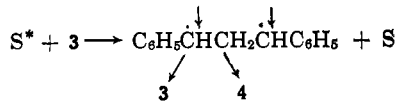
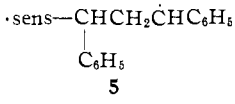
An obvious mechanism for the reaction involves energy transfer with breaking of the weak carbon–carbon bond connecting the two ring members which bear the phenyl substituents.



Mechanisms in which the sensitizers become permanently bonded to the substrates seem highly unlikely since biradicals such as **5** would be expected to cyclize rather than re-form the three-membered ring by elimination reactions.



Acknowledgment.—This study was supported by the National Science Foundation.

(5) This report is abstracted in part from the freshman honors report of this author.

(6) National Science Foundation Predoctoral Fellow, 1962–present.

(7) National Science Foundation Predoctoral Fellow, 1959–1963.

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RECEIVED MARCH 3, 1964

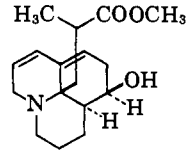
Synthesis of *Lycopodium* Alkaloids. I. A Synthetic Proof for the Structure of Lyconnotine

Sir:

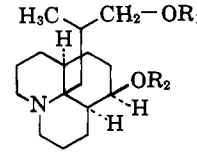
Recently, structure I was proposed[1] for lyconnotine, an alkaloid from *Lycopodium annotinum* L. We describe here a synthesis of the lyconnotine transformation products VI and VII, which firmly establishes the lyconnotine structure and provides an interesting route for the synthetic elaboration of other *Lycopodium* alkaloids.

Compounds VI and VII were obtained from lyconnotine in the following way. The alkaloid, m.p. 123°, was reduced with lithium aluminum hydride in ether and the resulting diol was hydrogenated with platinum in ethanol to give the diol II, m.p. 188–189°, infrared maxima ($CHCl_3$) 3600 and 3450 cm.$^{-1}$. *Anal.* Found: C, 72.27; H, 10.68; N, 5.27; O, 11.56. Its acetylation in acetic anhydride–pyridine yielded the diacetate III, infrared maximum (CCl_4) 1735 cm.$^{-1}$, n.m.r.[2] peaks at τ 5.0 (1H; broad singlet), 6.0 (2H's; octet, J_{AB} = 10.5 c.p.s., J_{AX} = 5.2 c.p.s., J_{BX} = 8.4 c.p.s.), and 7.96 (two acetate methyls, singlet), which on selective hydrolysis with potassium carbonate in aqueous methanol gave the monoacetate IV, infrared maxima (CCl_4) 3600 and 1735 cm.$^{-1}$, n.m.r. peaks at τ 5.07 (1H, broad singlet) and 7.95 (one acetate methyl, singlet). Treatment of the hydrochloride of IV with phosphorus tribromide in benzene, followed by a reduction of the resulting salt with zinc dust in acetic acid, gave the monoacetate V, infrared maximum (CCl_4) 1735 cm.$^{-1}$. Hydrolysis of V with potassium hydroxide yielded the alcohol VI, m.p. 157–158°, infrared maximum (CCl_4) 3640 cm.$^{-1}$, n.m.r. peaks at τ 6.2 (1H, broad singlet) and 8.95 (two methyl groups; doublet, J = 5.6 c.p.s.), mass spectrum peaks at m/e = 251 (molecular ion), 194 (very strong), 192, and 176 (strong), which in the form of its hydrochloride was oxidized with chromium trioxide in 90% acetic acid to give the ketone VII, infrared maximum (CCl_4) 1710 cm.$^{-1}$.

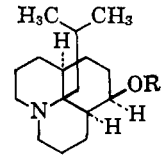
The stereochemistry of compounds I–VII follows from the lactonization of lyconnotine[1] and the fact that all the compounds show Bohlmann bands[3,4] in their infrared spectra.



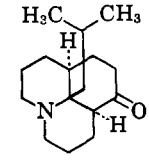
I



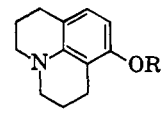
II, $R_1 = R_2 = H$
III, $R_1 = R_2 = CH_3CO$
IV, $R_1 = H$, $R_2 = CH_3CO$



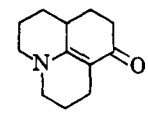
V, $R = CH_3CO$
VI, $R = H$



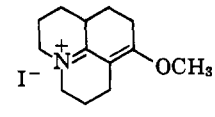
VII



VIII, $R = CH_3$
IX, $R = H$



X



XI

Compounds VI and VII were synthesized in the following way. Prolonged treatment of *m*-anisidine with boiling 1-bromo-3-chloropropane[5] gave a mixture of the methoxyjulolidine VIII and the hydroxyjulolidine IX, m.p. 135°, ultraviolet maxima 218 (4.35), 256 (3.74), and 299 mμ (3.43). *Anal.* Found: C, 75.02; H, 7.95; N, 7.51; O, 8.83. Phenol IX, isolated in a 30% yield, was reduced with Raney nickel at 140° and 55 atm. pressure to give a 40% yield of X, b.p. 156° at 0.5 mm., ultraviolet maximum 315 mμ (3.91), infrared maxima (CCl_4) 1625 and 1555 cm.$^{-1}$, analyzed as the picrate, m.p. 165–166°. *Anal.* Found: C, 51.42; H, 4.73; N, 12.92; O, 31.10. Treatment of X with boiling methyl iodide gave an 80% yield of the salt XI,[6] m.p.

(1) F. A. L. Anet, M. Z. Haq, N. H. Khan, W. A. Ayer, R. Hayatsu, S. Valverde-Lopez, P. Deslongchamps, W. Riess, M. Ternbah, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 751 (1964).

(2) All n.m.r. data were obtained at 60 Mc. with tetramethylsilane as internal standard.

(3) F. Bohlmann and C. Arndt, *Ber.*, **91**, 2167 (1958).

(4) Treatment of ketone VII with sodium methoxide gave a mixture of about equal amounts of VII and an epimer. This new ketone must be the *trans-cis* isomer, since it moves faster on alumina and its infrared spectrum shows no Bohlmann bands.

(5) For the synthesis of unsubstituted julolidine, see G. Pinkus, *Ber.*, **25**, 2798 (1892).

(6) For a comparable O-alkylation, see N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959).

112–114°, ultraviolet maxima, 218 (4.11) and 303 mμ (4.25), infrared maximum ($CHCl_3$) 1593 cm.$^{-1}$. *Anal.* Found: C, 46.22; H, 6.03; N, 4.33; O, 5.13; I, 38.13.

An ether suspension of XI was treated with an excess of isobutyllithium and the resulting enol ether was hydrolyzed with hydrochloric acid to give an 8% yield[7] of the racemic ketone VII, m.p. 44–45°, picrate m.p. 161–162°, identical (infrared spectrum, t.l.c.) with the lyconnotine degradation product.[8] Lithium aluminum hydride reduction of the synthetic ketone VII in ether gave a quantitative yield of the racemic alcohol VI, m.p. 134–135°, identical (infrared and n.m.r. spectra, t.l.c.) with the degradation product VI.

(7) Yields up to 35% were obtained in alkylations of XI with less bulky lithium compounds and Grignard reagents.

(8) No isomeric isobutyl ketone was found in the reaction mixture. Thus, both the alkylation and the enol ether hydrolysis are stereospecific.

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RECEIVED APRIL 13, 1964

BOOK REVIEWS

Medicinal Chemistry. Volume VI. Edited by E. E. CAMPAIGNE, Professor of Chemistry, Indiana University, and W. H. HARTUNG, Professor of Pharmaceutical Chemistry, Medical College of Virginia. John Wiley and Sons, Inc., 605 Third Ave., New York 16, N. Y. 1963. x + 356 pp. 15.5 × 23.5 cm. Price, $10.00.

The sixth volume of this serial publication contains three chapters: "Non-barbiturate Hypnotics" by Keith W. Wheeler, "Spinal Cord Depressant Drugs Derived from Polyhydroxy Alcohols" by Edward J. Pribyl, and "X-ray Contrast Media" by James O. Hoppe. It represents a continuing effort on the part of the Division of Medicinal Chemistry of the American Chemical Society to "provide comprehensive and systemic summaries of available data on the biological properties of substances already studied. The correlation of structure and activity in such summaries stimulates the visualization of new molecular structures and leads to the synthesis and testing of new compounds." This latest volume meets the objectives quoted from the preface to the series. The wisdom of the approach—the classic one of molecular modification—was amply demonstrated to lead to superior drugs during a 2-day symposium of the Division in New York last September. Nevertheless, one can not visualize how the approach will lead directly to truly novel chemical types of medicaments. For such creativity, the medicinal chemist must either continue to depend upon serendipity or look to a better understanding of biological phenomena upon which to build rationales.

The 245-page chapter by Wheeler represents a completion of the tabulation of hypnotics which began with the single chapter Volume IV on "Barbituric Acid Hypnotics" by Wilbur J. Doran. Dr. Wheeler has brought order out of confusion for the reader in regard to the difference between sedatives, hypnotics, and anesthetics. He has sensibly decided for the purposes of the review to treat all such substances as central nervous system depressants but to center attention for comparative purposes upon hypnotic activity. He defines a hypnotic as a drug which causes loss of the righting reflex in animals. A hypnotic dose has been reached when an animal placed on its back can no longer right itself.

Author Wheeler has done about all that could be expected of of him in view of the aims of the series of volumes. His labors will save the interested investigator much time and effort. Many well-known hypnotics, such as chloral hydrate, ethchlorvynol, ethinamate, glutethimide, and paraldehyde are listed. Of course, tables of hundreds of unsuccessful candidates, some of which may not have been adequately evaluated, fill the main part of the chapter.

Buried in Tables 15 and 16 is the infamous thalidomide (Contergan). Chemically known as α-(N-phthalimido)glutarimide, it should have been listed also in Table 2, "Other Clinically Tested Non-barbiturate Hypnotics." Thalidomide was synthesized in 1953 and introduced in Germany as a hypnotic in 1956. The author covers the literature through 1960. Although the unfortunate cases of phocomelia, or deformities of the limbs in infants, were not fully recognized as being associated with use of the drug by pregnant women until 1961, a strong case for addition in proof of such important facts might have been made since the volume was only recently printed.

No drug may prove to have had so much influence upon the pharmaceutical industry as might be seen in future practices of the Federal Drug Administration, yet, ironically, thalidomide was never released for sale in this country. It is difficult to see how regulations short of stopping the flow of all new drugs could have prevented the thalidomide tragedy, since animal tests do not reveal its cruel side effects. Yet the drug dramatically rescued Kefauver legislation from the trash can and placed it into stringent new regulations which may cut the flow of new medicaments to a trickle. Thalidomide remains as an ideal hypnotic except for use in pregnant women. But it will not become available because of the obvious risk in keeping it in the medicine cabinet.

The 44-page chapter on spinal cord depressants by Pribyl covers polyhydroxy alcohols and derivatives based upon the prototype mephenesin. In contrast to curariform agents which relax skeletal musculature by acting peripherally, mephenesin-like compounds act by depression of the spinal cord. Such drugs have afforded the greatest relief of spastic conditions. The search continues for compounds that might show greater specificity or longer duration of effect. Most of the tabulated substances were evaluated pharmacologically by measurement of the degree of depression of the central nervous system. Thus, structure–activity correlations are discussed in terms of relative depressant or paralyzing effects. Obviously, complete estimate of the value of a compound can not rest upon that basis. Such factors as acute toxicity, side effects, absorption, and solubility play important roles in final judgments.

Meprobamate (2-methyl-2-propyl-1,3-propanediol dicarbamate, Miltown or Equanil) referred to popularly as the tired businessman's tranquilizer and relaxant, of course, falls within the scope of the chapter, even though it is not, as mephenesin, used therapeutically as a valuable substitute for curare for relaxation of musculature in surgical procedures.

The author has failed at times to adhere to the accepted practice of lower case for nonproprietary drug names and capitalization for trade or proprietary names. For example, Myanesin is incorrectly represented in lower case on p. 247, while Metrazol, a proprietary name, is inconsistently represented (pp. 249, 253, 256, and 258).

Unlike the authors of the first and third chapters who refer the reader to the literature for chemical preparative procedures, Dr. Pribyl thoughtfully outlines more than three pages of general methods of preparation. After all, the title of the volume does include the word chemistry.

Although the author has appropriately covered his topic in accord with the title of the chapter, the reader may regret the omission of remaining chemical types of centrally acting skeletal muscle relaxants, *e.g.*, the benzoxazolinones represented by chlorzoxazone, especially since the group is a small one.

Sixty pages, with five references extending into the year 1961, cover the topic "X-ray Contrast Media," a rather specialized area of medicinal chemistry. While the usual objective of drug