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Efficient synthesis of imidazopyridodiazepines from *peri* annulation in imidazo[1,2-*a*]pyridine

C. Dechambre,[a] Jean M. Chezal,[a] E. Moreau,[a] F. Estour,[b] B. Combourieu,[c] G. Grassy,[d] A. Gueiffier,[e] C. Enguehard,[e] V. Gaumet,[a] Olivier Chavignon[a] and Jean C. Teulade[a,*]

[a]*UMR INSERM 484, Faculté de Pharmacie, 28 pl. H. Dunant, B.P. 38, 63001 Clermont-Ferrand Cedex 1, France*
[b]*Laboratoire de Pharmacochimie, Faculté de Médecine et de Pharmacie, 22 bd Gambetta, 76183 Rouen Cedex, France*
[c]*SEESIB, UMR CNRS 6504, 24 avenue des Landais, 63177 Aubiere Cedex, France*
[d]*CNRS-UMR 9955, INSERM U-414, Faculté de Pharmacie, 15 av. Ch. Flahault, 34060 Montpellier, France*
[e]*Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, 31 Av. Monge 37200 Tours, France*

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Abstract—In 3-amino imidazopyridines, complete C(5) regiospecificity yielded corresponding TIBO-like derivatives (±)-**3a**, **6a** and (±)-**8a**–**c**. The structures of these polycyclic compounds containing the azaindole moiety were determined by 1D and 2D NMR, and by X-ray crystallography.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have, together with nucleoside reverse transcriptase inhibitors (NRTIs), become firmly established in the treatment of HIV-1 infections. These agents are specifically inhibitory to HIV-1 replication and are targeted at the HIV-1 reverse transcriptase (RT). Recently, several compounds have been formally licensed for clinical use (Nevirapine) and others are at the preclinical and/or clinical development stage (e.g. Tivirapine and imidazodipyridodiazepine UK-129,485) (Fig. 1).[1]

On these criteria, more than thirty different classes of NNRTIs can be considered, including benzodiazepine, pyridinone, thiocarboxanilide, quinoxaline and imidazopyridazine derivatives. Among these last, 4,5,6,7-**T**etrahydro**I**midazo[4,5,1 - *jk*][l,4]**B**enzodiazepi - 2(*1H*)-thi**O**ne, assigned the acronym TIBO,[2] was the first member of a series of potent selective and non-competitive inhibitors of HIV-l reverse transcriptase. From SAR studies, structural modifications have been made in the search for new compounds to block replication of resistant strains.[3] The presence of imidazodiazepine units in drug candidates by the exchange of a phenyl ring for a pyridine moiety[4] induced us to explore the azaindole system, conceived as a prototype for a new class of potential HIV-RT inhibitors.

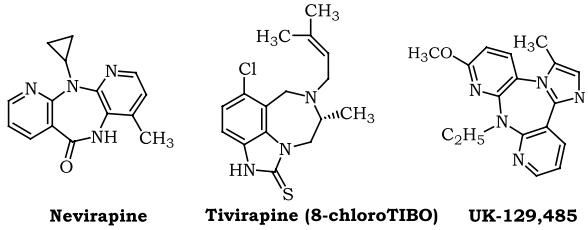

Figure 1. Structural formulae of the non nucleoside reverse transcriptase inhibitors (NNRTIs).

In a previous paper,[5] we described a new family of imidazopyridodiazepines obtained by initial *N*-addition followed by cyclocondensation on the valuable nucleophile-reactive 5-position of the imidazo[1,2-*a*]pyridine (IP) moiety. To produce potential therapeutic NNRTIs, we have developed the synthesis of analogues by changing substituents at the C-2 position of IP and we elucidated the mechanism of this heteroannulation method using 2-phenyl-3-aminoIP **1a** as starting material.

These compounds were obtained from 2-substituted-3-amino IP **1a**–**d** and different aldehydes via ring closure in 1,2-dichlorobenzene. During our study of annulated imidazole synthesis, in preliminary experiments conducted by heating amine **1a** with excess propanal in

Keywords: imidazo[1,2-*a*]pyridine; *peri* annulation; imidazopyridodiazepine; mechanism.

* Corresponding author. Tel.: +33-4-73-178000; fax: +33-4-73-178012; e-mail: j-claude.teulade@u-clermont1.fr

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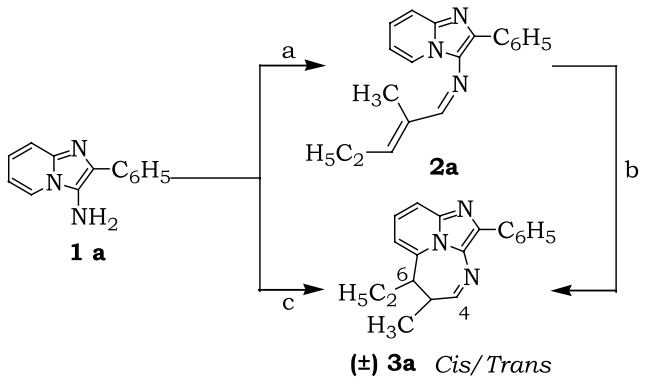


Scheme 1. *Reagents and conditions*: Method A: (a) C_2H_5CHO, toluene, Δ; (b) 1,2-dichlorobenzene, Δ. Method B: (c) C_2H_5CHO, 1,2-dichlorobenzene, Δ.

refluxing toluene the imino compound **2** was formed with 45% yield. The intermediate **2a** was shown to have *ZE* configuration by NOESY measurement (Scheme 1, method A). The cyclization was performed at 180°C in 1,2-dichlorobenzene to afford two imidazopyridodiazepine (IPD) diasteroisomers (±)-**3a**[6] *cis*/*trans* (10/90). Compound **3a** was also obtained by direct thermolysis of **1a** and the propanal in 1,2-dichlorobenzene (yield: 60%) (Scheme 1, method B).

The connectivity of the partial structures was demonstrated by an HMQC experiment, giving a basis for the structural assignment of (±)-**3a**. In addition, straightforward determination of different *J* coupling constants and selective irradiation enabled us to assign *cis* and *trans* configurations for (±)-**3a**. For *cis*-isomer (±)-**3a** we found $J_{4,5}=3$ Hz and $J_{5,6}=1.2$ Hz versus 4 and 5 Hz, respectively for *trans*-isomer (±)-**3a**, which is characteristic of a *cis*/*trans* cyclanic system. Relative configurations of the two chiral centers C(5) and C(6) were elucidated by NOESY measurement.

In this context, we now discuss the energy of intermediates of the Pictet–Spengler[7] (P-S)-like cyclocondensation and the transition states (TS) between them in the formation of diazepine (±)-**3a**. Recently, Novàk and co-workers[8] reported the synthesis of tetrahydroazepinoindoles by *peri* annulation. It is well established that two reaction pathways may be engaged in the P-S cyclization process in the IP, namely (a) a direct intramolecular electrophilic attack of C(5) of the bicyclic ring system[9] to give the intermediates IN1 and IN3 or (b) an electrophilic attack of the carbon C(3) to form spiro intermediate IN2[8,10] (Fig. 2).

The calculated heats of formation of the diazepine intermediates IN1 with (6a*S*,6*R*) and (6a*S*,6*S*) stereochemistry with $\Delta H=135.7$, 132.4 kcal/mol, respectively are 37.3–40.7 kcal/mol lower than those of the spiro intermediates IN2 SR (or SS). On the other hand, the energies of the transition states (calculated using a SADDLE subroutine followed by gradient optimization using an NLLSQ procedure (gradient<0.001 kcal/mol)) TS2 and TS3 were very high compared with TS1 with an energy barrier ΔH (TS3)–ΔH (IN1) for the process IN2→IN1 of 73.4 kcal/mol. The spiro form was not directly involved in the formation of diazepines (±)-**3a** and the key step was the direct attack of the 5-position of the imidazopyridine nucleus. The process probably corresponds to an intramolecular proton transfer from C(6a) of IN1 to the anionic C(5) center of IN3 (evidenced by the energies or HOMO densities). This proton transfer process presents a low potential energy barrier, favoring the conversion of the intermediate IN3 into the IPD (±)-**3a**. However, the most unexpected result was obtained from the analysis of the rearrangement process of IN2→IPD. Considering IN2, the AM1 calculations indicated that in the alternative reaction of **2a**, the spiro form participates only in the C(3)-N(4) ring-opening reaction to promote the imino pyrrole structure (ImPy) **4**. Ring-opening reactions of nitrogen bridgehead compounds have been described,[11] including for the IP series.[12] As expected, **2a** reacted to give (±)-**3a** *with also* **4** in low yield. Unfortunately, owing to the difficulties encountered during purification, formation of the unstable **4** was established by mass spectroscopy only ($m/z=289$). This result agrees

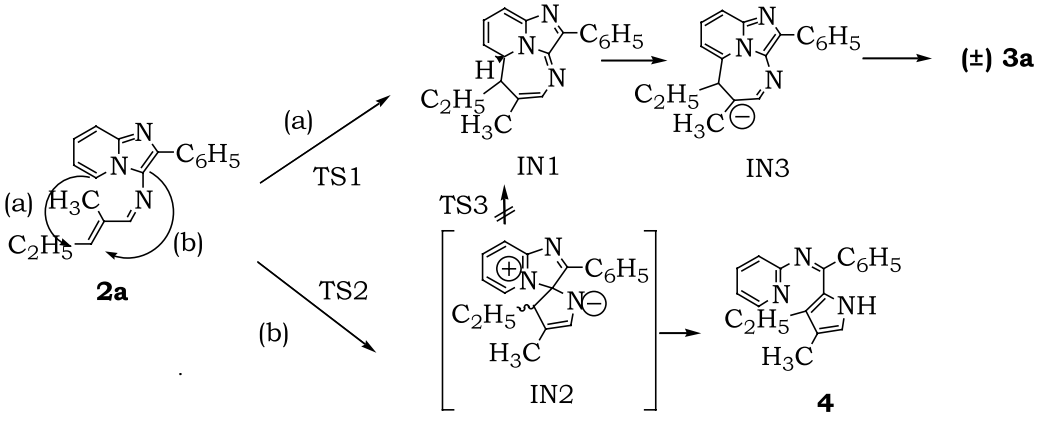
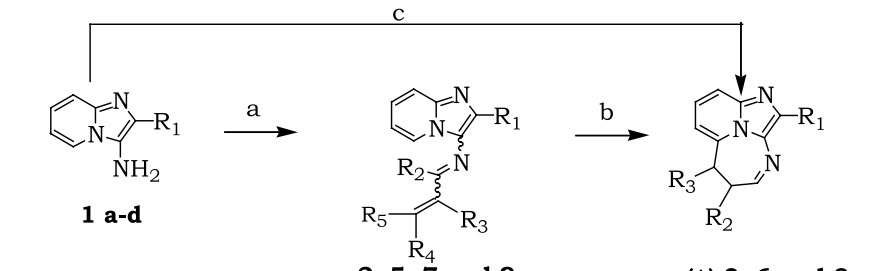


Figure 2. Energy calculations for the formation of diazepine (±)-**3a**.



a: $R_1 = C_6H_5$
b: $R_1 = o\text{-}CH_3OC_6H_5$
c: $R_1 = Cl$
d: $R_1 = CO_2C_2H_5$

	R_2	R_3	R_4	R_5
2a	H	CH_3	H	C_2H_5
5a	H	H	H	H
7a-d	H	H	H	CH_3
9a	CH_3	H	CH_3	CH_3

	R_2	R_3
3a	CH_3	C_2H_5
6a	H	H
8a-c	H	CH_3

Scheme 2. *Reagents and conditions*: (a) RCOR′, toluene, Δ; (b) 1,2-dichlorobenzene, Δ; (c) RCOR′, 1,2-dichlorobenzene, Δ.

Entry	Amino reagents	oxo reagents RCOR'		Method A[a]		Method B[b]
		R	R'	Conditions (a)	Conditions (b)	Conditions (c)
1	**1a**	$C_2H_5CH{=}C(CH_3)$	H	**2a** (45%)	**3a** (61%)	**3a** (60%)
2	**1a**	$C_2H_5CH(OH)$-$C(CH_3)$	H	**ND**[c]	**3a** (97%)	**3a** (99%)
3	**1a**	$CH_2{=}CH$	H	**5a** (55%)	**6a** (42%)	**6a** (45%)
4	**1a**	CH_3-CH=CH	H	**7a** (70%)	**8a** (98%)	**8a** (99%)
5	**1a**	CH_3	CH_3	**9a** (60%)	**ND**[c]	**ND**[c]
6	**1b**	CH_3-CH=CH	H	**7b** (45%)	**8b** (90%)	**8b** (90%)
7	**1c**	CH_3-CH=CH	H	**7c** (60%)	**8c** (90%)	**8c** (91%)

Figure 3. [a]Method A: (a) RCOR′, toluene, Δ; (b) 1,2-dichlorobenzene, Δ. [b]Method B: RCOR′, 1,2-dichlorobenzene, Δ. [c]Not detected.

with the participation of the spiro form intermediate and is consistent with the theoretical interpretation of the relative reactivity of the azaindoles based on the AM1 data. To complete our previous work on the synthesis and reactivity of 2-phenyl-3-aminoIP **1a**, we investigated the influence of oxo reagents and the influence of the C-2 position (Scheme 2 and Fig. 3).

Treatment of **1a** with 2-methylpentenal in refluxing toluene gave imine **2a**, which cyclized ring-stereospecifically onto the C-5 position to give the [1,3]diazepine moiety (±)-**3a** with a *cis*/*trans* ratio of 20/80 (Fig. 3, entry 1, method A). Interestingly, reaction of **1a** with 3-hydroxy-2-methylpentanal proceeded to give also the tricyclic structure (±)-**3a** with a 50/50 ratio (Fig. 3, entry 2, method A). Electrocyclization of **1a** with crotonaldehyde was performed (Fig. 3, entry 4, method A) and led to [1,3]diazepine (±)-**8a** in excellent yield (99%). In similar conditions, with acrolein, the crystalline diazepine **6a** was generated and identified by the single crystal method (Fig. 3, entry 3, method A). The dihedral angle between the planes of the IP ring and the phenyl group C(2a)-C(2)-C(11)-C(16) is −28.0° (above the IP plane), whereas a dihedral angle of −74.7° prevails for C(4)-C(5)-C(6)-C(6a). Interestingly, the bond lengths N(3)-C(4) (1.271 Å) and C(4)-C(5) (1.477 Å), C(5)-C(6) (1.518 Å), C(6)-C(6a) (1.483 Å) are characteristic of double and single bonds, respectively (Fig. 4).[13]

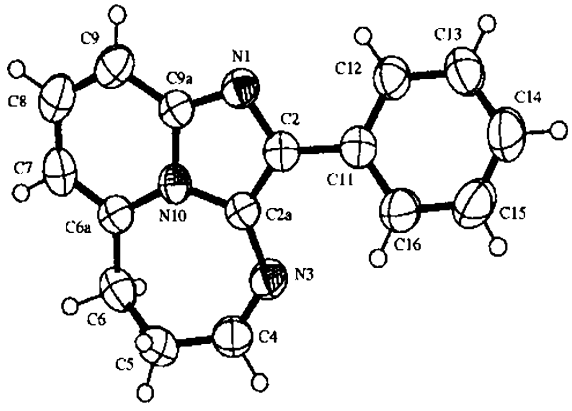
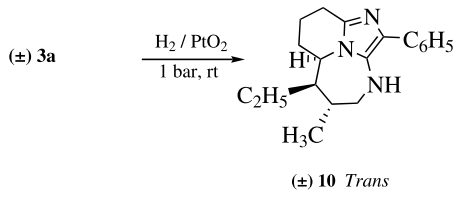


Figure 4. X-Ray analysis of **6a**.



Scheme 3.

The influence of the ketone derivatives on the cyclization was then studied. Treatment of the imine **9a** in refluxing 1,2-dichlorobenzene resulted in decomposition and recovery of starting material at lower temperature (Fig. 3, entry 1, method A). Direct thermolysis in refluxing 1,2-dichlorobenzene afforded (±)-**3a**, **6a** and (±)-**8a** (Fig. 3, entries 1–5, method B).

To expand the scope of the method, we turned our attention to the 2-imidazolic substituent. The presence in **1b**[14a] of 3′-methoxyphenyl offered the possibility of comparing the selectivity of the ring fusion via thermolysis to the C(5) IP or C(2′), C(6′) phenyl positions. The amine **1b** exhibited similar behavior to the 5-position. Treatment of **1b** with crotonaldehyde afforded (±)-**8b** in good yield, identified from their NMR and mass spectral data (Fig. 3, entry 6).

Substitution of the phenyl group by chlorine had no marked influence on the reaction course. Thus, condensation of compound **1c**[14b] with crotonaldehyde yielded the [1,3]diazepine structure **9c** (Fig. 3, entry 7). In contrast, the use of ester **1d**[14b] as the starting material with the same method gave the enimine **2d** as sole products (Fig. 3, entry 8).

Thus, we obtained a series of imidazopyridodiazepine compounds that were identifiable as potential NNRTIs against HIV-1 virus. We then investigated the reaction of compound (±)-**3a** by catalytic hydrogenation identifiable by the TIBO structure in terms of alterations of the diazepine moiety. In the Roe conditions (PtO_2, AcOH),[15] a mixture of (±)-**3a** afforded the piperidine compound (±)-**10** *trans* in 77% yield. Inspection of simple models of the annulated diazepine (±)-**10** reveals some conformational mobility of the tricyclic system (Scheme 3).[16]

In the ^{1}H NMR spectrum of the crystalline diazepine (±)-**10** *trans* there is no ^3J coupling between the bridgehead proton H(6a)/H(6), H(6)/H(5), and H(7α)/H(8α), suggesting a conformation with dihedral angles between these hydrogens close to 90°, supported by AM1 calculations (Fig. 5).

The relative configurations for the stereocenters in the tricyclic nuclei (i.e. C(5), C(6) and C(6a)) of compound (±)-**10** *trans* were assigned from NOESY data. For diazepine (±)-**10** *trans*, the NOESY spectrum showed close correlations between Me(5) and H(5), H(4α), H(6) and H(6a), and also between H(5) and H(4β), CH_2CH_3, or between H(6a) and H(6), H(4α) and H(7α), respectively. In addition, by saturation of Me(5) ($\delta = 1.22$), no

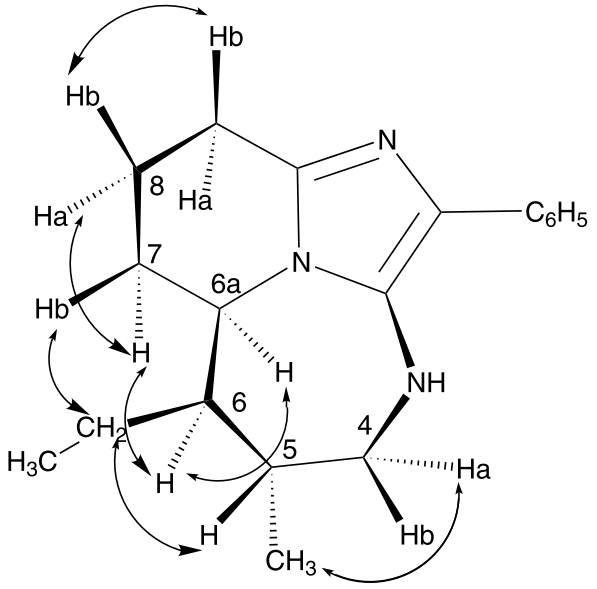


Figure 5. NOESY correlations of diazepine (±)-**10** for configuration assignments.

NOE enhancement over the diastereotopic CH_2CH_3, ($\delta = 1.35$, 1.01) was observed, consistent with a *trans* orientation for these groups. Consequently, we assigned the relative configuration of imidazopiperidinodiazepine (±)-**10** *trans* as 5*R**,6*R**,6a*R**.

In conclusion, we describe a synthesis of new [1,3]diazepine derivatives (±)-**3a**, **6a**, (±)-**8a**–**c** and (±)-**10** in an imidazo[1,2-*a*]pyridine series. This method can be generalized with simple or α,β-unsaturated aldehydes in good yields. Consideration of Pictet–Spengler intermediates indicates that the cyclization process was a direct intramolecular electrophilic attack of the heterocyclic ring system. Further application of the Pictet–Spengler reaction approach to the synthesis of various fused-imidazopyridine derivatives is currently in progress.

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6. Compound (±)-**3a** as an oil: IR 1675, 1445, 1345, 775, 695 cm^{-1}; (*cis*)-isomer: ^1H NMR δ 0.76 (t, 3 H, $J=7$ Hz), 0.81 (d, 3 H, $J=7$ Hz), 1.22 (m, 1 H), 1.38 (m, 1 H), 3.00 (m, 1 H), 3.26 (m, 1 H), 6.76 (dd, 1 H, $J=1$, 7 Hz), 7.25 (dd, 1 H, $J=7$, 9 Hz), 7.38 (t, 1 H, $J=7$ Hz), 7.49 (t, 2 H, $J=7$ Hz), 7.56 (dd, 1 H, $J=1$, 9 Hz), 7.75 (dd, 1 H, $J=1.5$, 5 Hz), 8.38 (d, 2 H, $J=7$ Hz); ^{13}C NMR δ 11.3, 16.9, 27.1, 43.4, 53.3, 114.3, 115.8, 121.7, 125.4, 128.0, 128.3 (2 C), 129.2 (2 C), 134.0, 139.8, 143.2, 144.5, 155.6; (*trans*)-isomer: ^1H NMR δ 0.76 (t, 3 H, $J=7$ Hz), 1.07 (m, 1 H), 1.49 (d, 3 H, $J=7$ Hz), 1.58 (m, 1 H), 2.65 (m, 1 H), 3.00 (m, 1 H), 6.60 (d, 1 H, $J=7$ Hz), 7.22 (dd, 1 H, $J=7$, 9 Hz), 7.36 (m, 1 H), 7.42 (t, 1 H, $J=7$ Hz), 7.56 (t, 2 H, $J=7$ Hz), 7.60 (dd, 1 H, $J=1$, 5 Hz), 8.45 (d, 2 H, $J=7$ Hz); ^{13}C NMR δ 11.5, 17.5, 21.8, 41.9, 50.8, 112.4, 115.2, 124.8, 127.6, 127.7 (2 C), 128.8 (2 C), 133.8, 139.8, 140.4, 144.7, 157.7; MS m/z 289 (M^+, 73), 260 (100), 233 (18); Anal. calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 78.95; H, 6.59; N, 14.46.
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13. Crystallographic data (excluding structure factors) for the structure **6a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications number CCDC 193333. Copies of the data can be obtained, free of charge, on application to CCDC 193333, 12 Union Road, Cambrige, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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16. Compound (±)-**10** *trans*: (yield: 77%); ^1H NMR δ 1.02 (m, 8 H), 1.53 (m, 1 H), 1.71 (m, 1 H), 1.85 (m, 1 H), 2.02 (m, 1 H), 2.15 (m, 2 H), 2.66 (m, 1 H), 2.79 (t, 1 H, $J=11.5$ Hz), 2.92 (m, 2 H), 3.75 (s, 1 H), 4.13 (dd, 1 H, $J=9.5$, 6.5 Hz), 7.18 (t, 1 H, $J=8$ Hz), 7.38 (t, 2 H, $J=8$ Hz), 7.68 (d, 2 H, $J=8$ Hz); ^{13}C NMR δ 15.8, 17.5, 18.1, 21.0, 25.5, 28.7, 42.5, 48.5, 48.7, 59.1, 126.0, 126.1 (2 C), 128.5 (2 C), 132.0, 135.4, 141.7; MS m/z 295 (M^+, 100), 212 (11), 184 (11), 105 (29), 77 (44), 55 (52). Anal. calcd for $C_{19}H_{25}N_3$: C, 77.25; H, 8.53; N, 14.22. Found: C, 77.21; H, 8.54; N, 14.25.