (5)	-0.1574 (4)	0.071 (2)
C11A	-0.1223 (7)	0.5388 (5)	-0.1836 (4)	0.052 (2)
C12A	-0.2239 (6)	0.5352 (5)	-0.2374 (4)	0.044 (2)
C13A	-0.1227 (6)	0.5070 (5)	-0.3853 (4)	0.063 (2)
C14A	-0.1930 (6)	0.6222 (5)	-0.4524 (4)	0.088 (2)
C15A	0.0182 (6)	0.5069 (5)	-0.3689 (4)	0.094 (3)
C16A	-0.5646 (6)	0.5834 (5)	-0.2020 (4)	0.101 (3)
C17A	-0.5267 (6)	0.7121 (5)	-0.3659 (4)	0.093 (2)
C18A	-0.2038 (7)	0.2413 (5)	-0.4229 (5)	0.091 (3)
C19A	-0.0682 (6)	0.1816 (5)	-0.4215 (5)	0.116 (3)
C20A	0.0973 (6)	0.4671 (5)	-0.1177 (4)	0.072 (2)
C21A	0.2097 (5)	0.3750 (5)	-0.1123 (4)	0.086 (2)
O1B	-0.4418 (4)	0.0730 (3)	0.2655 (2)	0.0592 (12)
O2B	-0.5698 (4)	0.0524 (3)	0.1374 (3)	0.0618 (13)
O3B	-0.2579 (4)	0.0152 (3)	0.4020 (3)	0.0651 (13)
N1B	-0.5379 (5)	0.1512 (4)	-0.0189 (4)	0.063 (2)
N2B	-0.1074 (5)	0.1177 (4)	0.3622 (4)	0.068 (2)
C1B	-0.3310 (6)	0.0584 (5)	0.2109 (4)	0.043 (2)
C2B	-0.3757 (6)	0.1173 (5)	0.1046 (4)	0.045 (2)
C3B	-0.4937 (6)	0.1085 (5)	0.0713 (5)	0.050 (2)
C4B	-0.4648 (7)	0.2076 (5)	-0.0839 (5)	0.067 (2)
C5B	-0.3508 (6)	0.2267 (5)	-0.0607 (4)	0.061 (2)
C6B	-0.3078 (6)	0.1824 (5)	0.0353 (5)	0.048 (2)
C7B	-0.1894 (6)	0.2128 (5)	0.0602 (4)	0.054 (2)
C8B	-0.1614 (6)	0.1744 (5)	0.1665 (4)	0.053 (2)
C9B	-0.0655 (6)	0.2098 (5)	0.1975 (5)	0.070 (2)
C10B	-0.0450 (6)	0.1803 (5)	0.2933 (5)	0.077 (2)
C11B	-0.1954 (6)	0.0813 (5)	0.3317 (5)	0.052 (2)
C12B	-0.2279 (5)	0.1060 (5)	0.2348 (5)	0.045 (2)
C13B	-0.2693 (6)	-0.0663 (5)	0.2385 (5)	0.071 (2)
C14B	-0.1569 (6)	-0.0891 (4)	0.1778 (4)	0.097 (3)
C15B	-0.3505 (7)	-0.1383 (5)	0.2552 (6)	0.192 (5)
C16B	-0.2172 (5)	0.3408 (4)	0.0147 (4)	0.075 (2)
C17B	-0.0693 (5)	0.1692 (4)	0.0120 (4)	0.076 (2)
C18B	-0.6875 (6)	0.0415 (5)	0.1008 (4)	0.071 (2)
C19B	-0.7523 (5)	-0.0245 (5)	0.1874 (4)	0.093 (2)
C20B	-0.2276 (7)	-0.0034 (5)	0.4998 (4)	0.089 (2)
C21B	-0.3117 (6)	-0.0647 (6)	0.5618 (4)	0.116 (3)

C3A—O2A—C18A—C19A	-179.3 (6)		
C18A—O2A—C3A—N1A	11.2 (10)		
C11A—O3A—C20A—C21A	-177.8 (5)		
C20A—O3A—C11A—N2A	-6.2 (9)		
C12A—C1A—C13A—C14A	-56.4 (7)		
C2A—C1A—C13A—C15A	-170.1 (6)		
C2A—C1A—C12A—C11A	165.6 (6)		
C12A—C1A—C2A—C3A	-170.3 (6)		
C5A—C6A—C7A—C8A	173.8 (6)		
C6A—C7A—C8A—C9A	-176.2 (6)		
C3B—O2B—C18B—C19B	179.2 (5)		
C18B—O2B—C3B—N1B	3.0 (8)		
C11B—O3B—C20B—C21B	174.0 (6)		
C20B—O3B—C11B—N2B	3.1 (8)		
C12B—C1B—C13B—C14B	-66.0 (7)		
C2B—C1B—C13B—C15B	-79.5 (8)		
C2B—C1B—C12B—C11B	165.5 (6)		
C12B—C1B—C2B—C3B	-162.7 (6)		
C5B—C6B—C7B—C8B	171.7 (6)		
C6B—C7B—C8B—C9B	-171.8 (6)		
D—H...A	H...A	D...A	D—H...A
O1A—H1A...O3A	2.03 (4)	2.646 (7)	132 (2)
O1B—H1B...O3B	1.99 (2)	2.665 (6)	139 (1)

The correctness of the choice of the space group was checked using the *TRACER* (Lawton & Jacobson, 1965), *NEWLAT* (Mugnoli, 1985), *LEPAGE* (Spek, 1988) and *MISSYM* (Le Page, 1987) programs, and the *SYMMOL* routine of the latest version of *PARST* (Nardelli, 1995). The high proportion of 'unobserved' data is due to high thermal motion, which may mask some disorder; all measured data were used for refinement. H atoms attached to C atoms were placed geometrically and O—H according to a difference synthesis, but with O—H = 0.82 Å and C—O—H = 109.5° constraints. In the riding-model refinement, methyl and OH groups had torsional freedom and $U(\text{H}) = 1.2U_{eq}(\text{C or O})$.

Data collection: local programs (Belletti, Uguzzoli, Cantoni & Pasquinelli, 1979). Cell refinement: *LQPARM* (Nardelli & Mangia, 1984). Data reduction: local programs. Program(s) used to solve structure: *SIR92* (Altomare *et al.* 1994). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1965), *ZORTEP* (Zsolnai & Pritzkow, 1994). Software used to prepare material for publication: *PARST* (Nardelli, 1983), *PARSTCIF* (Nardelli, 1991b).

Table 2. Selected geometric parameters (\AA , °)

O1A—C1A	1.419 (6)	O1B—C1B	1.421 (7)
O2A—C3A	1.367 (9)	O2B—C3B	1.362 (8)
O2A—C18A	1.437 (10)	O2B—C18B	1.454 (9)
O3A—C11A	1.352 (7)	O3B—C11B	1.361 (7)
O3A—C20A	1.431 (9)	O3B—C20B	1.446 (8)
N1A—C3A	1.321 (12)	N1B—C3B	1.319 (9)
N1A—C4A	1.325 (10)	N1B—C4B	1.335 (9)

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: CF1097). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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4-(4-Chlorophenyl)-4-hydroxy-*N,N*-dimethyl- α,α -diphenyl-1-piperidinebutanamide *N*-Oxide Hydrate (Loperamide *N*-Oxide Hydrate)[†]

OSWALD M. PEETERS, NORBERT M. BLATON AND CAMIEL J. DE RANTER

Laboratorium voor Analytische Chemie en Medicinale Fysicochemie, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium. E-mail: maurice.peeters@farm.kuleuven.ac.be

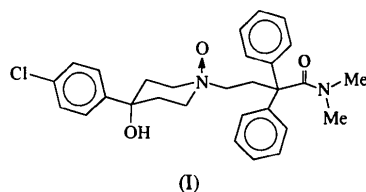
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Abstract

The crystal structure of the title compound, C₂₉H₃₃ClN₂O₃·2.25H₂O, has been determined. The three C—N(piperidyl) bond lengths reflect the tetravalency of the piperidine N atom. A strong intermolecular hydrogen bond between the hydroxyl and the *N*-oxide of neighbouring molecules forms endless chains in the *b* direction of the *C2/c* space group. The positions of the water molecules are partially occupied.

Comment

Loperamide *N*-oxide, (I), is a prodrug of loperamide, a specific long-acting antidiarrhoeal drug. In order to compare the structure of loperamide *N*-oxide with that of loperamide itself (Germain, Declercq, Van Meersche & Koch, 1977), its crystal structure has been determined.



The conformation of the molecule and the atomic numbering scheme are given in Fig. 1. The overall conformation of (I) is very similar to that of loperamide. Corresponding torsion angles agree within 4° except for the N11—C16—C17—C18 torsion angle with values of 174.2 and –156.1 (2)° for loperamide and its *N*-oxide, respectively. The presence of the *N*-oxide lengthens the N—C bonds from a mean value of 1.468 Å in loperamide to a mean value of 1.505 Å in (I). These values agree well with the mean values of 1.471 and 1.509 Å found in 1,2-dipiperidinoethane mono-*N*-oxide

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