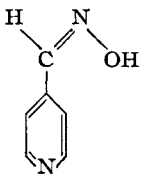
Photochemical Isomerization. Synthesis of Anti-isonicotinaldehyde Oxime Derivatives

Sir:

Some of the best-known compounds capable of reaction with anticholinesterases and reactivation of inhibited acetylcholinesterases are *N*-alkyl derivatives of syn-isonicotinaldehyde oximes (1–3). However, the corresponding quaternary salts of anti-isonicotinaldehyde oxime (I) have not been examined because of the lack of a good method for synthesizing the anti-isomer. That



I

this is a serious problem and has existed for many years is evident from reading a current review (4) on the use of oximes in anticholinesterase therapy.

The anti-isomer has been prepared previously from isonicotinaldehyde and hydroxylamine in basic media at 10–15° (5). Slow titration with acetic acid resulted in the precipitation of I. However, the procedure was not satisfactory because of inconsistent reproducibility. Out of 10 attempts, only two runs led to the isolation of the anti-isomer and then only in yields of less than 5% (6). Other investigators have been unsuccessful in obtaining any of the anti-isomer using the same procedure. Photochemical isomerization of syn-isonicotinaldehyde oxime is proposed in this communication as a simple and convenient method of synthesizing the anti analog.

The anti-isomer is obtained by irradiating a concentrated acetone solution of syn-isonicotinaldehyde oxime. Thus 17 hr. of irradiation at 0–5° of a 15-ml. acetone solution containing 1.2 Gm. of syn-isonicotinaldehyde oxime, m.p. 132–133°, (Aldrich Chemical Co.) in a 24/40 ₹ 13-mm. i.d. tube fitted with an 8-in. quartz tube 2537 Å. lamp (Ultraviolet Products, Inc., San Gabriel, Calif.) resulted in the precipitation of crude I. The irradiation was interrupted twice to scrape the solid, which had collected on the tube above the solution level, back into the reaction mixture. At the end, the reaction tube was allowed to warm to room temperature, the solid was thoroughly ground, and the mixture was filtered. One recrystallization from hot water gave 180 mg. (15%) of a nearly colorless solid, m.p. 169–171° [reported (5) m.p. 165–167°].

Confirmation of configuration was obtained through a comparison of NMR spectra of the isomers in deuterated methanol and acetone (5). Deuterated water also was used but is less acceptable because of the poor solubility of the anti compound. Infrared absorption of the residue from an evaporated portion of the reaction solution indicated a mixture of anti- and syn-isomers. The experiment was repeated a number of times and gave an average yield of 28% for crude material. Higher yields were obtained by further irradiating a concentrate of filtrates from two runs.

The experiment described represents the best conditions found for the isomerization. Irradiation in aqueous alkali for 90 min. at 36°, in acetonitrile for 24 hr. at 36°, or in boiling acetone for 24 hr. led to a recovery of syn-isonicotinaldehyde oxime.

The photochemically induced syn–anti isomerization of a number of aromatic aldoximes was cited by Amin and De Mayo (7). Isonicotinaldehyde oxime (presumably the syn-isomer) was irradiated in acetic acid. The primary purpose was to test for the formation of amide. The authors did not find isonicotinamide and did not indicate whether geometrical isomerization occurred.

The photochemical syn–anti isomerization of a pyridine carboxaldoxime described in this communication is not unique. However, the significance of the work lies in the solution of a serious problem of medical-chemical research interest which has existed for many years (4). A shortcoming of the previous observation that the methiodide of anti-isonicotinaldehyde oxime is 2.5 times less effective in reactivating GB-inhibited enzyme (5) is that insufficient material was available to study whether any isomerization was occurring. Also because of the difficulty of synthesizing anti-isonicotinaldehyde oxime, there have been no other reports of anti-isonicotinaldehyde oxime or its quaternary derivatives. Now the quaternary salts can be synthesized readily, also the molecular complementarity

theory on the reactivation of inhibited acetylcholinesterase advanced by Wilson (8) may be examined more easily.

Clearly, the photolysis procedure described in this communication may be applicable to the isomerization of other heterocyclic aldoximes and their quaternary derivatives.

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Books

REVIEW

The National Formulary. 12th ed. Prepared by the Committee on National Formulary under the supervision of the Council, by the authority of the American Pharmaceutical Association. Published by the American Pharmaceutical Association, 1965. Distributed by Mack Publishing Co., Easton, Pa. xliv + 618 pp. 15 × 23 cm. Price $10 (Domestic and Foreign).

The twelfth edition of the "National Formulary" represents an innovation in the history of the N.F. For the first time, inclusion of drugs and medicinal chemicals is based solely upon therapeutic merit. Formerly, the extent of use of a particular item was the primary basis of acceptance.

The 783 monographs, 248 of which are new admissions, cover a wide range of therapeutic classifications, and include many new drug entities as well as those whose value has been recognized for some time. In addition, the monographs, including many of those retained from previous editions, incorporate the latest improvements in analytical procedures which utilize recent technical and instrumental developments. These newer techniques make possible an important addition to the official specifications of certain tablets—a test for the uniformity of composition between individual units of the prepared dosage form. This new standard of formulation requires that assays be run on single tablets.

The value of N.F. XII as a reference is enhanced by the inclusion of tables of approximate and exact apothecary and metric equivalents, the latest (1961) table of atomic weights, thermometric equivalents in centigrade (Celsius) and Fahrenheit degrees, an alcoholometric table, a comprehensive synopsis of the federal regulations governing narcotic drugs, and a thorough index.

N.F. XII will be official from September 1, 1965.

NOTICES

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