by Oddo[4] they were forced to revise their conclusions. Hess observed that no ethane was evolved until the reaction mixture (which consisted of *N*-methylpyrrole, ethylmagnesium bromide, and acid halide) was decomposed with water.[5] To explain this phenomenon and the acylation which took place, Hess invoked the existence of an unstable tertiary amine-Grignard reagent complex which somehow reacts with the acid chloride only in the presence of water to form the 2-acyl-1-methylpyrrole and ethane.[5]

Our interest in pyrrole chemistry attracted our attention to the somewhat labored interpretation of this reaction.[5,6] The fact that carbonation[3,5] of the mixture of *N*-methylpyrrole and ethylmagnesium bromide does not result in the formation of *N*-methylpyrrole carboxylic acid[7] and the observation[5] that *ethane is not evolved until the mixture is decomposed with water* suggested that the reaction was not due to interaction of *N*-methylpyrrole with the Grignard reagent but that the 2-acyl-*N*-methylpyrrole was formed as the result of a Friedel-Crafts type acylation catalyzed by magnesium bromide, the latter arising out of equilibrium (2).[8]

$$2CH_3CH_2MgBr \rightleftharpoons (CH_3CH_2)_2Mg + MgBr_2 \quad (2)$$

Indeed, when a mixture of *N*-methylpyrrole and magnesium bromide in ether was treated with acetyl chloride a vigorous reaction ensued and 2-acetyl-*N*-methylpyrrole was isolated in about the same yield as when acetyl chloride was added to a mixture of *N*-methylpyrrole and ethylmagnesium bromide under the conditions of Hess and Wissing.[3] No acylation was observed when ether solutions of *N*-methylpyrrole and acetyl chloride were mixed in the absence of magnesium bromide or Grignard reagent.

It is considered that these experiments fully substantiate the hypothesis that the reaction of the so-called *N*-methylpyrrole Grignard reagent with acid chlorides is in reality an acylation of *N*-methylpyrrole catalyzed by magnesium bromide.[9]

(4) B. Oddo, *Ber.*, **47**, (1914). See also F. Runge, *Organometallverbindungen*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1932, p. 223.

(5) K. Hess, *Ber.*, **48**, 1969 (1915).

(6) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., N. Y., 1954, p. 80.

(7) Two of the illustrations given on p. 80 of ref. 6 (the reaction of the so-called *N*-methylpyrrole Grignard reagent with ethyl chloroformate and halogen) represent work not actually recorded in the literature.

(8) The author is indebted to Professor A. C. Cope who pointed out this possibility at a symposium "The Chemistry of High Nitrogen Compounds," sponsored by the Office of Ordnance Research, U. S. Army, and held at Duke University, March 28–29, 1956.

(9) A recent paper by H. J. Anderson, *Can. J. Chem.*, **35**, 20 (1957), has demonstrated that boron trifluoride etherate is also a useful acylating catalyst for *N*-methylpyrrole.

EXPERIMENTAL

To a solution of 8 g. (0.1 mole) of *N*-methylpyrrole in 25 ml. of anhydrous ether was added 10 ml. of a solution of magnesium bromide in ether.[10] There was no evidence of a reaction. Addition of 8 g. of acetyl chloride in 20 ml. of chilled ether to the ice-cold mixture resulted in a vigorous reaction and immediate separation of a yellow precipitate. The product was decomposed with ice water and steam-distilled. The distillate was neutralized with sodium carbonate and extracted thoroughly with ether. The ether was dried and distilled giving 3.8 g. (31%) of a fraction boiling at 85–95° (22 mm.). Redistillation gave 3.2 g. of 2-acetyl-1-methylpyrrole, b.p. 88–93° (22 mm.), lit. 75–76° (15 mm.),[3] 88–91° (21 mm.).[9]

Reaction of *N*-methylpyrrole with ethylmagnesium bromide and acetyl chloride[3] gave a 25% yield of redistilled 2-acetyl-1-methylpyrrole.

A solution of 4 g. of *N*-methylpyrrole in 15 ml. of cold anhydrous ether was mixed with 4 g. of acetyl chloride in 15 ml. of cold anhydrous ether. There was no evidence of a reaction. Upon decomposition with ice water and working up in the usual manner, there was recovered 3.3 g. of *N*-methylpyrrole.

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(10) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

Preparation of 3-Dehydroreserpic Acid Lactone and Its Conversion to Reserpic Acid Lactone

EUGENE FARKAS, EDWARD R. LAVAGNINO, AND RICHARD T. RAPALA

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The reaction of the yohimbine alkaloids with mercuric acetate has been summarized recently by Weisenborn[1] and Wenkert.[2] Concurrently the authors had also studied and utilized this reaction to obtain compounds of this class with a double bond in the 3:4 position. It was hoped that reduction of such dehydro derivatives would afford the naturally occurring epiallo bases. The present paper describes the results of this study.

The dehydrogenation proceeded normally by removal of two hydrogens in the case of yohimbane, yohimbine, and isoreserpine, giving good agreement with published results.[1,2] Similarly, dehydrogenation occurred with reserpine, deserpidine, reserpic acid lactone, and isoreserpic acid lactone while heating at reflux in 10% acetic acid. Contrary to the published work,[1] compounds in the epiallo series were dehydrogenated under these slightly more vigorous conditions. A possible explanation for this discrepancy can be found in the

(1) F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.*, **78**, 2022 (1956).

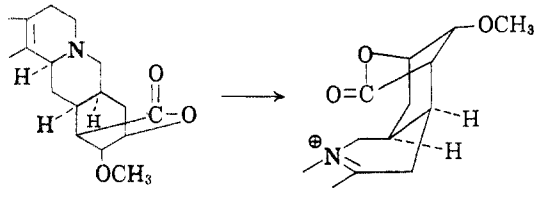
(2) E. Wenkert and D. K. Roychaudhuri, *J. Org. Chem.*, **21**, 1315 (1956).

observed partial epimerization at C_3 of isoreserpic acid lactone while heating in the same solvent.

Hydrogenation of $\Delta^3(^4)$-dehydroyohimbine and reserpine using Adams' catalyst in either neutral or acetic acid solution furnished yohimbine and isoreserpine, respectively, under all conditions. Furthermore, reduction with sodium borohydride readily gave the same products.

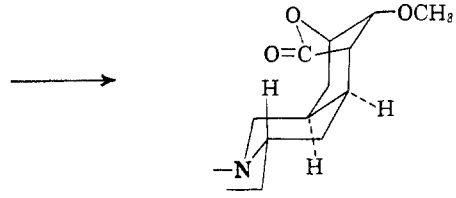
The dehydrogenation of the 3-iso and 3-normal reserpic acid lactones never went to completion, and although the salts obtained in these studies were consistently gelatinous, a flavianate salt was finally crystallized and characterized. The gelatinous chloride salt of the dehydrolactone, however, upon reduction with sodium borohydride, gave as the sole product reserpic acid lactone.[3] Thus, another route was available for proceeding from the isoreserpine series to the normal series. A small amount of the reserpic acid lactone could also be obtained by liberating the free base from the impure dehydro salt. This material was present because of the difficulty of purification of the gelatinous chloride salt. The purity of the dehydro-11-methoxy indole compounds was determined by measurement of the intense ultraviolet absorption near 285 mμ.

A possible reason for the hydrogen addition from the more hindered top side of the molecule (II) can be attributed to coordination of the borohydride anion with the carbonyl oxygen of the lactone and subsequent attack of the hydride anion from the top.[4] Molecular models confirm the possibility for this complex formation. Another explanation would necessitate a ready epimerization at C_3 of the hydrogenation product under the slight alkaline conditions of the reduction. The latter possibility was eliminated by recovery of the starting isoreserpic acid lactone (I) after treatment under the same reaction conditions.



I

II



III

(3) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *J. Am. Chem. Soc.*, **78**, 2023 (1956).

(4) This possibility was first suggested by Dr. R. B. Turner of The Rice Institute during a discussion of this problem.

EXPERIMENTAL[5]

Mercuric acetate dehydrogenation. Using a modification of Leonard's procedure[6] in a small flask equipped with a condenser and nitrogen inlet tube was placed 0.5 g. of isoreserpic acid lactone, 0.5 g. of mercuric acetate, and 30 ml. of 10% acetic acid solution. The solution was heated at reflux at about 95° for 14 hr. at which time some solid had separated, and the solution had darkened. Hydrogen sulfide was bubbled through the solution to remove any starting reagent, and the mixture was filtered. The filtrate was treated in several ways depending on the purpose of the succeeding experiments.

A. When further synthetic work was contemplated, the chloride was prepared by adding 5 ml. of concentrated hydrochloric acid and evaporating to dryness under vacuum. The residue containing some sulfide salts was recrystallized to give the gelatinous dehydrolactone chloride in 70% yield as determined by ultraviolet measurements. Similar results were obtained using reserpic acid lactone as the starting material.

B. The same flavianate was obtained from both reserpic acid and isoreserpic acid lactone after dehydrogenating by the above procedure. The filtrate, after removing the sulfide salts, was concentrated to about 15 ml. under vacuum, and there was added 10 ml. of a 5% solution of flavianic acid in methanol. Several crops of material were obtained by concentration of the solution to give 0.41 g. of the yellow-orange dehydrolactone flavianate, m.p. 220–223° dec., λ_{max}^{EtOH} 384 mμ, log ϵ 4.45, λ_{max}^{Nujol} 5.66 μ.

Anal. Calcd. for $C_{32}H_{30}N_4SO_{12}$: C, 55.30; H, 4.37; N, 8.1. Found: C, 55.07, 55.04; H, 4.58, 4.60; N, 8.22.

Reserpic acid lactone flavianate. The lactone, 0.10 g., was dissolved in 4 ml. of reagent methanol, and 4 ml. of a 5% solution of flavianic acid in methanol was added. After standing for 2 hr. the solution was concentrated to effect crystallization, giving on cooling 0.04 g. which on recrystallization had m.p. 230–232° dec. The ultraviolet spectrum did not show the same intense absorption as the dehydro compound.

Anal. Calcd. for $C_{32}H_{32}N_4SO_{12}$: C, 55.17; H, 4.63. Found: C, 54.72; H, 4.95.

Reduction of dehydroreserpic acid lactone with sodium borohydride. Because of the difficulty encountered in obtaining an anhydrous crystalline salt of the dehydro compound (which would not give a complex reaction with the borohydride reagent) the amorphous vacuum-dried chloride salt was used. The crude material, 0.25 g., which by ultraviolet measurements was at least 34% dehydrolactone and 10–15% starting lactone was dissolved in 30 ml. of reagent methanol.

A. To one half of the solution was added an excess of reagent sodium borohydride (0.1 g.) and the solution was kept at room temperature for 1 hr. After the usual work-up, the residue was recrystallized from acetone to give 0.034 g. of reserpic acid lactone, m.p. 285–288°, identical in every respect with an authentic sample. During a large number of reductions of the dehydrolactone in various degrees of purity no isoreserpic acid lactone could be found, thus indicating the stereospecificity of the method.

B. In contrast, direct liberation of the material was undertaken by basifying the remaining 15 ml. of solution with dilute ammonium hydroxide. After extraction with chloroform and the usual work-up the material was recrystallized from acetone to give only 0.014 g. of the lactone, m.p. 282–285°, once again identical in all respects with an authentic sample.

(5) Melting points were determined on the Fisher-Johns block.

(6) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 442 (1955).

Acknowledgment. The authors are grateful to Dr. H. Boaz, P. Landis, and L. Howard for the physical chemical data and G. M. Maciak, W. L. Brown, H. L. Hunter, and Gloria Beckmann for the microanalyses.

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Pyridineamidoximes

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In a recent publication,[1] Buu-Hoï, *et al.* reported that the 5-chloro-, 3,5-dichloro-, 5-bromo- and 5-iodo-salicylamidoximes inhibited the *in vitro* growth of *Mycobacterium tuberculosis* $H_{37}Rv$ at a concentration of the order of one microgram per milliliter. In view of the above findings, an investigation of the amidoximes derived from the pyridine monocarboxylic acids was undertaken.

The pyridineamidoximes were prepared according to the procedure of Tiemann and Krüger,[2] which involves the heating of the appropriate cyanopyridine at 80–85° with an aqueous solution of hydroxylamine. In the case of 3-pyridineamidoxime, the reaction was carried out in a sealed tube at 70°.[3] If the cyanopyridine was not soluble in water, as was the case with 2-cyanopyridine, sufficient ethyl alcohol was added to effect solution.

The pyridineamidoximes reported here were tested for *in vitro* tuberculostatic activity but were found to be inactive.

EXPERIMENTAL[4,5]

2-Pyridineamidoxime. A solution of 2.1 g. (0.030 mole) of hydroxylamine hydrochloride and 1.9 g. (0.015 mole) of sodium carbonate monohydrate in 10 ml. of water was heated to 60°. Three grams (0.029 mole) of 2-cyanopyridine was added in one portion, followed by sufficient ethyl alcohol (approximately 7 ml.) to dissolve the 2-cyanopyridine. The temperature of the mixture was raised to 85° and maintained for 2 hr. The alcohol was removed under reduced pressure and a tan oil separated from solution. On cooling to 0°, the oil solidified. The crystalline solid was filtered, washed twice with 10 ml. of ice-cold water, and dried in a vacuum desiccator over calcium chloride. The crude product (3.9 g.; 98%) melted at 114–116°. A sample recrystallized from water and dried *in vacuo* at 110° melted at 115.5–116°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.5; H, 5.1; N, 30.6. Found: C, 52.9; H, 5.0; N, 30.4.

3-Pyridineamidoxime. Prepared according to the procedure of Michaelis[3] in 70% yield, m.p. 127.5–128°.

4-Pyridineamidoxime. A solution of 2.1 g. (0.030 mole) of hydroxylamine hydrochloride and 1.9 g. (0.015 mole) of sodium carbonate monohydrate in 10 ml. of water was heated to 60°. Three grams (0.029 mole) of 4-cyanopyridine was added in one portion. An exothermic reaction took place causing the temperature to rise to 75°. Almost immediately a mass of colorless crystals separated from solution. Heating was continued at 80° for 0.5 hr. to complete the reaction. The suspension was cooled to 0°, filtered and dried in a vacuum desiccator over calcium chloride. The crude product (3.6. g.; 90%) melted at 175–177°. Recrystallization from ethyl alcohol gave colorless needles, m.p. 178–179°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.5; H, 5.1; N, 30.6. Found: C, 52.9; H, 5.1; N, 30.4.

Acknowledgment. The author wishes to thank Irene Melvin for performing the *in vitro* testing of compounds reported in this paper.

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(1) N. P. Buu-Hoï, M. Welsch, N. D. Xuong, and K. V. Thang, *Experientia*, **10**, 169 (1954).
(2) F. Tiemann and P. Krüger, *Ber.*, **17**, 1685 (1884).
(3) L. Michaelis, *Ber.*, **24**, 3439 (1891).
(4) All melting points are uncorrected.
(5) Carbon and hydrogen analyses by Schwarzkopf Microanalytical Laboratory.

Kinetics of the Thermal Isomerization of 2-*tert*-Butyl-3-Phenyloxazirane

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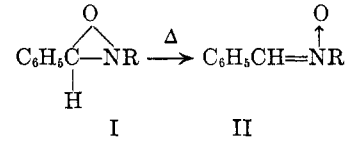
The observation[1] that 2-*tert.*-alkyl-3-phenyloxaziranes (I) isomerize on heating to the corresponding nitrones (II) and the novelty of the oxazirane ring system prompted the immediate investigation



I II

R = *tert*-alkyl

of the kinetices of this reaction. This kinetic study was primarily designed to determine the enthalpy and entropy of activation for the rearrangement of 2-*tert.*-butyl-3-phenyloxazirane, III, in diethyleneglycol diethyl ether (diethyl carbitol) solvent over a 40° temperature range.

Preliminary experiments showed that the rearrangement of III to *N-tert.*-butyl benzaldoxime, IV, proceeded quantitatively in the 60–100° temperature range and that the ultraviolet absorption spectra of these two materials were sufficiently different in acetonitrile to afford an analytical method for IV in the presence of III. The nitrone (IV) has an extinction coefficient of 1.68×10^4 at λ_{max} 298 mμ while III has an extinction coefficient of only 92 at this same wave length.

The isomerization of III to IV was carried out in diethyl carbitol solvent at 60, 85, and 100° and the

(1) W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956).