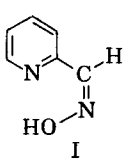
Synthesis and Configurational Analysis of Picolinaldehyde Oximes

Sir:

During the past decade, continuing interest in the synthesis of geometrically isomeric pyridine aldoximes as starting materials in the preparation of chemotherapeutics for anticholinesterase poisoning has resulted in only moderate success.[1]

The syn-isomers of picolinaldehyde and isonicotinaldehyde oximes are easily prepared, either when a neutralized aqueous solution of hydroxylamine hydrochloride is heated with the pyridine carboxaldehyde (3) or when the picoline is oximated in liquid ammonia with sodamide and an alkyl nitrite (4).[2] In 1961, a report appeared on the preparation of anti-isonicotinaldehyde oxime from the aldehyde and hydroxylamine in basic media at 10–15° (5). However, the procedure is not satisfactory because of inconsistent reproducibility. A simpler and more convenient method of synthesizing anti-isonicotinaldehyde oxime involves photochemical isomerization of the syn-isomer (6). To the authors' knowledge, isonicotinaldehyde oxime is the only pyridine aldoxime which up to the present has been shown to exist in two stable geometrical forms.

This communication reports the synthesis of anti-picolinaldehyde oxime (I) and a configurational analysis of both geometrical isomers.



I

The preparation involves forming an equilibrium mixture of both syn- and anti-isomers, separating the isomers by taking advantage of solubility differences, then purifying the anti-isomer by chromatography.

Thus, 150 Gm. of syn-picolinaldehyde oxime (Aldrich Chemical Co.) was refluxed in 500 ml. of benzene for 15 min. The solution was stirred magnetically while allowing it to cool to room temperature and then was filtered. The filtrate was evaporated to dryness to give 3.0 Gm. of solid, m.p. 86–92°. The solid was dissolved in the minimum amount of chloroform at room temperature, and the solution was chromatographed on a 22-mm. × 25-cm. 60–100-mesh Florisil column. Chloroform was used throughout the separation; the anti-isomer passed through the column more rapidly than its syn-analog. The various fractions were evaporated, and the residues not showing free OH infrared absorption in dilute chloroform were combined to give 1.06 Gm. of anti-picolinaldehyde oxime, m.p. 97–98°. [Reported m.p. 114° for syn-picolinaldehyde oxime (3).]

Anal.—Calcd. for $C_6H_6N_2O$: C, 59.0; H, 5.0; O, 13.1. Found: C, 58.9; H, 4.7; O, 13.0.

The configurations of the isomeric picolinaldehyde oximes were assigned on the basis of infrared absorption. There is general agreement (7–9) that anti-picolinaldehyde oxime should show an intramolecular O—H- - -N bond. A broad OH absorption (maximum 2790 cm.$^{-1}$) was observed for 5% I in chloroform. An OH frequency of 2600 cm.$^{-1}$ has been found in chloroform or carbon tetrachloride for compounds involving a chelated hydroxyl group and a heterocyclic nitrogen atom (10). The infrared absorption of syn-picolinaldehyde oxime obtained similarly in chloroform showed a sharp band at 3574 cm.$^{-1}$ which is characteristic of a free OH group.

Thin-layer chromatography of commercial picolinaldehyde oxime indicated the presence of a trace of the anti-isomer. The possibility exists that all that was accomplished by the treatment described was a separation of the isomers. However, the syn-picolinaldehyde oxime was recovered and used again a number of times with the same results. The total amount of anti-isomer far exceeded what could have

[1] There are two recent reviews by Ellin and Wills on medical-chemical interest in pyridine aldoximes (1, 2).

[2] Only one isomer of isonicotinaldehyde oxime (m.p. 132–133.5°) was obtained by the sodamide method. The anti-configuration was suggested without reference to the previous assignment of syn (5), in which both isomers were compared.

been accounted for as an impurity in the starting material. Syn-antiequilibrium mixtures also have been obtained by melting the syn-isomer or by photochemical irradiation in acetone at 5°.

Experiments on the stability and physical and chemical properties of I are underway. These will be reported in full publications at a later time.

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Theoretical Relationship Between Dose, Elimination Rate, and Duration of Pharmacologic Effect of Drugs

Sir:

Recent communications have dealt with the relationship between rate of decline of pharmacologic effects and drug elimination rate (1, 2), with the kinetics of multiple pharmacologic effects (3), as well as with the apparent potentiating effect of a second dose of drug administered immediately upon recovery from the effects of the initial dose (4). The purpose of this communication is to consider the quantitative relationship between dose, elimination rate, and duration of pharmacologic effect of a given drug.

Let it be assumed that (*a*) the intensity of a pharmacologic effect at any time is a function of body drug content at that time, (*b*) drug metabolites are essentially inactive (particularly with respect to the type of pharmacologic activity under consideration), (*c*) a minimum body drug content, d_m, is necessary to elicit a measurable pharmacologic effect, and (*d*) the drug is eliminated from the body by an exponential process or processes, the sum of whose rate constants is independent of dose.

The time necessary to decrease initial body drug content, d_0 (which would usually represent an amount of drug administered intravenously), to d_m can be calculated by rearranging the exponential expression for drug elimination

$$\log d_m = \log d_0 - \frac{K}{2.3}t \qquad \text{(Eq. 1)}$$

to

$$t = K_1(\log d_0 - \log d_m) \qquad \text{(Eq. 2)}$$

where K is the first-order drug elimination rate constant, $K_1 = 2.3/K$, and t is the duration of the pharmacologic effect. Rearranging Eq. 2 yields

$$t = K_1 \log d_0 - k \qquad \text{(Eq. 3)}$$

where $k = K_1 \log d_m$. Accordingly, a plot of duration of pharmacologic effect *versus* the logarithm of the dose (given intravenously or by other routes which afford rapid absorption relative to the rate of elimination) should be linear. While this linear relationship is well known (5, 6), it apparently has not been recognized that the first-order rate constant for drug elimination (K) can be calculated from the slope of the line since $K = 2.3/K_1$. The minimum effective dose (d_m) can be calculated from the intercept value since $\log d_m = k/K_1$. This method should be useful for determining the elimination rate constant (or half-life) of drugs in certain instances where measurement of drug concentration in blood, urine, or tissue is not possible but where a sufficiently accurate assessment of the duration of a given pharmacologic effect is feasible. A similar approach can be used (under certain special conditions) to determine absorption rate constants, as will be demonstrated by Lands *et al.* (7).

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