

## Imine-Enamine Tautomerism

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Hantzsch conditions with *N*-benzylamine gave carbocycle **3** rather than a dihydropyridine when isoxazole-aldehyde **2** was employed.

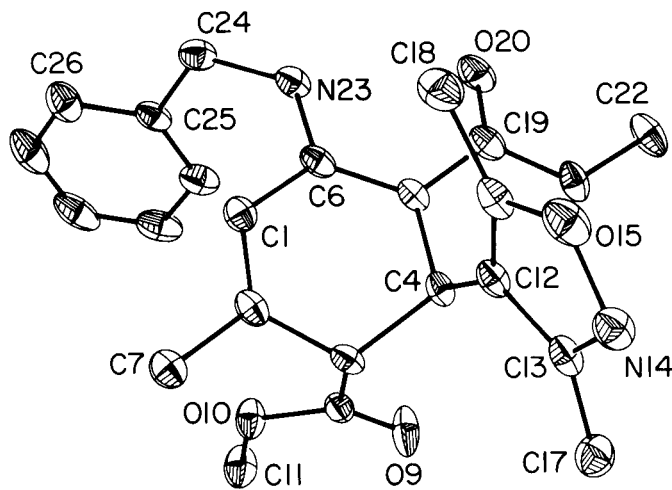
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The Hantzsch pyridine synthesis has been known for over a century [3] and remains today a facile and versatile method for the synthesis of functionally complex pyridines and dihydropyridines [4]. Recently, renewed interest in this reaction has emerged due to the discovery that Hantzsch esters such as nifedipine (**1**) possess important biological activity as calcium channel blockers [5]. We have previously reported that the reaction of **2** with aqueous ammonia under standard Hantzsch conditions proceeds to the dihydropyridine [6]. In the course of related studies on isoxazoles [7] we attempted to prepare an *N*-substituted-4-isoxazolyl-1,4-dihydropyridine *via* the Hantzsch pyridine route from 3,5-dimethylisoxazole-4-carboxaldehyde (**2**). By products in the Hantzsch dihydropyridine synthesis are rare; however, the use of primary amines for the source of nitrogen often leads to low yields or no reaction [4b]. We have discovered the major isolable product with *N*-substituted nitrogen sources to be a novel isoxazolylcarbocycle (*i.e.*, **3**). The resulting product **3** is worthy of note. We herein detail the crystal and

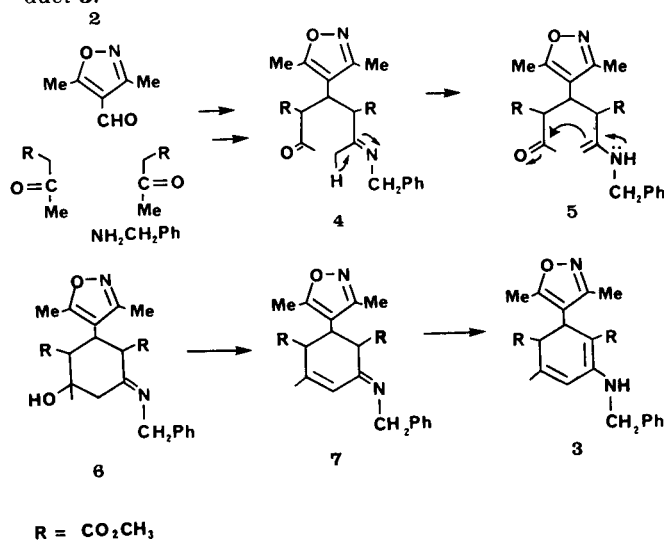
molecular structure of this product of the "failed" Hantzsch synthesis.

3,5-Dimethylisoxazole-4-carboxaldehyde (**2**) was treated with two equivalents of methyl acetoacetate and one equivalent of benzylamine and warmed to reflux, the normal conditions which lead to Hantzsch dihydropyridine products with unsubstituted nitrogen (*i.e.*, aqueous ammonia). A yellow crystalline product was obtained from this reaction mixture, and the <sup>13</sup>C nmr data indicated a lack of symmetry not consistent with the expected Hantzsch ester [6]. Single crystal x-ray study [8] of this compound, however, revealed that it contained a carbocyclic ring **3** (Figure).

This novel compound probably arises by initial imine enamine tautomerism from the intermediate **4** to **5** as shown in the Scheme. Intramolecular nucleophilic attack of the enamine of **5** on the carbonyl as shown gives rise to alcohol **6**. Dehydration of alcohol **6** to unsaturated imine **7** is followed by rapid tautomerisation to the observed product **3**.



Figure



Scheme

Table 1

Atom Coordinates ( $\times 10^4$ ) and Thermal Parameters ( $\text{\AA}^2 \times 10^3$ )

Atom	x	y	z	U [1]
C(1)	11140(2)	2998(1)	7395(1)	20(1)
C(2)	9731(2)	4026(1)	7540(1)	19(1)
C(3)	7558(2)	3984(1)	7685(1)	19(1)
C(4)	7092(2)	2801(1)	8241(1)	20(1)
C(5)	8698(2)	1703(1)	7837(1)	21(1)
C(6)	10640(2)	1815(1)	7412(1)	21(1)
C(7)	10213(2)	5237(1)	7543(1)	23(1)
C(8)	6881(2)	4155(1)	6714(1)	20(1)
O(9)	5371(2)	3915(1)	6625(1)	37(1)
O(10)	8095(2)	4648(1)	5989(1)	26(1)
C(11)	7456(2)	4946(2)	5068(1)	30(1)
C(12)	6638(2)	2909(1)	9352(1)	20(1)
C(13)	4757(2)	3520(1)	9916(1)	23(1)
N(14)	4713(2)	3467(1)	10866(1)	26(1)
O(15)	6630(2)	2803(1)	10954(1)	31(1)
C(16)	7737(2)	2478(1)	10037(1)	24(1)
C(17)	2935(2)	4169(1)	9562(1)	30(1)
C(18)	9801(3)	1746(2)	10006(1)	34(1)
C(19)	8179(2)	532(1)	7956(1)	23(1)
O(20)	9300(2)	-429(1)	7654(1)	32(1)
O(21)	6257(2)	595(1)	8471(1)	28(1)
C(22)	5594(3)	-527(1)	8653(1)	33(1)
N(23)	12157(2)	869(1)	7049(1)	24(1)
C(24)	14105(2)	972(1)	6439(1)	25(1)
C(25)	14098(2)	1499(1)	5393(1)	24(1)
C(26)	15874(3)	1753(1)	4793(1)	33(1)
C(27)	15944(3)	2203(2)	3822(1)	43(1)
C(28)	14263(3)	2411(2)	3445(1)	42(1)
C(29)	12512(3)	2146(2)	4029(1)	37(1)
C(30)	12431(3)	1694(1)	5001(1)	29(1)

[1] Equivalent isotropic U defined as one-third of the trace of the orthogonalized  $U_{ij}$  tensor.

Table 2

Bond Lengths ( $\text{\AA}$ )

C(1)-C(2)	1.335(2)	C(1)-C(6)	1.469(2)
C(2)-C(3)	1.511(2)	C(2)-C(7)	1.499(2)
C(3)-C(4)	1.548(2)	C(3)-C(8)	1.531(2)
C(4)-C(5)	1.516(2)	C(4)-C(12)	1.516(2)
C(5)-C(6)	1.382(2)	C(5)-C(19)	1.450(2)
C(6)-N(23)	1.357(2)	C(8)-O(9)	1.203(2)
C(8)-O(10)	1.325(2)	O(10)-C(11)	1.452(2)
C(12)-C(13)	1.415(2)	C(12)-C(16)	1.363(2)
C(13)-N(14)	1.316(2)	C(13)-C(17)	1.496(2)
N(14)-O(15)	1.411(2)	O(15)-C(16)	1.356(2)
C(16)-C(18)	1.486(2)	C(19)-O(20)	1.227(2)
C(19)-O(21)	1.356(2)	O(21)-C(22)	1.443(2)
N(23)-C(24)	1.449(2)	C(24)-C(25)	1.523(2)
C(25)-C(26)	1.399(2)	C(25)-C(30)	1.384(3)
C(26)-C(27)	1.395(2)	C(27)-C(28)	1.379(3)
C(28)-C(29)	1.382(3)	C(29)-C(30)	1.395(2)

Dihydropyridines have previously been utilized for carbocyclic ring formation by Birch [9] and later by Danishefsky [10]. The isoxazolidiene **3** represents a uni-

Table 3

Bond Angles ( $^\circ$ )

C(2)-C(1)-C(6)	122.1(1)	C(1)-C(2)-C(3)	119.1(1)
C(1)-C(2)-C(7)	122.7(1)	C(3)-C(2)-C(7)	118.1(1)
C(2)-C(3)-C(4)	112.3(1)	C(2)-C(3)-C(8)	112.9(1)
C(4)-C(3)-C(8)	109.5(1)	C(3)-C(4)-C(5)	111.1(1)
C(3)-C(4)-C(12)	111.0(1)	C(5)-C(4)-C(12)	115.2(1)
C(4)-C(5)-C(6)	120.2(1)	C(4)-C(5)-C(19)	118.6(1)
C(6)-C(5)-C(19)	121.1(1)	C(1)-C(6)-C(5)	119.2(1)
C(1)-C(6)-N(23)	117.4(1)	C(5)-C(6)-N(23)	123.4(1)
C(3)-C(8)-O(9)	123.9(1)	C(3)-C(8)-O(10)	112.5(1)
O(9)-C(8)-O(10)	123.5(1)	C(8)-O(10)-C(11)	115.9(1)
C(4)-C(12)-C(13)	123.2(1)	C(4)-C(12)-C(16)	132.7(1)
C(13)-C(12)-C(16)	104.1(1)	C(12)-C(13)-N(14)	112.0(1)
C(12)-C(13)-C(17)	128.3(1)	N(14)-C(13)-C(17)	119.7(1)
C(13)-N(14)-O(15)	105.7(1)	N(14)-O(15)-C(16)	108.2(1)
C(12)-C(16)-O(15)	110.1(1)	C(12)-C(16)-C(18)	135.1(1)
O(15)-C(16)-C(18)	114.8(1)	C(5)-C(19)-O(20)	126.1(1)
C(5)-C(19)-O(21)	112.1(1)	O(20)-C(19)-O(21)	121.8(1)
C(19)-O(21)-C(22)	116.7(1)	C(6)-N(23)-C(24)	125.2(1)
N(23)-C(24)-C(25)	115.0(1)	C(24)-C(25)-C(26)	118.5(2)
C(24)-C(25)-C(30)	122.7(1)	C(26)-C(25)-C(30)	118.8(1)
C(25)-C(26)-C(27)	120.2(2)	C(26)-C(27)-C(28)	120.4(2)
C(27)-C(28)-C(29)	119.7(2)	C(28)-C(29)-C(30)	120.2(2)
C(25)-C(30)-C(29)	120.7(2)		

Table 4

Anisotropic Thermal Parameters ( $\text{\AA}^2 \times 10^3$ )

Atom	$U_{11}$	$U_{22}$	$U_{33}$	$U_{23}$	$U_{13}$	$U_{12}$
C(1)	25(1)	21(1)	16(1)	1(1)	-4(1)	-7(1)
C(2)	28(1)	19(1)	12(1)	1(1)	-6(1)	-9(1)
C(3)	24(1)	15(1)	16(1)	-1(1)	-3(1)	-4(1)
C(4)	26(1)	18(1)	15(1)	1(1)	-3(1)	-8(1)
C(5)	31(1)	16(1)	16(1)	0(1)	-6(1)	-7(1)
C(6)	31(1)	17(1)	13(1)	1(1)	-6(1)	-5(1)
C(7)	29(1)	20(1)	22(1)	0(1)	-8(1)	-9(1)
C(8)	22(1)	18(1)	19(1)	1(1)	-3(1)	-5(1)
O(9)	35(1)	56(1)	28(1)	15(1)	-13(1)	-27(1)
O(10)	27(1)	39(1)	17(1)	8(1)	-7(1)	-15(1)
C(11)	31(1)	45(1)	18(1)	8(1)	-10(1)	-17(1)
C(12)	30(1)	14(1)	17(1)	1(1)	-3(1)	-10(1)
C(13)	33(1)	18(1)	18(1)	0(1)	-2(1)	-11(1)
N(14)	36(1)	22(1)	19(1)	-1(1)	-2(1)	-7(1)
O(15)	46(1)	27(1)	18(1)	2(1)	-7(1)	-9(1)
C(16)	35(1)	19(1)	18(1)	2(1)	-4(1)	-10(1)
C(17)	31(1)	29(1)	28(1)	-2(1)	-3(1)	-7(1)
C(18)	39(1)	31(1)	31(1)	6(1)	-12(1)	-7(1)
C(19)	35(1)	19(1)	17(1)	2(1)	-8(1)	-8(1)
O(20)	44(1)	16(1)	33(1)	-1(1)	-6(1)	-9(1)
O(21)	36(1)	21(1)	27(1)	2(1)	-4(1)	-16(1)
C(22)	48(1)	24(1)	34(1)	6(1)	-12(1)	-21(1)
N(23)	31(1)	16(1)	21(1)	0(1)	-3(1)	-2(1)
C(24)	28(1)	22(1)	22(1)	-1(1)	-4(1)	1(1)
C(25)	33(1)	15(1)	21(1)	-2(1)	-4(1)	-1(1)
C(26)	41(1)	28(1)	29(1)	-3(1)	-1(1)	-10(1)
C(27)	63(1)	28(1)	29(1)	-2(1)	9(1)	-16(1)
C(28)	74(1)	24(1)	20(1)	1(1)	-5(1)	-5(1)
C(29)	56(1)	27(1)	26(1)	-1(1)	-14(1)	2(1)
C(30)	37(1)	24(1)	23(1)	0(1)	-6(1)	-0(1)

The anisotropic temperature factor exponent takes the form:  
 $-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + \dots + 2hka^*b^*U_{12})$

Table 5

H Coordinates ( $\times 10^4$ ) and Thermal Parameters ( $\text{\AA}^2 \times 10^3$ )

Atom	x	y	z	U
H(1)	12524	3031	7273	23
H(3)	6811	4658	8086	21
H(4)	5882	2675	8119	22
H(7a)	11627	5190	7420	28
H(7b)	9556	5557	8183	28
H(7c)	9679	5760	7044	28
H(11a)	8490	5286	4631	38
H(11b)	6203	5535	5161	38
H(11c)	7337	4242	4784	38
H(17a)	1800	4433	10099	37
H(17b)	2628	3619	9178	37
H(17c)	3240	4859	9149	37
H(18a)	9994(27)	1469(20)	10652(13)	40
H(18b)	10532(27)	2083(20)	10312(13)	40
H(18c)	10870(27)	2111(20)	9639(13)	40
H(18d)	10670(27)	1524(20)	9305(13)	40
H(18e)	10132(27)	910(20)	9644(13)	40
H(18f)	9794(27)	883(20)	10318(13)	40
H(22a)	6121(33)	-984(18)	9142(15)	43
H(22b)	6615(33)	-1125(18)	8487(15)	43
H(22c)	5813(33)	-863(18)	8056(15)	43
H(22d)	4517(33)	-460(18)	8280(15)	43
H(22e)	4022(33)	-319(18)	8936(15)	43
H(22f)	4824(33)	-581(18)	9367(15)	43
H(23)	11756(30)	159(18)	7079(15)	48(6)
H(24a)	14626	1485	6760	29
H(24b)	14974	177	6392	29
H(26)	17048	1616	5052	38
H(27)	17167	2373	3411	50
H(28)	14308	2735	2780	49
H(29)	11347	2275	3764	44
H(30)	11206	1516	5402	34

## X-Ray Data and Structure Determination.

Diffraction data were measured with a Syntex P2, diffractometer equipped with a locally modified low-temperature device. All calculations were performed with the Nicolet SHELXTL system, running on a Data General Eclipse S/230 computer.

## Crystal Data.

Formula  $C_{23}H_{26}N_2O_5$ ,  $M_r = 410$ , crystal selected from a sample recrystallized from deuteriochloroform, parallelepiped of dimensions  $0.24 \times 0.47 \times 1.05$  mm, mounted with the long direction near the diffractometer  $\phi$  axis, triclinic space group  $P\bar{1}$ , cell dimensions at 140 K,  $a = 7.075(1)$ ,  $b = 11.382(2)$ ,  $c = 13.980(2)$ ,  $\text{\AA}$ ,  $\alpha = 84.06(1)$ ,  $\beta = 75.29(1)$ ,  $\gamma = 75.85(1)^\circ$ ,  $Z = 2$ ,  $Cu K\alpha$ ,  $\lambda = 1.5418$   $\text{\AA}$ , graphite monochromator,  $\mu = 7.6$   $\text{cm}^{-1}$ ,  $d_{calc} = 1.29$   $\text{Mg m}^{-3}$ ,  $1^\circ \omega$  scan at  $58.6^\circ \text{min}^{-1}$  [8], bg offset  $\pm 1^\circ$ , scan/bg time ratio = 1, max  $2\theta = 132^\circ$ , 3639 unique reflections measured, 3368 with  $I > 3\sigma(I)$  used in refinement of 297 parameters, anisotropic thermal motion for C, N and O, H atoms riding on C in idealized geometry, H on N(23) free, H atom disorder at C(18) and C(22) included in model, final  $R = 0.041$ ,  $R_w = 0.048$ .

## Structure.

The molecule is depicted in Figure 1, showing the structure to be that of **3**. Some bond distances ( $\text{\AA}$ ): C(1) - (2) 1.335(2), C(1) - C(6) 1.469(2), C(5) - C(6) 1.382(2), C(6) - N(23) 1.357(2), N(14) - O(15) 1.411(2). N(23) environment is planar, the two C-N-H angles differ by  $6^\circ(1)$ . Dihedral angles ( $^\circ$ ): C(3)C(4)C(12)C(13) 79, C(5)C(6)N(23)C(24) 168.

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que system which may hold much promise for the construction of bicyclic carbocycles. This tactic is being pursued in our laboratories, and our progress will be reported in due course.

## EXPERIMENTAL

## Synthesis.

A mixture of 1.2 g of isoxazolealdehyde **2** (9.8 mmoles), 2.4 g of methyl acetoacetate (20 mmoles), 1.1 g of *N*-benzylamine (10 mmoles), and 50 ml of methanol were heated to reflux for 24 hours. The reaction mixture was cooled, and the yellow solid which precipitated was filtered. Recrystallization from methanol gave 0.74 g of **3** as a yellow solid, mp  $160$ - $162^\circ$  C (18%);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  9.26 (1H, br, t,  $J = 6$  Hz), 7.2 (s, 5H), 6.17 (d, 1H,  $J = 1.4$  Hz), 4.42 (d, 2H,  $J = 6$  Hz), 4.369 (d, 1H,  $J < 1$  Hz), 3.608 (s, 3H), 3.478 (s, 3H), 2.805 (d, 1H,  $J < 1$  Hz), 2.11 (s, 3H), 2.08 (s, 3H), 1.785 (d, 3H,  $J = 1.4$  Hz);  $^{13}\text{C}$  nmr (deuteriochloroform): 171.42, 169.99, 165.22, 159.5, 154.2, 143.53, 139.12, 128.75, 127.32, 126.729, 117.849, 115.406, 85.25, 52.477, 51.047, 50.63, 46.639, 30.668, 24.469, 11.481, 10.587; ms:  $m/z$  410 ( $M^+$ , 16.28), 379 ( $M-31$ , 2.2), 351 ( $M-59$ , 30.46), 319 (12.62), 310 (4.14), 301 (2), 278 (2.5), 242 (5.2), 222 (2), 174 (2.2), 106 (4.9), 91 (tropylium ion, 100), 77 (1.8), 65 (6.6), 59 (3.62).

Anal. Calcd. for  $C_{23}H_{26}N_2O_5$ : C, 67.30; H, 6.38; N, 6.82. Found: C, 67.22; H, 6.72; N, 6.82.

Performing the reaction in a pressure vessel at  $80^\circ$  for 15 hours gave a 24% yield.

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