SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF SOME STEROIDAL AMINES AND AMIDES

(Order No. 66-9305)

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University of Maryland, 1966

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There are many useful antibiotics available for combating infectious disease. However, the usefulness of these drugs is limited by side effects, the development of resistant strains, problems in absorption, narrow spectrums of activity, lack of stability, etc. There still exists a need for improved antibacterial agents and an even greater need for a good, wide-spectrum, and non-toxic antifungal agent.

Numerous reports of steroids with some antimicrobial activity have appeared in the literature. Earlier reports from our laboratory have described the preparation and antimicrobial screening of azasteroids.

The present study deals with the synthesis and antimicrobial screening of various novel azasteroids. The synthetic section of this work describes the preparation of open and closed A and B-ring steroidal amines and amides.

4-Cholesten-3-one was prepared from cholesterol by Oppenauer oxidation. 3,5-Seco-4-norcholestan-5-on-3-oic acid (XLIV) was obtained by ozonolysis of 4-cholesten-3-one.

Two methods were used to prepare 4-(γ-hydroxypropyl)-4-aza-5-cholesten-3-one (XLV). In method A the keto acid (XLIV) was allowed to react with 1-amino-3-propanol to obtain XLV. In the alternate method B treatment of 4-oxa-5-cholestan-3-one (XLI) with 1-amino-3-propanol gave N-(γ-hydroxypropyl)-3,5-seco-4-norcholestan-5-on-3-amide (XLII) which was then refluxed in acetic acid and the resulting acetate ester hydrolyzed to give XLV.

The enamine lactam (XLV) was reduced in acetic acid over platinum at 100° and 250 p.s.i. to yield, after hydrolysis of the resulting acetate esters, 4-(γ-hydroxypropyl)-4-aza-5α-cholestan-3-one (XLVI) and 4-(γ-hydroxypropyl)-4-aza-5α-cholestane (XLIX). When XLV was reduced in acetic acid over platinum at room temperature and 200 p.s.i. a single product, XLVI, was obtained. Lithium aluminum hydride reduction of XLVI gave XLIX.

The reaction of 4-oxa-5α-cholestan-3-one (L) with ethylamine, 1-amino-3-propanol, hexahydrobenzylamine, and phenylethylamine yielded N-ethyl-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide (LI), 5β-hydroxy-N-(γ-hydroxypropyl)-3,5-seco-4-nor-3-cholestanamide (LII), N-hexahydrobenzyl-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide (LIII), and 5β-hydroxy-N-phenylethyl-3,5-seco-4-nor-3-cholestanamide (LIV) respectively.

The N-ethyl derivative (LI) was reduced with lithium aluminum hydride to obtain 3-ethylamino-5β-hydroxy-3,5-seco-4-norcholestane (LV).

Treatment of XLIV in a Clemmensen reduction gave 3,5-seco-4-norcholestan-3-oic acid (LVI). This acid (LVI) was then treated with thionyl chloride and the resulting acid chloride (LVII) allowed to react with ethylamine to obtain N-ethyl-3,5-seco-4-nor-3-cholestanamide (LVIII). Lithium aluminum hydride reduction of LVIII gave 3-ethylamino-3,5-seco-4-norcholestane (LIX). Treatment of LIX with hydrogen chloride gave 3-ethylamino-3,5-seco-4-norcholestane hydrochloride (LX).

Reaction of 3β-hydroxy-17a-oxa-D-homo-5α-androstan-17-one (LXI) with methylamine and hexahydrobenzylamine yielded 3β,13α-dihydroxy-N-methyl-13,17-seco-17-androstanamide (LXII) and N-hexahydrobenzyl-3β,13α-dihydroxy-13,17-seco-17-androstanamide (LXIII). The attempted preparation of N-benzyl-3β,13α-dihydroxy-13,17-seco-17-androstanamide (LXIV) and N-cyclohexyl-3β,13α-dihydroxy-13,17-seco-17-androstanamide (LXV) by treating LXI with benzylamine and cyclohexylamine failed. Lithium aluminum hydride reduction of the N-methyl amide (LXII) gave 3β,13α-dihydroxy-17-methylamino-13,17-seco-androstane (LXVI). Attempts to prepare a picrate derivative of LXVI were unsuccessful.

Treatment of 16α-bromo-3β-hydroxy-5-androsten-17-one (LXVII) with ethylenediamine gave 1',2',5',6'-tetrahydropyrazino[b-16,17]-3β-hydroxy-androst-5,16-diene (LXVIII).

The attempted synthesis of quinoxalino[b-17,16]-3β-hydroxy-androst-5-ene (LXX) by treating LXVII with o-phenylenediamine failed. Treatment of 16-oximino-androst-5-en-3β-ol-17-one (LXXI) with o-phenylenediamine in an attempt to prepare LXX also was unsuccessful. The attempt to synthesize 16β-anilino-5-androsten-17-on-3β-ol (LXIX) by treating LXVII with aniline failed.

An attempt to prepare the ring D-lactone (LXI) by treating 3β-hydroxy-5α-androstan-17-one (LXXII) with m-chloroperbenzoic acid failed as did the attempt to synthesize indolo-[b-7,6]-5α-cholest-6-en-3β-ol-3-acetate (LXXIV) by treating 7-oxo-5α-cholestan-3β-ol-3-acetate (LXXIII) with phenylhydrazine.

The amines LV,LX, and XLIX were found to be inhibitory to the gram-positive organism Gaffkya tetragena. However, only LV and XLIX were active against the yeast Candida albicans. Microfilm $3.00; Xerography $4.00. 75 pages.

SYNTHESIS OF ANALOGS OF IBOGAINE

(Order No. 66-9308)

John David Warthen, Jr., Ph.D.
University of Maryland, 1966

Director: Francis M. Miller

Ibogaine, isolated from Tabernanthe iboga Baillon, is an indole alkaloid with central stimulating properties and weak anticonvulsant properties. The most fascinating effect of this alkaloid seems to be an anxiety type response in normal subjects and an activation of psychotic processes in schizophrenic subjects.

Since ibogaine possessed an isoquinuclidine moiety fused to a seven-membered ring, the preparation of analogs of this alkaloid posed an interesting synthetic problem. These analogs were also synthesized with the hope that they would have some pharmacological action similar to or more specific than the parent alkaloid.

An attempt was made to alkylate 2-azabicyclo[2.2.2]octan-3-one with 3-(2'-bromoethyl)-indole to yield 2-[2'-(3"-indolyl)-ethyl]-2-azabicyclo[2.2.2]octan-3-one, but without complete success. A mixture of isomers, which could not be separated, were the result of this reaction. Attention was then drawn to the alkylation of 2-azabicyclo[2.2.2]octan-3-one with 3-indoleglyoxylyl chloride. The resulting product, 2-[2'-(3"-indolyl)-glyoxylyl]-2-azabicyclo[2.2.2]octan-3-one, was reduced with lithium aluminum hydride to yield 2-[2'-(3"-indolyl)ethyl]-2-azabicyclo[2.2.2]octane. The picrate salt of this reduced product was prepared for characterization. Following the same reaction sequences as above, the 5-methoxyindole derivatives also were synthesized.

An attempt was made to synthesize analogs of ibogaine with the isoquinuclidine system in the α-position of an indole nucleus. 2-Acetamido-5-carbethoxyacetophenone was prepared for use as a starting product by ozonization of ethyl 2,3-dimethylindole-5-carboxylate and hydrolysis of the resulting ozonide, ethyl 2,5-dimethyl-2,5-epoxy-3,4,1-benzodioxazepine-7-carboxylate. This acetophenone derivative was selectively hydrolyzed to yield 2-amino-5-carboxyacetophenone and

2-amino-5-carbethoxyacetophenone. The phenylhydrazones of these three acetophenone derivatives were synthesized and subjected to the Fischer indole synthesis.

Attempted synthesis of 2-(2'-acetamido-5'-carbethoxyphenyl)-indole by cyclization of 2-acetamido-5-carbethoxyacetophenone phenylhydrazone resulted in the formation of ethyl 6-methyl-11H-indolo[3,2-c]quinoline-2-carboxylate. Cyclization of 2-amino-5-carboxyacetophenone phenylhydrazone yielded 2-(2'-amino-5'-carboxyphenyl)-indole. Attempted synthesis of 2-(2'-amino-5'-carbethoxyphenyl)-indole by cyclization of 2-amino-5-carbethoxyacetophenone phenylhydrazone in the presence of acetone resulted in the preparation of ethyl 6,6-dimethyl-5H-indolo[3,2-c]quinoline-2-carboxylate.

Microfilm $3.00; Xerography $3.00. 55 pages.

CHEMISTRY, PHYSICAL

TRANSIENT POTENTIALS

(Order No. 66-9878)

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Chairman: Henry Eyring

The faces of gold and silver electrodes were scraped with an air turbine-to-pulley operated drill in N_2-saturated solutions of various salts. The open circuit transient potentials showed peak potentials which varied in a manner qualitatively similar to the variance of zero charge potential (z.c.p.) for the metal in those solutions. A trend of relative adsorbabilities is established for anions on gold: $I^- > Br^- > OH^- > Cl^- > ClO_4^- = SO_4^= > F^-$ and on silver: $Br^- > Cl^- > OH^- > SO_4^= > ClO_4^-$. The pH dependence of the peak potentials is explained by the trends given and by competing Faradaic reactions. The effects of reactions are shown and used to predict the scraping speed. Good agreement was found with the stroboscopically determined value of 14,500 r.p.m.

The peak potential was observed to be insensitive to changes in the salt by use of different small, highly hydrated cations. But for rubidium, caesium, and tetraalkylammonium compounds a more cathodic peak potential was found with increasing cation size. It is proposed that metal-molecule complexes are formed; the molecule is adsorbed as a unit with the negative end towards the metal. The coverage of complexes is estimated by considering the species as additional potential determining dipoles.

A theoretical treatment is made to determine the free energy of adsorption of Cl^-, Br^-, OH^-, and F^- as a function of their equilibrium separation from the mercury, silver, and gold electrodes. An electrostatic approach with contributions from dehydrating the anions upon adsorption is used to show the inversion of adsorbabilities for Cl^- and OH^- on silver and gold.

A study was made of the z.c.p. of mercury streamed in solutions of tetraalkylammonium compounds at different activities. The z.c.p. became more anodic with larger cations indicating increasing cation adsorption. However, a strong dependence on anion was found. The results differed markedly from those of the capillary electrometer. It is proposed that in addition to relative affinities for adsorption, the relative rates of adsorption establish the potential determining ions.

Microfilm $3.00; Xerography $6.60. 137 pages.

THE CRYSTAL AND MOLECULAR STRUCTURE OF TETRAMETHYLBIPHOSPHINE-BIS(MONOBORANE).

(Order No. 66-10,535)

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Chairman: Professor Donohue

The crystal structure of the "lump" form of $P_2(CH_3)_4 \cdot 2B$ was determined by single crystal x-ray diffraction techniques. The unit cell was found to be monoclinic with the following dimensions: a = 6.78 ± 0.02 A, b = 11.64 ± 0.02 A, c = 20.41 ± 0.02 A, and $\beta = 95°$. The space group was found to be $P2_1$ with six molecules in the unit cell. A three dimensional Patterson function was used to obtain the coordinates of the phosphorus atoms and a three dimensional Fourier synthesis, phased on these atoms, was calculated to obtain the coordinates of the remaining non-hydrogen atoms. The refinement of the structure was carried out with a second three dimensional Fourier synthesis, followed by least squares treatment which ultimately included the coordinates and anisotropic thermal parameters of the non-hydrogen atoms. The hydrogen atom coordinates were calculated, and were then incorporated in the structure factor calculations, but were not treated as variables in the refinement. This investigation shows conclusively that crystals of the "lump" form of $P_2(CH_3)_4 \cdot 2BH_3$ contain three conformational isomers of the molecule in the ratio of 1:1:1. The P-P, P-C, and P-B bond lengths are 2.205 ± 0.004 A, 1.827 ± 0.010 A and 1.951 ± 0.021 A, respectively. These values correspond to single covalent bonds between these atoms. The P-C and P-B bond lengths are shorter than the sum of the covalent single bond radii due to the partial ionic character of the bonds. The valence angles about the phosphorus atoms are distorted slightly from the tetrahedral val Comparisons of the bond distances and angles in this compo were made with those in related substances.

Microfilm $3.00; Xerography $4.40. 81 pag

MATHEMATICAL THEORY OF ELECTROCHEMICAL DEMINERALIZATION IN FLOWING SYSTEMS

(Order No. 66-9566)

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The University of Oklahoma, 1966

Major Professor: George W. Murphy

A theory has been developed to mathematically describe explain the concentration changes occurring in a demineral tion cell containing porous carbon electrodes. Because of t complex nature of the carbon electrodes, the demineralizat cell is represented by a relatively simple model to facilitat the mathematical treatment. This model consists of a seri of solution compartments separated by permselective mem branes, the electrodes being represented by compartments fixed volume. Using this model an equation was derived wh fits the concentration-time curve for the effluent from the mineralization cell.

The theoretical equation contains three parameters wh can be determined by a fitting procedure. In principle the rameters can be expressed in terms of operating condition cell geometry and electrode characteristics.

The theoretical equation was tested against experiment

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