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A PYRANO-PYRAZOLINE:

A NOVEL BINUCLEAR HETEROCYCLIC SYSTEM[1].

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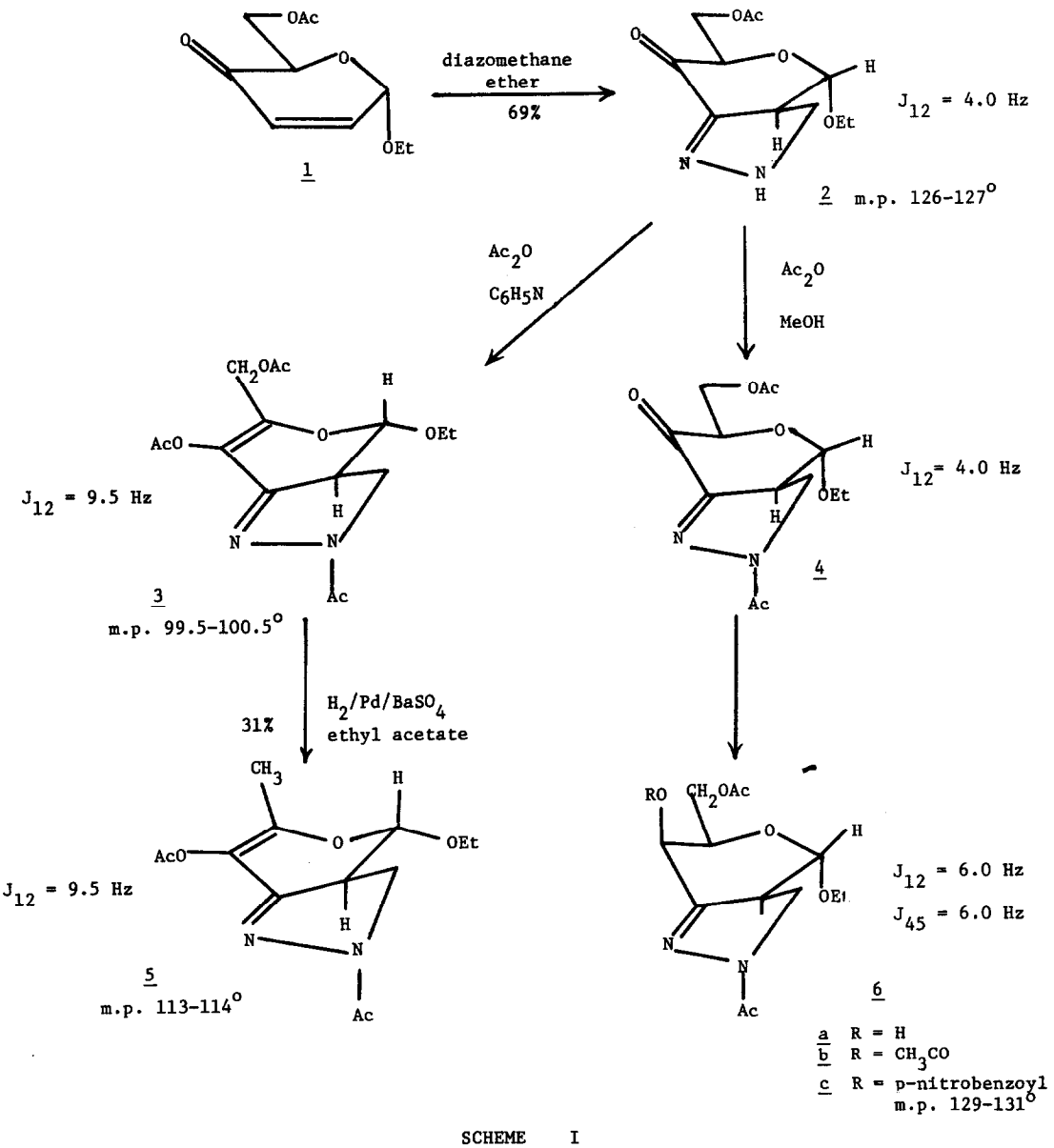
Branched-chain[4] and N-containing[5] sugars occur frequently as components of pharmacologically active substances, many antibiotics containing members belonging to both classes[6]. Our interest in carbohydrate enones[7] as vehicles for modifying sugar nuclei focussed upon compound 2, which should be readily obtainable from 1. This "pyrano-pyrazoline"[8] (2) belongs to both classes of sugars, being branched-chain as well as N-containing, and in this communication we report some aspects of the chemistry of this novel binuclear heterocyclic system. Interestingly, one of its derivatives 3 was found to be a mild antithrombotic agent[10].

A slight excess of crystalline enone 1[7] (2.4 g; 11.2 mmol) when added to a stirred solution of diazomethane in ether (46 ml of 0.235 M; 10.8 mmol) at room temperature, dissolves immediately, and within one minute a flocculent precipitate of 2 (1.96 g; 69%) is formed which may be recrystallized from EtOAc - Pet. Ether (30-60°) m.p. 126-127° $[\alpha]_D^{23}$-164.1° (c = 5.53 in $CHCl_3$) Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.71; H, 6.14; N, 11.05. The assignment of structure 2 follows from the expected approach of the dipolarophile to the enone 1[11], the 1-pyrazoline initially formed, undergoing rearrangement to the conjugated 2-pyrazoline[12]. For 2: uv_{max}^{MeOH} 326.5 nm (ε=9,905) $ir_{max}^{CHCl_3}$ cm^{-1} 3325 (N-H), 1745 (ester), 1706 (C=O), 1553 (C=N)[13]. The orientation at carbon-2 is discussed below.

Compound 2 is stable if kept in the refrigerator, but it is decomposed by acids or bases. Esterification with acetic anhydride and pyridine at 0°C gave 3 (82.4%) as was readily apparent from three acetyl resonances in the nmr spectrum at τ 7.70, 7.74 and 7.90[14]. For 3 recrystallized from EtOH-hexane (1:3): m.p. 99.5-100.5° $[\alpha]_D^{23}$-176.1° (c = 3.5 in $CHCl_3$) m/e 340. Anal. Calcd. for $C_{15}H_{20}N_2O_7$: C, 52.94; H, 5.92; N, 8.23.Found: C 53.10; H, 6.06; N, 8.06. uv_{max}^{MeOH} 300 nm (ε=21,561), 208 nm (ε=5,710); $ir_{max}^{CHCl_3}$ cm^{-1}, 1760 (enol acetate), 1740 (primary acetate), 1650 (N-acetate and C = C-O). The nmr data is discussed below. Esterification with acetic anhydride and methanol prevented formation of the enol acetate, the product, 4,


OAc
OEt
1
diazomethane
ether
69%
OAc
H
OEt
H
N
N
H
2
m.p. 126-127°
J12 = 4.0 Hz
Ac2O
C6H5N
Ac2O
MeOH
CH2OAc
H
AcO
O
OEt
J12 = 9.5 Hz
H
N
N
Ac
3
m.p. 99.5-100.5°
OAc
H
OEt
H
N
N
Ac
4
J12 = 4.0 Hz
31%
H2/Pd/BaSO4
ethyl acetate
CH3
H
AcO
O
OEt
J12 = 9.5 Hz
H
N
N
Ac
5
m.p. 113-114°
RO
CH2OAc
H
OEt
N
N
Ac
J12 = 6.0 Hz
J45 = 6.0 Hz
6
a R = H
b R = CH3CO
c R = p-nitrobenzoyl
m.p. 129-131°

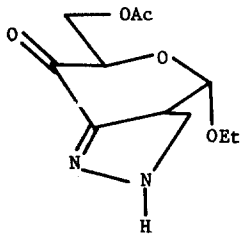
SCHEME I

being obtained as a syrup: $ir_{max}^{CHCl_3}$ 1740 (primary acetate), 1681 (C=O and N-acetate), 1586 (C=N)[13] cm^{-1}. Treatment of 4 with acetic anhydride and pyridine gave crystalline 3 in quantitative yield.

Compound 3 showed some *in vitro* antithrombotic activity by inhibiting ADP and collagen induced platelet aggregation[10]. It was of interest to see whether modifications of 3 would affect the level of this activity. Attempts to achieve selective acid or base hydrolysis either failed, or destroyed the molecule. With Pd on $BaSO_4$ (1 atm, r.t.), hydrogenolysis of the allylic ester occurred[15] while the unsaturated chromophores remained intact! The product 5 crystallized from chloroform-hexane in 31% yield m.p. 113-114°. $[\alpha]_D^{23}$ - 206° (c = 3.25 in $CHCl_3$) Anal. Calc. for $C_{13}H_{18}O_5N_2$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.35; H, 6.48; N, 9.76. uv_{max}^{MeOH} 295 nm (ε = 22,050) ir_{max}^{CHCl} 1760 cm^{-1}. Compound 5 showed no biological activity.

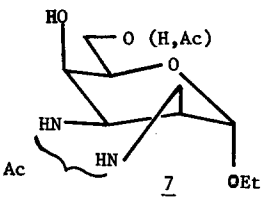
Atmospheric hydrogenation of 3 in ethanol, in the presence of a platinum catalyst caused massive destruction, including loss of the ester groups! However, under similar conditions, the keto-imine, 4 consumed one molar amount of hydrogen. The product, 6a, underwent acetylation with Ac_2O-Py, but not with Ac_2O-MeOH; it was therefore an alcohol rather than an amine[16]. The derived diacetate, 6b, was non-crystalline, but the p-nitrobenzoate 6c gave acceptable analytical data: m.p. 129-131°. Anal. Calcd for $C_{20}H_{23}N_3O_9$: C, 53.45; H, 5.16; N, 9.35. Found: C, 53.33; H, 5.12; N, 9.25.

The imino group in the N-acetates 4, 5 and 6 was unexpectedly stable toward hydrogenation. On the other hand, the unacetylated imino-ketone 2 consumed three moles of hydrogen to give a complex mixture, 7, containing N-$COCH_3$ and O-$COCH_3$ (1665 and 1735 cm^{-1} respectively).



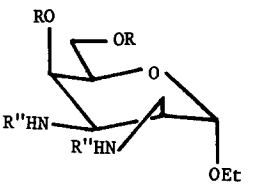
2

J_{12} = 4.0 Hz



7

J_{12} < 1.0 Hz



8 R = H; R' = R'' = Ac
9 R = R' = R'' = Ac
10 R = R'' = H; R' = Ac

J_{12} < 1.0 Hz

SCHEME II

Per-N-acetylation (Ac_2O/H_2O) gave a di-N-acetate, 8, which crystallized as the hemihydrate; with Ac_2O-Py, 8 gave the tetracetate 9. Saponification of 8 or 9 with strong base stopped at a mono-N-acetate, judged to be 10, since the material was destroyed by sodium metaperiodate under conditions where 8 was unaffected.

In Schemes I and II, values for $J_{1,2}$ obtained from 220MHz spectra of compounds 2-10 ($CDCl_3$,TMS) are shown. The remarkable range of values (<1·0 to 9.5 Hz) can be accommodated only by trans-arrangement of the 1,2-substituents, whose relative dihedral angle changes as the system is modified chemically. The most compelling evidentiary data, are the small values of $J_{1,2}$ for compounds 7 to 10, which is diagnostic of trans-1,2-diequatorial hydrogens in pyranosides[17].

Of the above compounds, only 3 displayed any biological activity (vide supra). Enone 1 reacted only slightly with ethyl diazoacetate, and not at all with diazoacetophenone. Reaction of the dipolarophiles with congeners of 1 is being investigated and will be reported in due course.

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8. By analogy with known fused systems[9],compound 2 is named ethyl 6-O-acetyl-α-D-threo-hexopyranosid-4-ulo [2,3:3',4']-2-pyrazoline
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14. Unlike 2 which readily gives the enolate ester (3), 1 is completely stable to the acetylation medium. Presumably the s-cis arrangement in 2 compares unfavourably with the s-trans system in 3; enone 1 is already s-trans.
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