Synthesis of 'A' Ring Isomazole Oxypropanolamines *via* Hydrolysis of 1*H*-Imidazo[4,5-*c*]pyridine Oxazolidin-2-ones

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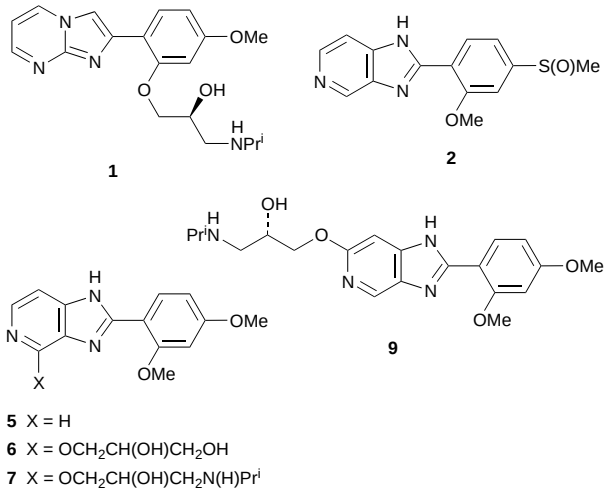
The base-catalysed hydrolysis of oxazolidin-2-one **15** gives an oxypropanolamine **7** and 4,5-dihydro-1*H*-imidazo[4,5-*c*]-pyridin-4-ones (**17–19**) and may occur by a B_{AL} mechanism.

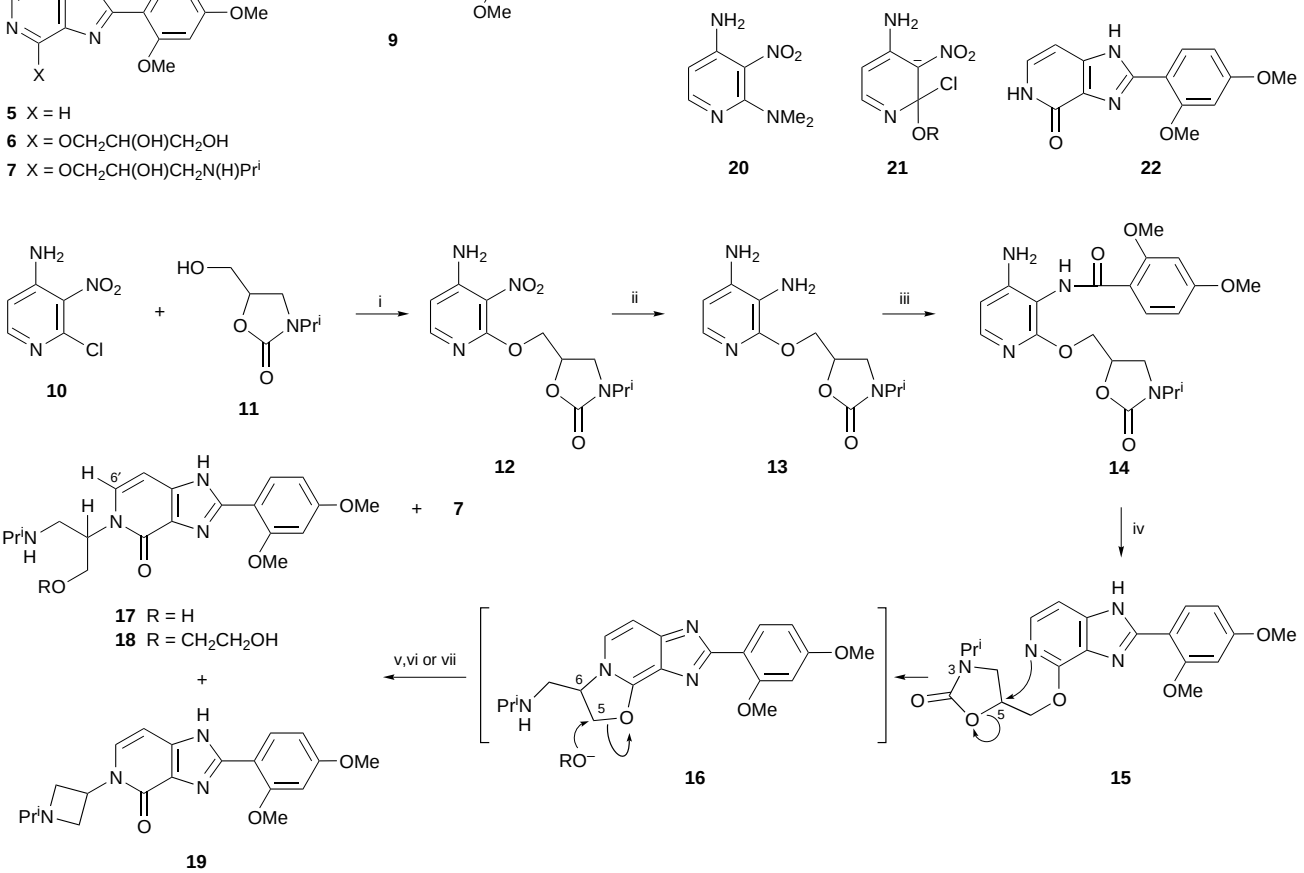
BW567C, (±)-**1**,[1] is a combined inotrope–β-adrenoceptor antagonist. In connection with our studies of the structure–activity relationships of **1**, isomazole (**2**) and its analogue (**5**),[2] we wished to synthesise and evaluate the pharmacological properties of the oxypropanolamines (±)-**7** and (±)-**9**.



Attempts to convert (±)-**6**[3] into (±)-**7** *via* monomethanesulfonate or epoxide intermediates were unsuccessful. An alternative route (Scheme 1) utilising the racemic oxazolidinone precursor **15** was therefore employed. The first and last stages in this synthesis, however, proved problematical.

Reaction of **10**[4–6] and racemic **11**[7–9] in *N*,*N*-dimethylformamide, containing an equivalent of NaOMe at 50 °C, gave the diamine **20** (55%) and **12** (5%). The poor conversion into **12**, and the distinctive deep-red colour of the reaction mixture, was attributed to the formation of either the sodium salt of **10** or a Meisenheimer complex **21**. To suppress these side reactions we reacted **10** and **11** in Bu^{t}OH at 80 °C in the presence of Bu^{t}OK and obtained a 60% yield of **12**.

Attempted deprotection[10] of the oxazolidinone **15** by reaction with 10 M NaOH in ethane-1,2-diol (1:10) at 120 °C gave the 4,5-dihydro-1*H*-imidazo[4,5-*c*]pyridin-4-ones **17** and **18**



Scheme 1 *Reagents and conditions:* i, KOBu^t, Bu^{t}OH, 80 °C (64%); ii, H_2, 10% Pd–C, MeOH (84%); iii, 2,4-dimethoxybenzoyl chloride, pyridine (58%); iv, $POCl_3$, pyridine (63%); v, 10 M NaOH–ethane-1,2-diol (1:10), 120 °C, **15**→**17** (20%), **18** (26%); vi, $Ba(OH)_2$, ethane-1,2-diol, 120 °C, **15**→**17** (26%), **18** (24%), **19** (16%); vii, 10 M NaOH–ethane-1,2-diol (1:1), 120 °C, **15**→**7** (24%), **17** (14%), **22** (5%)

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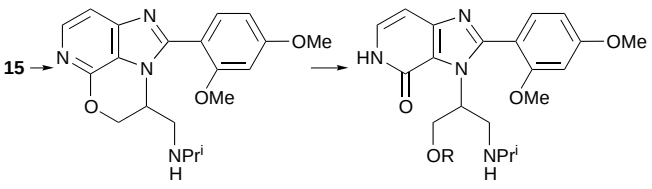
as the major products. When the above reaction was carried out using $Ba(OH)_2$ as the base, **17** and **18** were again formed along with a third product, assigned structure **19**.

The formation of **17–19** may be explained by deprotonation of **15** to give the anion which reacts at the pyridyl rather than the imidazo nitrogen. Intramolecular nucleophilic attack at C-5 of the oxazolidinone with concomitant oxygen–alkyl ring cleavage would give a carbamate anion which would readily lose carbon dioxide to produce **16**. Reaction of **16** with ^{-}OH or $HO[CH_2]_2O^{-}$ may then proceed by a similar, although intermolecular, mechanism ($B_{AL}2$, Ingold notation[15]) but with two possible regiochemical outcomes. Intermolecular nucleophilic attack at C-5 and oxygen–alkyl ring cleavage would give **17** and **18**, while **7** would be the product arising from C-6 attack. The azetidine **19** would result from **16** by intramolecular attack at C-5 by the side-chain amine. Products such as **23–25** (Scheme 2), arising from intramolecular nucleophilic attack by imidazo nitrogen on the oxazolidinone group of **15**, were not detected.



23 **24** R = H; **25** R = CH_2CH_2OH

Scheme 2

With the knowledge gained from this reaction sequence the preparation of the isomeric BW567C analogue, **9**, proved straightforward. Thus, hydrolysis of oxazolidinone **31** gave **9** along with the rearrangement product **32** (Scheme 5). Interestingly, however, base-catalysed hydrolysis of oxazolidin-2-one **33**[24] gave a tricycle **34** as the sole product (Scheme 6). This reaction probably occurs by a similar B_{AL} mechanism and will be described in detail elsewhere.

Oxypropanolamines **7** and **9** were found to be inactive as inotropic agents (*cf*. diol **6** and oxazolidinone **15**, which are moderately potent inotropes). **7** was also devoid of *β*-blocking properties but **9** was found to be a *β*-adrenoceptor antagonist (pK_B 5.9).

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Techniques used: IR, mass spectrometry, ^1H NMR, NOE, spin decoupling

References: 25

Schemes: 6

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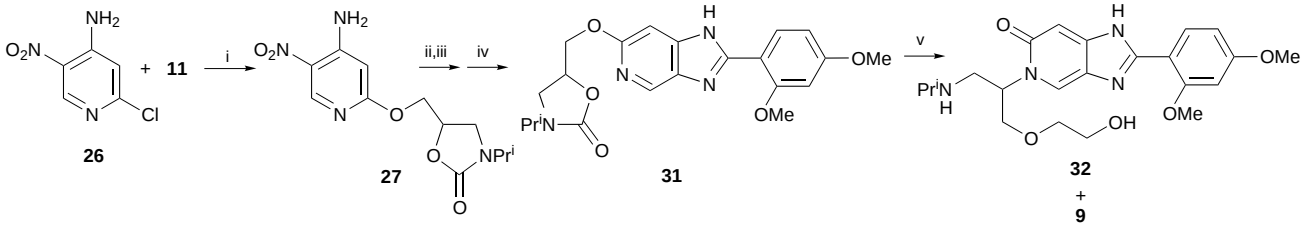
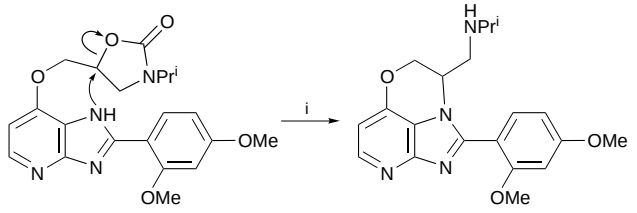


26 **27** **31** **32** + **9**

Scheme 5 *Reagents and conditions:* i, KOBu^t, Bu^{t}OH, 80 °C (36%); ii, H_2 10% Pd–C, MeOH (60%); iii, 2,4-dimethoxybenzoyl chloride, pyridine (73%); iv, $POCl_3$, pyridine (74%); v, 10 M NaOH–ethane-1,2-diol (1:1), 120 °C, **31**→**9** (36%), **32** (12%)



33 **34**

Scheme 6 *Reagent:* i, 10 M NaOH–ethane-1,2-diol (1:10), 120 °C (60%)

We also postulated that increasing the $[^{-}OH]$:$[HOCH_2CH_2O^{-}]$ ratio would favour attack at C-6 of the 5,6-dihydroimidazo[4,5-*c*]oxazolo[3,2-*a*]pyridine intermediate **16** by ^{-}OH since this pathway should be the least susceptible to steric hindrance. When we carried out the deprotection of **15** using 10 M NaOH–ethane-1,2-diol (1:1, *i.e.* just enough solvent to solubilise the mixture) the products were **7** (25%), **17** (14%) and **22** (5%). While a pathway *via* **16** explains this product distribution, **7** may also be derived, at least in part, from **15** by the 'normal' hydrolysis mechanism $B_{AC}2$,[15,16] *i.e.*, nucleophilic attack at the carbonyl carbon and oxygen–acyl ring cleavage.

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24 Prepared *via* reaction of **11** with 4-chloro-3-nitropyridin-2-amine.