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Oxidative Aminomercuration of 2-Propyn-1-ols. Stereoselective Syntheses and Structures of *cis*-[1,4]Oxazino[3,2-*b*]-1,4-oxazine Derivatives

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The reactions of 2-propyn-1-ols **1** with 2-amino alcohols **7** and mercury(II) chloride start with an oxidative aminomercuration step followed by a series of highly stereoselective processes leading to *cis*-[1,4]oxazino[3,2-*b*]-1,4-oxazine derivatives **10**. *X*-Ray analyses of **10c, f, g** show that these compounds have the same geometrical arrangement around their central fusion bond in such a way that anomeric stabilisation reaches a maximum.

Oxidative Aminomercurierung von 2-Propin-1-olen. Stereoselektive Synthese und Struktur von *cis*-[1,4]Oxazino[3,2-*b*]-1,4-oxazin-Derivaten

Die Reaktion von 2-Propin-1-olen **1** mit 2-Aminoalkoholen **7** in Gegenwart von Quecksilber(II)-chlorid beginnt mit einer oxidativen Aminomercurierung, gefolgt von hoch stereoselektiven Reaktionsschritten, die zu *cis*-[1,4]Oxazino[3,2-*b*]-1,4-oxazin-Derivaten **10** führen. Nach den Röntgenstrukturanalysen von **10c, f, g** zeigen diese Verbindungen die gleiche Anordnung um die zentrale Bindung, und zwar so, daß die anomere Stabilisierung ein Maximum erreicht.

The addition of aliphatic and aromatic amines to terminal alkynes in the presence of mercury(II) salts has been shown to occur in a catalytic fashion[1]. However, when 2-propyn-1-ols (propargyl alcohols) (**1**; $R^1-CHOH-C\equiv CH$) were used as acetylenic systems, a subsequent redox reaction leads to nearly quantitative precipitation of metallic mercury. Using primary alkyl- and arylmonoamines in this oxidative aminomercuration process, we have recently synthesized *N*-substituted α-imino ketones, α-diimines, and α-aminopropionamidines[2], whereas with the help of primary 1,2-diamines, 2,3-dihydro-5-methylpyrazines and 2-methylquinoxalines were obtained[3]. In these reactions, 2-propyn-1-ols behave as α-dicarbonyl synthons and, thus, α-imino carbonyl compounds **2** were the species first formed, which may then react with a second amino group depending on the nucleophilicity of the amine, the nature of the carbonyl group in **2**, and the inter- or intramolecular course of the condensation step.

With this in mind, we felt that 2-amino alcohols were attractive substrates to be tested as nucleophilic agents in this type of reaction. The first arising question is

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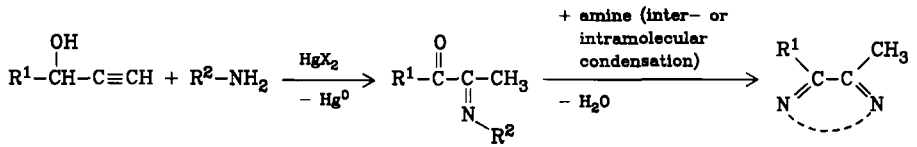

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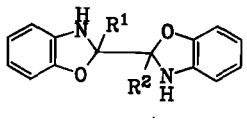
the competition between oxy- and aminomercuration; nevertheless, the latter should be expected to occur because of the reversible character of the oxymercuration processes[4]. In addition, following this initial amino attack, the corresponding intermediates type **2** or **3** would probably have suitable geometries to lead to heterocyclic compounds *via* condensation reactions. In this context, the closely related condensation reactions between α-dicarbonyl compounds and *o*-aminophenol have been reported to afford 2,2′,3,3′-tetrahydro-2,2′-bibenzoxazole[5] derivatives[6] (**4**), whereas either 2,2′-bioxazolidine derivatives[7,8] (**5**), or perhydro-[1,4]oxazino[3,2-*b*]-1,4-oxazine derivatives[7e,10,11] (**6**) have been claimed as products when aliphatic 2-amino alcohols are substituted for *o*-aminophenol.



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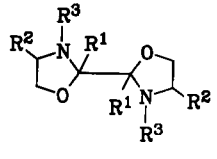

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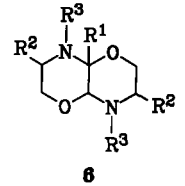

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In the light of these precedents we studied the reactions of 2-propyn-1-ols with 2-amino alcohols and a mercury(II) salt.

Syntheses and Structures of *cis*-[1,4]Oxazino[3,2-*b*]-1,4-oxazine Derivatives

The reactions are carried out using stoichiometric amounts of a 2-propyn-1-ol **1** and mercury(II) chloride and an excess of *o*-aminophenol or the appropriate aliphatic 2-amino alcohol **7**, in the presence of catalytic amounts of trifluoroacetic acid as condensation and cyclisation catalyst. The NMR data of the crude reaction products indicate in each case the nearly exclusive presence of a single compound which, from spectroscopic and *X*-ray evidence (see later), has a *cis*-[1,4]oxazino[3,2-*b*]-1,4-oxazine type structure **10**. Mercury(II) acetate instead of the chloride does not change significantly the yields in heterobicycles **10d–g** derived from aliphatic 2-amino alcohols, but it gives rise to lower yields in products **10a–c** coming from *o*-aminophenol, due to easier oxidation of this compound than of aliphatic 2-amino alcohols.

The formation of heterobicycles **10** can be rationalized through the intermediates **8** and **9** (analogous to the above mentioned **2** and **3**, resp.) and admitting two further intramolecular additions of both hydroxy groups to the C=N double bonds in the linear intermediate **9**. Although for this latter double hydroxyl ad-

dition two different reaction paths (a and b) can be envisaged, only the path a, leading to heteromonocycles of six members, seems to be operative under our reaction conditions. (The not-observed path b would lead to the corresponding type **4** or **5** structures).

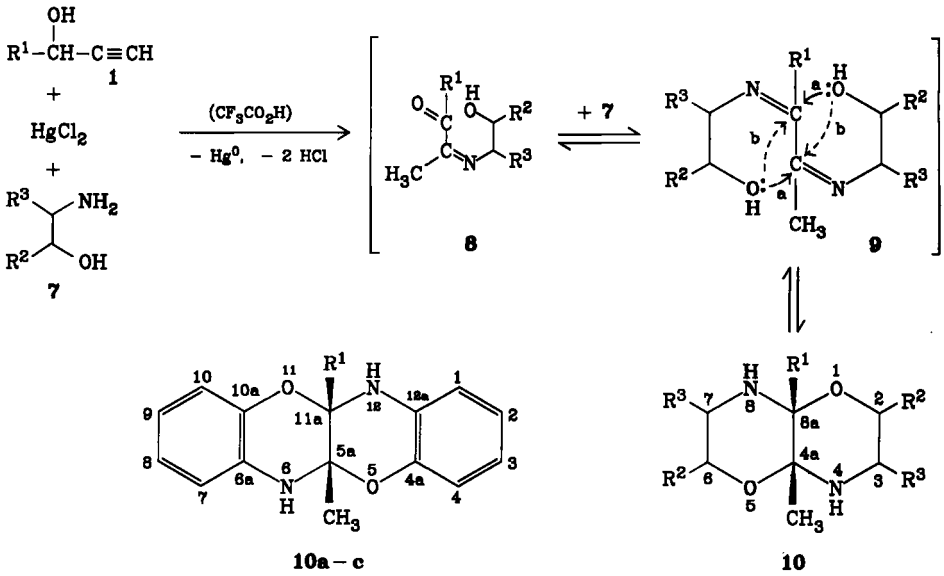

Table 1. Compounds **10** prepared

	R^1	R^2	R^3	Reaction temp. (°C)	Yield (%)[a]
10a	H		benzo	70	79
b	CH_3		benzo	70	66
c	C_6H_5		benzo	101	40
d	H	CH_3	H	25	78
e	H	H	CH_3CH_2	25	52
f	CH_3	CH_3	H	62	63
g	CH_3	H	CH_3CH_2	62	56

[a] Yields of crude reaction products, based on **1**.

^1H and ^{13}C NMR data of compounds **10a–c** reveal the existence of only one pair of enantiomers, despite the chiral character of both bridgehead carbon atoms. However, since the lack of appropriate hydrogen substituents precludes the observation of coupling constants, and since the ^1H and ^{13}C chemical shifts are expected to be very similar for both conceivable 2,2′,3,3′-tetrahydro-2,2′-bibenzoxazole (type **4**) or (the actual) 5a,6,11a,12-tetrahydro[1,4]benzoxazino[3,2-*b*]-[1,4]benzoxazine structures, NMR techniques do not allow an unequivocal iden-

tification. Thus, the *cis*-fused benzoxazino-benzoxazine structure for compounds **10a–c**[12] is deduced from the *X*-ray structural analysis of **10c** (see below).

1-Amino-2-propanol and 2-amino-1-butanol used as starting materials **7** in the synthesis of compounds **10d–g** are chiral molecules and, hence, **10d–g** have four chiral centres (two bridgehead carbon atoms and two peripheral carbon atoms bearing either R^2 or R^3 substituents). Nevertheless, the ^1H and ^{13}C NMR spectra of **10d–g** show the presence of a single pair of enantiomers. ^1H NMR coupling constants clearly allow to discard the 2,2′-bioxazolidine (type **5**) structure and prove a morpholino-morpholine (type **6**) one, in which the R^2 or R^3 substituents are exclusively placed in equatorial positions. In addition, the ^{13}C NMR spectra of **10f** and **g** only display five and six resonance signals, resp. (*i.e.* half of the number of carbon atoms), thus revealing the existence of some element of symmetry. Assuming rigid chair conformations, molecular models show that the above requirements can only be satisfied in the three structures **A–C**, whose stereochemical features are summarized in Table 2:

Table 2. Stereochemistry of the possible pair of enantiomers **A–C**[a] for compounds **10d–g**[b]

Compound	A[c]	B	C
10d, 10f	*endo-cis-RRRR* *endo-cis-SSSS*	*exo-cis-RSRS* *exo-cis-SRSR*	*trans-RSSR*[d] *trans-SRRS*[d]
10e, 10g	*exo-cis-RRRR* *exo-cis-SSSS*	*endo-cis-RSRS* *endo-cis-SRSR*	*trans-RSSR*[e] *trans-SRRS*[e]

[a] See Figure 1. – [b] The absolute configurations of the chiral carbon atoms are given in the IUPAC numbering order (2, 4a, 6, 8a for **10d** and **f**; 3, 4a, 7, 8a for **10e** and **g**). – [c] Actual conformations. – [d] It would degenerate in a *meso*-form for **10f**. – [e] It would degenerate in a *meso*-form for **10g**.

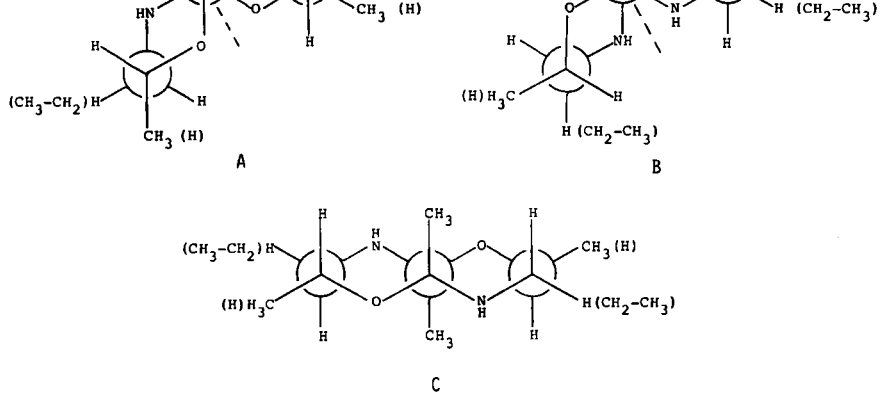

Fig. 1. Possible arrangements for compound **10f** (**10g**)

A) A pair of enantiomeric *cis*-heterodecalins whose staggered Newman's projections of the central fusion bond would show the nitrogen atoms placed *anti* to each other, and the oxygen atoms in a *gauche* relationship. The four chiral carbon atoms would have the same (*R* or *S*) absolute configuration. In compounds **10d,f** ($R^2 = CH_3$, $R^3 = H$) the R^2 substituents would occupy the *endo*-positions, but in **10e,g** ($R^2 = H$, $R^3 = CH_3CH_2$) the R^3 substituents would occupy the *exo*-positions. Fig. 1 (**A**) represents this possibility (the all-*R* enantiomer) for compounds **10f** and **g**, and shows the existence of a two-fold axis of symmetry.

B) Another pair of enantiomeric *cis*-heterodecalins, conformer to **A** by inversion of the chair conformation in both rings, in which the oxygen atoms would be placed *anti* and the nitrogen atoms *gauche* around the central fusion bond. Both peripheral carbon atoms bearing either R^2 ($=CH_3$) or R^3 ($=CH_2CH_3$) substituents would have the same absolute configurations, but opposite to those of the bridgehead carbon atoms. The R^2 substituents in compounds **10d,f** and the R^3 substituents in **10e,g** would occupy the *exo*- and the *endo*-positions, respectively. Figure 1 (**B**) represents this arrangement (the enantiomer having *R*-bridgehead and *S*-peripheral substituted carbon atoms) for compounds **10f** and **g**, and also shows the existence of a two-fold axis of symmetry.

C) A *trans*-heterodecalin structure in which the peripheral carbon atoms bearing either R^2 ($=CH_3$) or R^3 ($=CH_3CH_2$) substituents would have opposite absolute configurations, but each of them the same as its nearest bridgehead carbon atom. Figure 1 (**C**) represents the *meso*-forms for compounds **10f** and **g**, with a centre of symmetry at the middle of the central fusion bond.

In order to ascertain the actual structure of compounds **10d–g**, the reactions of 3-butyn-2-ol (**1**; $R^1 = CH_3$), mercury(II) chloride and (*R*)-(−)-1-amino-2-propanol or (*R*)-(−)-2-amino-1-butanol were carried out under conditions similar to those employed for the racemic amino alcohols. The NMR spectra of the crude reaction products were identical, regardless of the racemic or optically pure nature of the starting amino alcohol. This finding enables us to discard the *trans*-heterodecalin arrangement (**C**), since this hypothetical structure in compounds derived from the (*R*)-(−)-amino alcohols cannot have any element of symmetry, because of the prefixed axial orientation of one out of the two R^2 (or R^3) substituents. That is to say, the NMR spectra of compounds **10d–g** when derived from racemic or optically pure amino alcohols would not be coincident for the arrangement **C**.

The alternative formation of the *cis*-heterodecalins **A** or **B** can be understood in stereochemical terms as the result of the attack of the hydroxy groups to the prochiral C=N double bonds in the intermediate **9**. For instance, the intermediate **9** derived from 3-butyn-2-ol (**1**; $R^1 = CH_3$) and (*R*)-(−)-1-amino-2-propanol [(−)-**7**; $R^2 = CH_3$, $R^3 = H$] would lead to the corresponding (2*R*,4a*S*,6*R*,8a*S*)-*exo-cis*-heterodecalin through a *si,si*-attack, but the corresponding (2*R*,4a*R*,6*R*,8a*R*)-*endo-cis*-heterodecalin would be reached by assuming a *re,re*-attack. However, the NMR spectra do not allow an unambiguous structural assignment and, thus, the actual type **A** (Fig. 1 and Table 2) *endo-cis*-structure for **10f** and *exo-cis*-structure for **10g**[13] are deduced from the *X*-ray analyses of these compounds (see below).

The actual type **A** structures for compounds **10f,g** can also be extended to compounds **10d,e** and can be rationalized in the light of the anomeric effect[14], assuming the current view that a significant source of this effect is a stabilisation due to an antiperiplanar n-σ^* interaction of a cyclic heteroatom (X) lone pair with the antibonding orbital of an α-placed C–Y bond (Y = "exocyclic" heteroatom). Type **A** structures have two nitrogen (X) atoms whose non-bonding lone pairs are placed antiperiplanar to two C–O (C–Y) bonds; the roles of both nitrogen and oxygen atoms are interchanged in type **B** structures. Thus, since the C–O bond is a stronger acceptor than the C–N bond and, also, as nitrogen is a stronger donor than oxygen, the consequence is a very strong preference for type **A** structures. In this context, it is remarkable that this preference is observed irrespective of the presence of two (**10a–c**), one (**10d–g**), or no[11] peripheral R^2 and/or R^3 substituents.

Table 3. Final atomic coordinates and thermal parameters for compound **10c**; $U_{eq} = \frac{1}{3}\Sigma[u_{ij} \cdot a_i^* \cdot a_j^* \cdot a_i \cdot a_j \cdot \cos(a_i,a_j)] \cdot 10^3$

ATOM	X/A	Y/B	Z/C	UEQ
C1	0.5564(4)	0.2509(5)	0.3518(5)	47(2)
C1'	0.4342(5)	0.2262(5)	-0.1405(5)	59(2)
C2	0.6454(5)	0.2504(5)	0.2632(6)	59(3)
C2'	0.3462(5)	0.2201(7)	-0.1890(7)	74(3)
C3	0.6613(5)	0.3232(6)	0.1590(6)	64(3)
C3'	0.3370(5)	0.1487(7)	-0.2844(7)	74(3)
C4	0.5894(5)	0.3985(5)	0.1429(5)	54(2)
C4'	0.4142(5)	0.0807(6)	-0.3297(6)	64(3)
C4a	0.5022(4)	0.3996(5)	0.2350(5)	44(2)
C4'a	0.5012(4)	0.0850(5)	-0.2809(5)	49(2)
O5	0.4326(3)	0.4759(3)	0.2167(3)	45(1)
O5'	0.5776(3)	0.0177(3)	-0.3304(3)	51(1)
C5a	0.3573(4)	0.5011(4)	0.3255(4)	37(2)
C5'a	0.6519(4)	-0.0027(4)	-0.2545(5)	45(2)
N6	0.2773(3)	0.5500(3)	0.2822(4)	44(2)
N6'	0.7376(4)	-0.0441(4)	-0.3325(4)	52(2)
C6a	0.2267(4)	0.4817(5)	0.2087(4)	39(2)
C6'a	0.7929(4)	0.0318(5)	-0.4293(5)	45(2)
C7	0.1759(4)	0.5299(5)	0.1247(5)	50(2)
C7'	0.8581(5)	-0.0068(5)	-0.5305(5)	55(2)
C8	0.1266(5)	0.4592(7)	0.0539(5)	65(3)
C8'	0.9125(5)	0.0731(7)	-0.6222(6)	72(3)
C9	0.1256(5)	0.3390(7)	0.0669(6)	68(3)
C9'	0.9000(5)	0.1896(7)	-0.6158(5)	67(3)
C10	0.1729(5)	0.2878(5)	0.1523(5)	58(2)
C10'	0.8359(4)	0.2297(5)	-0.5143(5)	53(2)
C10a	0.2227(4)	0.3613(5)	0.2234(4)	43(2)
C10'a	0.7851(4)	0.1497(5)	-0.4205(5)	44(2)
O11	0.2683(3)	0.3094(3)	0.3093(3)	42(1)
O11'	0.7279(3)	0.1945(3)	-0.3171(3)	47(1)
C11a	0.3127(4)	0.3825(4)	0.3944(4)	37(2)
C11'a	0.6883(4)	0.1155(4)	-0.2077(5)	41(2)
N12	0.3942(3)	0.3266(4)	0.4264(4)	42(2)
N12'	0.6015(4)	0.1629(4)	-0.1385(4)	48(2)
C12a	0.4838(4)	0.3243(4)	0.3381(5)	39(2)
C12'a	0.5127(4)	0.1584(5)	-0.1854(5)	48(2)
C13	0.4090(4)	0.5864(5)	0.4001(5)	49(2)
C13'	0.6036(5)	-0.0959(5)	-0.1532(5)	53(2)
C14	0.2305(4)	0.3959(4)	0.5089(5)	38(2)
C14'	0.7715(4)	0.1111(4)	-0.1319(5)	42(2)
C15	0.2586(4)	0.4271(5)	0.6168(5)	49(2)
C15'	0.7430(5)	0.0763(5)	-0.0077(5)	52(2)
C16	0.1854(5)	0.4438(6)	0.7204(6)	65(3)
C16'	0.8170(5)	0.0732(6)	0.0632(6)	61(3)
C17	0.0832(5)	0.4323(7)	0.7169(7)	73(3)
C17'	0.9176(6)	0.1070(6)	0.0121(7)	70(3)
C18	0.0541(5)	0.4000(7)	0.6106(6)	69(3)
C18'	0.9462(6)	0.1415(7)	-0.1113(7)	71(3)
C19	0.1268(5)	0.3809(6)	0.5068(5)	56(2)
C19'	0.8738(5)	0.1446(5)	-0.1826(6)	56(2)

The above results imply a high degree of stereoselectivity which can only be achieved if the progress of the reaction from the imino carbonyl intermediate **8** takes place through a series of equilibria[15]. Thus, each enantiomer of the racemic **8** is able to select the amino alcohol with the appropriate absolute configuration in order to minimize 1,3-diaxial interactions in compounds **10d–g**. In this way, the ring closures can be viewed as thermodynamically controlled.

X-Ray Analyses of Compounds 10c, f, and g

The final atomic coordinates for the non-hydrogen atoms are given in Tables 3–5 according to the IUPAC numbering schemes presented in the figures. Tables 6 and 7 show selected geometrical parameters.

The three compounds present Csp^3-Csp^3 lengths ranging from 1.506(4) to 1.550(6) Å, with angles between 106.7(4) and 115.1(4)°. The aromatic bond ranges

Table 4. Final atomic coordinates and thermal parameters for compound **10f**; U_{eq} as in Table 3

ATOM	X/A	Y/B	Z/C	UEQ
O1	0.3117(1)	0.2073(1)	0.6763(2)	393(6)
C2	0.3942(2)	0.1829(2)	0.6228(3)	420(9)
C3	0.3822(2)	0.1768(2)	0.4921(3)	430(10)
N4	0.3450(1)	0.2747(2)	0.4511(2)	407(8)
C4a	0.2607(2)	0.2964(2)	0.4992(2)	385(9)
O5	0.2028(1)	0.2118(1)	0.4664(2)	376(6)
C6	0.1182(2)	0.2131(2)	0.5184(3)	419(9)
C7	0.1278(2)	0.2132(3)	0.6499(3)	473(10)
N8	0.1821(2)	0.3012(2)	0.6851(3)	458(8)
C8a	0.2680(2)	0.3009(2)	0.6350(2)	386(9)
C9	0.4253(3)	0.0828(3)	0.6769(4)	564(12)
C10	0.2266(2)	0.3971(2)	0.4462(3)	499(11)
C11	0.0699(2)	0.1191(3)	0.4740(4)	538(12)
C12	0.3170(3)	0.3958(2)	0.6782(3)	520(12)

Table 5. Final atomic coordinates and thermal parameters for compound **10g**; U_{eq} as in Table 3

ATOM	X/A	Y/B	Z/C	UEQ
O1	0.6281(4)	0.2247(3)	0.6075(3)	40(1)
C2	0.7579(7)	0.1970(7)	0.6669(5)	46(2)
C3	0.7390(6)	0.1835(5)	0.7957(5)	43(2)
N4	0.6739(5)	0.2863(4)	0.8337(5)	41(2)
C4a	0.5376(6)	0.3121(4)	0.7797(4)	39(2)
O5	0.4426(4)	0.2177(3)	0.8026(3)	38(1)
C6	0.3108(6)	0.2190(7)	0.7380(5)	44(2)
C7	0.3310(6)	0.2229(5)	0.6107(4)	40(2)
N8	0.4149(5)	0.3226(4)	0.5897(5)	42(2)
C8a	0.5525(6)	0.3217(4)	0.6489(4)	38(2)
C9	0.8790(7)	0.1608(7)	0.8598(6)	57(3)
C10	0.9383(10)	0.0461(8)	0.8444(9)	74(3)
C11	0.4798(9)	0.4168(6)	0.8339(6)	53(2)
C12	0.1901(7)	0.2267(6)	0.5434(7)	50(2)
C13	0.1180(10)	0.1160(7)	0.5287(9)	72(3)
C14	0.6327(7)	0.4270(6)	0.6142(6)	52(2)

are 1.363(10)–1.400(8)Å and 116.8(5)–122.5(5)°. The O–C(fusion) length is higher than the other O–C lengths, while the N–C(fusion) is lower than the other N–C lengths in compounds **10f** and **g**. The presence of the fused benzo rings in compound **10c** lowers significantly the N–Csp^2 length with respect to the corresponding N–Csp^3 length in the other two compounds.

Table 6. Selected bond lengths (Å) and angles (°) for **10c**

Molecule	undashed	dashed	Molecule	undashed	dashed
O5-C4a	1.384(7)	1.381(7)	O11-C10a-C6a-N6	-0.1(8)	2.7(8)
O5-C5a	1.464(6)	1.462(8)	C10a-C6a-N6-C5a	27.3(7)	21.4(7)
O11-C11a	1.463(6)	1.471(6)	C6a-N6-C5a-C11a	-55.7(5)	-53.1(6)
O11-C10a	1.386(7)	1.388(6)	C6a-C10a-O11-C11a	6.1(7)	9.5(7)
N12-C12a	1.389(6)	1.392(8)	C10a-O11-C11a-C5a	-34.0(5)	-40.1(6)
N12-C11a	1.423(7)	1.424(7)	C14-C11a-C5a-C13	60.8(6)	61.2(6)
N6-C5a	1.420(7)	1.422(7)	C14-C11a-C5a-N6	-63.8(5)	-61.1(6)
N6-C6a	1.381(7)	1.400(6)	O11-C11a-C5a-O5	-57.8(5)	-55.5(5)
C11a-C5a	1.550(6)	1.543(7)	O11-C11a-C5a-N6	57.0(5)	60.2(5)
			N12-C11a-C5a-O5	58.9(5)	59.2(5)
C4a-O5-C5a	116.5(4)	116.0(4)	N12-C11a-C5a-C13	-61.8(5)	-62.9(6)
C11a-O11-C10a	119.2(4)	118.1(4)	C12a-N12-C11a-C5a	-45.4(6)	-44.0(6)
C11a-N12-C5a	118.6(4)	118.3(4)	C4a-O5-C5a-O11a	-47.1(5)	-48.0(6)
C6a-N6-C5a	116.5(4)	117.1(4)	C11a-N12-C12a-C4a	16.4(7)	15.2(8)
C11a-N12-H12	115(3)	115(3)	N12-C12a-C4a-O5	-1.1(8)	-0.7(8)
C12a-N12-H12	122(3)	120(3)	C5a-O5-C4a-C12a	19.4(7)	19.5(7)
C6a-N6-H6	118(4)	121(5)			
C5a-N6-H6	115(4)	112(5)			

Table 7. Selected bond lengths (Å) and angles (°) for **10f** and **g**

Molecule	10f	10g	Molecule	10f	10g
C2-O1	1.440(3)	1.416(7)	C8a-O1-C2-C3	-55.3(3)	54.0(6)
C8a-O1	1.459(3)	1.454(8)	N4-C3-C2-O1	56.1(3)	-54.4(6)
C4a-O5	1.455(3)	1.471(6)	C2-C3-N4-C4a	-62.1(3)	60.2(6)
C6-O5	1.428(3)	1.422(7)	C3-N4-C4a-C8a	59.3(3)	-59.0(6)
C3-N4	1.462(4)	1.451(8)	N4-C4a-C8a-O1	-51.5(3)	49.5(5)
C4a-N4	1.433(4)	1.436(7)	N4-C4a-C8a-C12/C14	70.4(3)	-71.3(6)
C7-N8	1.463(4)	1.455(8)	C10/C11-C4a-C8a-C12/C14	-50.6(3)	50.7(7)
C8a-N8	1.436(4)	1.441(7)	C10/C11-C4a-C8a-N8	70.7(3)	-70.9(6)
C4a-C8a	1.556(4)	1.541(7)	O5-C4a-C8a-O1	66.1(3)	-67.1(5)
			O5-C4a-C8a-N8	-50.7(3)	50.6(5)
C2-O1-C8a	116.6(2)	116.7(4)	C6-O5-C4a-C8a	54.4(3)	-51.0(5)
C4a-O5-C6	116.1(2)	114.8(4)	C7-N8-C8a-C4a	56.1(3)	-59.0(6)
C3-N4-C4a	113.4(2)	115.4(4)	C8a-N8-C7-C6	-59.1(3)	60.5(6)
C8a-N8-C7	114.2(2)	113.4(4)	C4a-O5-C6-C7	-57.2(3)	56.5(7)
C4a-N4-H4	108(2)	107(3)	N8-C7-C6-O5	55.8(3)	-57.6(6)
C3-N4-H4	109(2)	118(4)			
C8a-N8-H8	110(3)	103(6)			
C7-N8-H8	114(3)	111(6)			

The conformation of the rings in **10f** and **10g** is that of a chair, more puckered around the nitrogen atoms. In **10c** this conformation becomes a distorted half chair, as the attached benzo rings flatten the corresponding fusion.

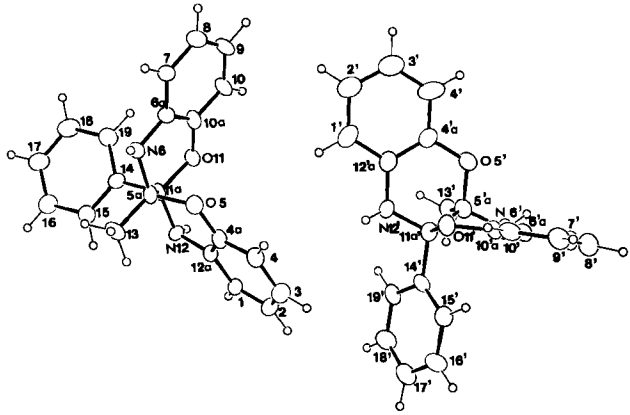

Fig. 2. ORTEP view[21], with the numbering scheme, for the two independent molecules present in the crystals of compound **10c**

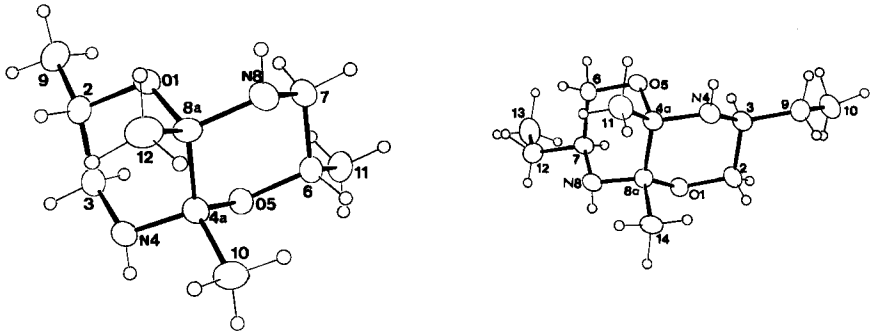

Fig. 3. ORTEP views[21] of **10f** (left hand side) and **10g** (right hand side). The molecule of **10g** shown is the enantiomeric one of that for which the atomic coordinates are given

Around the central fusion bond the geometry is the same for the three compounds: in a staggered conformation, the substituent carbon atoms are at *cis*-position with respect to the rings, the nitrogen atoms are antiperiplanar to each other, while the oxygen atoms remain *gauche* to each other and antiperiplanar to the carbon substituents (see Figures 2–3).

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Experimental Part

All the reagents and solvents used were of the best commercial grade available and handled in conventional manner. – Melting points: Büchi-Tottoli apparatus (uncorrected). – Elemental analyses: Perkin-Elmer 240 elemental analyser. – ^{1}H NMR spectra: Varian EM 390 and Bruker WH 400 spectrometers. – ^{13}C NMR spectra: Varian FT 80-A and Varian XL 100 FT spectrometers. – Mass spectra: Finnigan MAT CH 5 instrument.

General Procedure for 5a,6,11a,12-Tetrahydro[1,4]benzoxazino[3,2-b][1,4]benzoxazines (**10a–c**): Mercury(II) chloride (5.43 g, 20 mmol) is added to a solution of the appropriate

propargyl alcohol **1** (20 mmol), *o*-aminophenol (5.46 g, 50 mmol), and trifluoroacetic acid (0.10 ml, 1.3 mmol) in dioxane (150 ml). After the mixture has been stirred and heated (see Table 1) during 24 h, it is cooled and the precipitated metallic mercury (> 85%) and ammonium salt are filtered off. The liquid phase is concentrated, treated with 3 M aqueous potassium hydroxide (10 ml) and extracted with ether (3 × 30 ml). The ethereal layer is dried over sodium sulfate, the volatile components are evaporated under reduced pressure, and the crude reaction product is recrystallized from ethanol. The following compounds are obtained in this way:

(5aR,11aR*)-5a,6,11a,12-Tetrahydro-5a-methyl[1,4]benzoxazino[3,2-b][1,4]benzoxazine* (**10a**): m.p. 218–219°C. – ^{1}H NMR ([D$_6$]DMSO): δ = 1.35 (s, CH$_3$), 5.05 (d, 11a-H), 6.5–6.9 (m, 8H$_{arom.}$), 7.2 (s, 6-H), 7.35 (d, 12-H). – ^{13}C NMR ([D$_6$]DMSO): δ = 22.6 (q), 79.8 (s), 80.0 (d), 114.8 (d), 115.4 (d), 116.7 (d), 117.3 (d), 119.6 (d), 120.1 (d), 121.5 (d), 121.7 (d), 130.1 (s), 131.7 (s), 142.9 (s), 143.3 (s). – MS: *m/z* = 254 (M$^+$, 100%), 147 (66), 65 (26), 42 (16).

$C_{15}H_{14}N_2O_2$ (254.3) Calcd. C 70.85 H 5.55 N 11.02 Found C 70.8 H 5.6 N 11.1

(5aR,11aR*)-5a,6,11a,12-Tetrahydro-5a,11a-dimethyl[1,4]benzoxazino[3,2-b][1,4]benzoxazine* (**10b**): m.p. 240–241°C. – ^{1}H NMR ([D$_6$]DMSO): δ = 1.4 (s, 2CH$_3$), 6.4–6.8 (m, 8H$_{arom.}$), 7.1 (s, 2NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 21.2 (q), 82.1 (s), 115.3 (d), 116.1 (d), 119.0 (d), 120.9 (d), 130.3 (s), 141.8 (s). – MS: *m/z* = 268 (M$^+$, 42%), 161 (100), 134 (63), 65 (20), 42 (18).

$C_{16}H_{16}N_2O_2$ (268.3) Calcd. C 71.62 H 6.01 N 10.44 Found C 71.5 H 5.9 N 10.6

(5aR,11aR*)-5a,6,11a,12-Tetrahydro-5a-methyl-11a-phenyl[1,4]benzoxazino[3,2-b][1,4]benzoxazine* (**10c**): m.p. 216–217°C. – ^{1}H NMR ([D$_6$]DMSO): δ = 1.35 (s, CH$_3$), 6.3–7.5 (m, 13H$_{arom.}$ and 2NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 21.2 (q), 81.6 (s), 86.1 (s), 114.7 (d), 115.1 (d), 116.0 (d), 119.0 (d), 119.7 (d), 120.7 (d), 121.0 (d), 127.3 (d), 127.7 (d), 128.7 (d), 130.3 (s), 130.8 (s), 140.6 (s), 142.0 (s), 144.0 (s).

$C_{21}H_{18}N_2O_2$ (330.4) Calcd. C 76.34 H 5.49 N 8.48 Found C 76.6 H 5.5 N 8.6

General Procedure for Octahydro-[1,4]oxazino[3,2-b]-1,4-oxazines (**10d–g**): Mercury(II) chloride (5.43 g, 20 mmol) is added to a solution of the appropriate propargyl alcohol **1** (20 mmol), an aliphatic racemic 2-aminoalcohol **7** (50 mmol), and trifluoroacetic acid (0.10 ml, 1.3 mmol) in chloroform (150 ml). The mixture is stirred for 24 h at room temp. (for **10d,e**) or under reflux (**10f,g**), and the precipitated metallic mercury (> 85%) and ammonium salt are filtered off. Volatile components are removed under reduced pressure, the crude reaction mixture is treated with *n*-hexane (3 × 30 ml), and insoluble matter is discarded. Compounds **10d,f,g** recrystallize from the concentrated and heated liquid organic phase; compound **10e** is purified by distilling at 0.001 Torr. The following compounds are obtained in this way:

(2R,4aR*,6R*,8aR*)-Octahydro-endo-2,4a,endo-6-trimethyl[1,4]oxazino[3,2-b]-1,4-oxazine* (**10d**): m.p. 64–65°C. – ^{1}H NMR (CDCl$_3$ + D$_2$O): δ = 1.04 (d, 2-CH$_3$), 1.07 (d, 6-CH$_3$), 1.30 (s, 4a-CH$_3$), 2.34 (dd, 3-H$_{eq}$, J_{gem} = –10.9, $J_{eq,ax}$ = 2.9 Hz), 2.36 (dd, 7-H$_{eq}$, J_{gem} = –11.0, $J_{eq,ax}$ = 2.4 Hz), 2.86 (dd, 3-H$_{ax}$, $J_{ax,ax}$ = 10.8 Hz), 2.87 (dd, 7-H$_{ax}$, $J_{ax,ax}$ = 10.3 Hz), 3.65 (m, 6-H$_{ax}$), 3.90 (m, 2-H$_{ax}$), 3.99 (s, 8a-H); (in CDCl$_3$, 2NH at 2.35, br. s). – ^{13}C NMR (CDCl$_3$): δ = 18.1 (q), 18.6 (q), 22.1 (q), 44.2 (t), 45.1 (t), 67.2 (d), 70.3 (d), 79.9 (s), 82.9 (d).

$C_9H_{18}N_2O_2$ (186.3) Calcd. C 58.04 H 9.74 N 15.04 Found C 57.9 H 9.8 N 15.2

(3R,4aR*,7R*,8aR*)-exo-3,exo-7-Diethyloctahydro-4a-methyl[1,4]oxazino[3,2-b]-1,4-oxazine* (**10e**): b.p. 64–66°C/0.001 Torr. – ^{1}H NMR (CDCl$_3$): δ = 0.9 (2 t, 2C*H*$_3$CH$_2$),

Table 8. Crystal analyses of **10c, f, g** at room temperature

Crystal data			
Formula	**10g**, $C_{12}H_{24}N_2O_2$	**10f**, $C_{10}H_{20}N_2O_2$	**10c**, $C_{21}H_{18}N_2O_2$
Crystal habit	Transparent, colourless, prismatic	Transparent, colourless, prismatic	Transparent, yellow, prismatic
Crystal size (mm)	0.33 × 0.07 × 0.45	0.19 × 0.16 × 0.51	0.08 × 0.10 × 0.36
Symmetry	Monoclinic, $P2_1/c$	Orthorhombic, *Pbca*	Triclinic, *P*-1
Unit cell determination: least-squares fit to $\Theta(Cu) < 45°$	76 reflexions	71 reflexions	78 reflexions
Unit cell dimensions (Å)	9.4211(2), 11.9380(3), 11.6523(3), 92.679(2)°	15.3417(4), 12.8911(3), 11.4193(2)	13.4022(4), 11.5321(4), 11.1157(3) 88.277(3), 78.142(2), 95.643(3)°
Packing: V (Å^3), Z	1309.1(1), 4	2258.4(1), 8	1671.0(1), 4
D (g · cm^{-3}), M, F(000)	1.159, 228.33, 1008	1.178, 200.28, 880	1.313, 330.39, 696
Experimental data			
Technique and stability	Cu-K_α. Four-circle PW 1100 Philips diffractometer. Graphite oriented monochromator. Two reflexions every 90 min		
	6.6% decay (inside capillar)	1.7% decay (inside capillar)	no variation
Collection mode: ($\omega/2\Theta$), 1.5° scan width, 1° × 1° det. apertures	$\Theta < 60°$	$\Theta < 65°$	$\Theta < 60°$
Total independent data	1922	1921	4963
Observed data ($I > 3\sigma(I)$)	1094	1289	2719
Solution and refinement	*X*-Ray 76 System[17] V_{ax} 11/750. Multan 80[18]. Least-squares on F_o only. Atomic factors from International Tables[19]		
Final shift/error	0.16	0.02	0.18
Parameters:			
no. of variables	241	207	595
degrees of freedom	853	1082	2124
ratio of freedom	4.5	6.2	4.6
Weighting scheme	Empirical as to give no trends in $<\omega\Delta^2>$ vs. $\lvert F_o \rvert >$ or $<\sin\Theta/\lambda>$		
Max. thermal factors (Å^2)	U_{33} (C16) = 0.098(6)	U_{11} (C12) = 0.071(2)	U_{22} (C24) = 0.113(6)
Extinction	10 strongest reflexions as unobs.	6 strongest reflexions as unobs.	No one excluded
Final ΔF peaks	0.24	0.21	0.26
Final R, R_w	0.072, 0.089	0.053, 0.063	0.067, 0.057

1.1–1.4 (m, $2CH_3CH_2$), 1.4 (s, 4a-CH_3), 2.45 (br. s, 2NH), 3.1–3.9 (several m, 2-, 3-, 6-, 7-H), 4.05 (s, 8a-H). – ^{13}C NMR ($CDCl_3$): δ = 11.3 (2 q), 23.6 (q), 26.4 (t), 26.7 (t), 49.0 (d), 50.3 (d), 69.3 (d), 71.6 (t), 82.5 (s), 86.0 (d).

$C_{11}H_{22}N_2O_2$ (214.3) Calcd. C 61.65 H 10.35 N 13.07 Found C 61.5 H 10.4 N 13.1

(2R,4aR*,6R*,8aR*)-Octahydro-endo-2,4a,endo-6,8a-tetramethyl[1,4]oxazino[3,2-b]-1,4-oxazine* (**10f**): m.p. 104–106°C. – ^{1}H NMR ($CDCl_3$): δ = 1.15 (d, 2-, 6-CH_3), 1.4 (s, 4a-, 8a-CH_3), 1.95 (s, 2NH), 2.4 (dd, 3-, 7-H_{eq}, $J_{gem} \cong 10.8$, $J_{eq,ax} \cong 3$ Hz), 3.05 (dd, 3-, 7-H_{ax}, $J_{ax,ax} \cong 10.8$ Hz), 3.75–4.15 (m, 2-, 6-H). – ^{13}C NMR ($CDCl_3$): δ = 19.1 (q), 22.4 (q), 45.9 (t), 68.0 (d), 83.6 (s). – MS: *m/z* = 100 ($M/2^+$, 76%), 58 (100), 43 (43), 42 (55).

$C_{10}H_{20}N_2O_2$ (200.3) Calcd. C 59.97 H 10.07 N 13.99 Found C 60.1 H 10.0 N 14.1

(3R,4aR*,7R*,8aR*)-exo-3,exo-7-Diethyloctahydro-4a,8a-dimethyl[1,4]oxazino[3,2-b]-1,4-oxazine* (**10g**): m.p. 109–111°C. – ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, $2CH_3CH_2$), 1.18–1.41 (m, $2CH_3CH_2$), 1.44 (s, 4a-, 8a-CH_3), 1.92 (br. s, 2NH), 3.28–3.44 (m, 3-, 7-H_{ax}), 3.51 (dd, 2-, 6-H_{ax}, $J_{gem} \cong J_{ax,ax} \cong 11.0$ Hz), 3.80 (dd, 2-, 6-H_{eq}, $J_{eq,ax} \cong 3.8$ Hz). – ^{13}C NMR ($CDCl_3$): δ = 9.8 (q), 21.7 (q), 25.2 (t), 48.6 (d), 68.2 (t), 84.3 (s).

$C_{12}H_{24}N_2O_2$ (228.3) Calcd. C 63.12 H 10.59 N 12.27 Found C 63.1 H 10.5 N 12.1

X-Ray Analysis Parameters: The main characteristics of the analysis are given in Table 8. Compound **10c** has two independent molecules in the unit cell[17–20].

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[3] *J. Barluenga, F. Aznar, R. Liz,* and *M.-P. Cabal,* Synthesis **1985**, 313.

[4] [4a] *J. Barluenga, L. Alonso-Cires,* and *G. Asensio,* Synthesis **1981**, 376. – [4b] *J. Barluenga, J. Pérez-Prieto, A.-M. Bayón,* and *G. Asensio,* Tetrahedron **40**, 1199 (1984).

[5] These compounds were earlier named as 2,2'-bibenzo-1,3-oxazolines.

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[9] [9a] *I. Butula* and *G. Karlovic,* German Pat. 2305740 (December 20, 1973) [Chem. Abstr. **80**, 82066q (1974)]. – [9b] *PLIVA Tvornica Farmaceutskih i Kemijskih Proizvoda,* French Pat. 2187761 (February 22, 1974) [Chem. Abstr. **81**, 13101f (1974)].

[10] *D. L. Rakhmankulov, S. S. Zlotskii, R. A. Karakhanov, S. N. Zlotskii, F. N. Latypova, N. E. Maksimova,* and *V. N. Uzikova,* U.S.S.R. Pat. 565034 (July 15, 1977) [Chem. Abstr. **87**, 201553c (1977)].

[11] A compound of this type has been obtained in the reaction between 2,2-dichloro-1-phenylethanone and 2-(methylamino)ethanol; see *P. L'Haridon, A. Le Rouzic,* and *M. Maunaye,* J. Chem. Res., Synop. **1980**, 349 (M. **1980**, 4172–4194).

[12] The corresponding products coming from the condensation reactions between *o*-aminophenol and the appropriate α-dicarbonyl compound have been previously described[6ab] as "2,2'-bibenzoxazolines" (type **4** structure).

[13] It should be pointed out that the product coming from the condensation reaction between biacetyl and 2-amino-1-butanol has been described[7e] to display identical ^{1}H and ^{13}C NMR spectra as compound **10g**, but, nevertheless, the authors proposed a "bioxazoli-

dine" (type **5**) structure. Since their assignment is based on mass, infrared, ^1H, and ^{13}C NMR spectra, we presumed that the mass spectrum may be the cause of this disagreement. In fact, we have observed in the mass spectrum of heterodecalin **10f** a peak (m/z = 100, 76%) which, at first glance, would be assigned to the $(M/2)^+$ fragment of an hypothetical type **5** structure.

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[139/85]