brain and to bufotenin and its congeners which are centrally active indoles.[5]

A large number of derivatives of I (n = 2) were prepared by an adaptation of the method of Speeter and Anthony[6] and by condensation of indolylalkanoic acids with the required phenylpiperazines followed by reduction where $n > 2$. These compounds were examined in some detail biologically. Maximum CNS-depressant activity was observed when the methylene bridge contained two or three carbon atoms and the indole nucleus was substituted by 2-methyl and 5,6-dimethoxy groups (I, n = 2 or 3, R^1,R^2 = OCH_3, R^3 = CH_3). An *o*-methoxy substituent in the phenyl ring generally caused an increase in peripheral adrenolytic activity without a concomitant increase in central effects. Some of the relevant pharmacological properties of a few representative members are summarized in Table I. The values for chlorpromazine (CPZ) are included for reference.

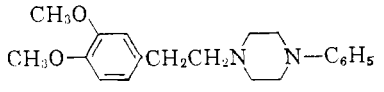
TABLE I

Test procedure[a]	II	III	IV	V	CPZ
Hexobarbital potentiation[b]	3.7	5.0	8.2	>128	4.4
Head withdrawal reflex[c]	6.5	>128	10.0	>128	8.0
Adrenolytic activity[d]	106	55	12.0	>800	44
Decrease in spontaneous activity[e]	0.56	3.7	7.1	45	4.7

[a] Results are expressed as ED_{50} values in mg./kg. p.o. except for adrenolytic data which are given as γ/kg. i.v. [b] D. W. Wylie, *Proc. Soc. Exp. Biol. Med.*, **98**, 716 (1956). [c] D. W. Wylie, *J. Pharmacol. Exp. Therap.*, **127**, 276 (1959); R. C. Rathbun, *et al.*, *ibid.*, **122**, 64A (1958). [d] F. P. Luduena, E. O'Malley and I. A. Oyen, *Arch. Intern. Pharmacodynamie*, **122**, 111 (1959). [e] L. S. Harris and F. C. Uhle, *J. Pharmacol. Exp. Therap.*, **132**, 251 (1961).

Although there was no quantitative correlation in this series between adrenolytic and central nervous system depressant activities (*cf.* II *vs.* IV),[7] compounds such as V which are essentially inactive as adrenolytic drugs are also relatively inactive in the CNS tests. Our observations tend to support the hypothesis[1,3] that tranquilizing activity is associated with peripheral adrenolytic action.

tem activity we started a parallel study in this series. Preliminary biological evaluation indicated that (i) was much less interesting than its indole counterpart. During the course of our work the Lilly



(i)

group (J. Mills, *et al.* Abstracts of the 132nd Meeting of the Amer. Chem. Soc., New York, N. Y., Sept. 8–13, 1957, p. 60, *et seq.*) generalized and developed Hiebel's original suggestion (ref. 1) and was able to show that a variety of chemically distinct adrenolytic agents can be converted to psychosedative drugs. One of these was (i). Mills, *et al.* seemed to focus their attention on modification of the 1,4-benzodioxanes, in particular, ethoxybutamoxane (2-dibutylaminomethyl-8-ethoxy-1,4-benzodioxane). Independently the area was explored by Bovet and his colleagues (see D. Bovet, *Gazz. chim. Ital.*, **89**, 196 (1959), and also by Boissier (J. R. Boissier, *et al.*, *Arch. Int. Pharmacodyn.*, **133**, 29 (1961)).

(5) E. Evarts, *Arch. Neurol. and Psychiat.*, **75**, 49 (1956); W. J. Turner and S. Merlis, *ibid.*, **81**, 121 (1959).

(6) N. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6209 (1954).

(7) This may be due to the differences in accessibility to the receptor sites in the central nervous system. The generic name for IV is solypertine.

Further studies with II (generic name, oxypertine) showed that low oral doses produced taming in untrained Rhesus monkeys while at higher doses sedation and catalepsy were observed. Unlike chlorpromazine, II did not potentiate the analgesic action of either morphine or meperidine. On the other hand, II like chlorpromazine, did act as a potent anti-emetic, and in rats did not release serotonin from either brain or heart. It did release norepinephrine from the heart[8]; so that II appears unique in that it can both release and block the action of norepinephrine.

Acknowledgement.—We wish to thank Miss L. Polak and J. MacAuliff for technical assistance.

(8) Private communication from Dr. S. Spector and Dr. A. Sjoerdsma of the National Heart Institute.

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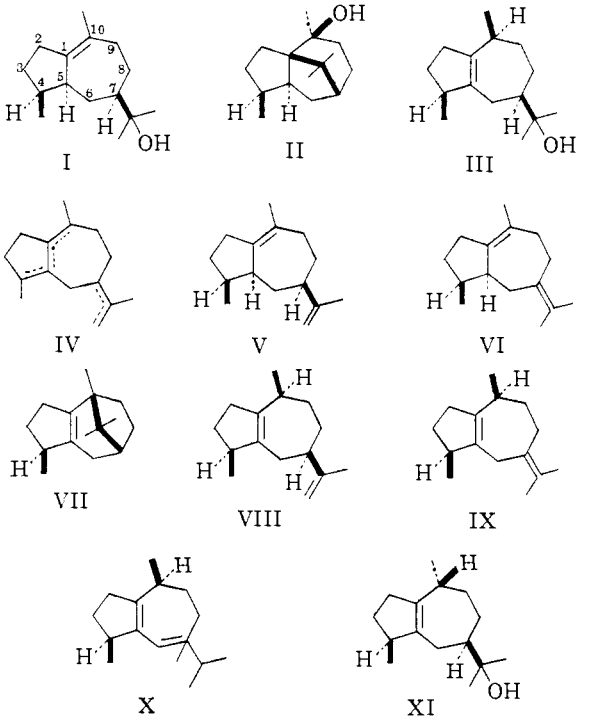
CONVERSION OF BULNESOL TO PATCHOULI ALCOHOL, GUAIOL, AND "δ-GUAIENE"[1]

Sir:

The simplest scheme for the biosynthesis of bulnesol[2] (I) from farnesyl pyrophosphate requires only two reactions, each involving formation of a ring. Because of the simplicity of this scheme and the ease with which bulnesol may be converted (on paper) by carbonium ion type reactions into patchouli alcohol[3] (II), guaiol[2,4] (III), "δ-guaiene"[5]



(1) Terpenoids. III.

(2) H. Minato, *Tetrahedron Letters*, **8**, 280 (1961); F. Šorm, L. Dolejš and A. Mironov, *Coll. Czech. Chem. Comm.*, **26**, 1015 (1961).

(3) G. Büchi, R. E. Eriksen and N. Wakabayashi, *J. Am. Chem. Soc.*, **83**, 927 (1961).

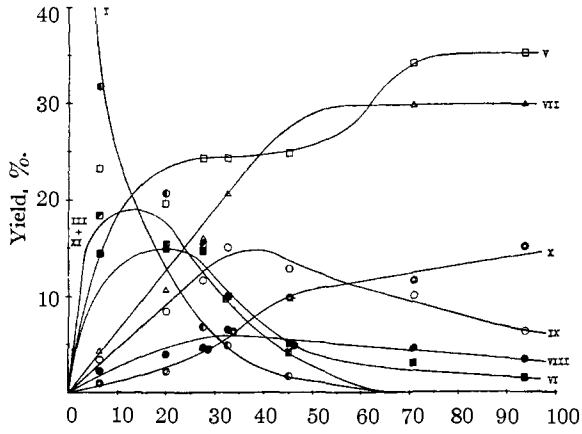


Fig. 1.[11]

(proposed to be (IV)) and α-chigadmarene[6] (proposed to have the constitution of (V)), bulnesol (I) is an attractive biogenetic precursor for these structurally related sesquiterpenoids. Of particular interest is the transannular reaction to yield patchouli alcohol (II), for which there is a laboratory precedent.[7]

We have tried to duplicate these proposed biosynthetic conversions of bulnesol (I) in the laboratory, without enzymes.

To get two bulnesenes by an unambigous route, bulnesyl acetate was pyrolyzed at 275°, giving α-bulnesene (V, 84%) and β-bulnesene (VI, 7%). α-Bulnesene (V, $[\alpha]^{25}D$ 0°) was not identical with α-chigadmarene[6] ($[\alpha]^{28}D$ −150°), but proved to be the same (infrared spectrum, refractive index, optical rotation) as the compound from patchouly oil called "δ-guaiene"[5,8] ($[\alpha]^{20}D$ + 0.3°). The finding that V occurs in the same plant as II lends some credence to the hypothesis that II is formed in nature from bulnesyl carbonium ion.

Bulnesol (I) was treated under a variety of conditions which should favor carbonium ion formation: When bulnesol (I) was refluxed with *p*-toluenesulfonyl chloride in 2,6-lutidine, a mixture of α- and β-bulnesenes (V, 31% and VI, 13%) was obtained. Bulnesol (I) was heated with alumina and pyridine,[9] yielding β-bulnesene (VI, 10%) and β-patchoulene[3] (VII, 60%), the latter identical (infrared, n.m.r., optical rotation, refractive index, vapor phase chromatographic retention time) with an authentic sample from the degradation of patchouli alcohol (II).[10] When bulnesol (I) in acetic acid was treated with a drop of sulfuric acid at room temperature, some double bond migrations were observed; the yields of the major products are shown in Fig. 1. α-Guaiene (VIII) and IX, which we now name β-guaiene, have been described previously[12]; γ-guaiene (X, λ_{max}^{EtOH} 256, ε 8900) and 10-epiguaiol (XI) are new compounds. All three guaienes from this reaction probably are mixtures of epimers at carbon 10.

Thus bulnesol (I) can be converted in the laboratory directly into guaiol (III) and "δ-guaiene" (V), and, since VII has been converted into II,[13] indirectly into patchouli alcohol (II).

A reaction similar to that shown in Fig. 1 was run in AcOD to gain information about double bond migrations during the reaction. The major components of samples withdrawn occasionally were analyzed by combustion (to give % deuterium incorporated) and by n.m.r. (to give information about the location of the deuterium). The guaiol (III) and 10-epiguaiol (XI) isolated after 14 hours contained slightly more than one deuterium each, located (as expected) almost exclusively at C_{10}, since in place of a doublet centered at 9.0 τ for the C_{10} methyl group in each undeuterated alcohol, a single peak at 9.0 τ was observed in each deuterated alcohol. Clearly, the configurations at C_4 and C_7 are largely unchanged in these conversions of I to III and XI. The β-patchoulene (VII) isolated after 14 hours contained 1.4 deuteriums, all but 0.3 of which were in methyl groups; undoubtedly most of the deuterium in this sample is in the *gem*-dimethyl group, and under these conditions the asymmetry at C_4 and C_7 is largely preserved in the I → VII reaction. These experiments, coupled with the demonstration that VII has the same configurations as II at C_4 and C_7,[13] confirm that bulnesol (I), patchouli alcohol (II) and guaiol (III) possess the same configurations at C_4 and C_7.[14]

(4) E. J. Eisenbraun, T. George, B. Riniker and C. Djerassi, *ibid.*, **82**, 3648 (1960); K. Takeda and H. Minato, *Tetrahedron Letters*, **22**, 33 (1960).

(5) F. Šorm, L. Dolejš, O. Knessl and J. Plíva, *Coll. Czech. Chem. Comm.*, **15**, 82 (1950).

(6) A. S. Rao, K. B. Dutt, S. Dev and P. C. Guha, *J. Indian Chem. Soc.*, **29**, 604, 620 (1952); the structure of α-chigadmarene is being reinvestigated (private communication with Dr. S. Dev).

(7) G. Le Ny, *Compt. rend.*, **251**, 1526 (1960).

(8) It is possible that "δ-guaiene" is the enantiomorph of V, but since an overwhelming majority of sesquiterpenoids have the configuration shown in V at their carbon corresponding to C_7 in I, this is quite unlikely.

(9) E. von Rudloff, *Canadian J. Chem.*, **39**, 1860 (1961).

(10) We are grateful to Dr. G. Büchi for authentic samples of II and VII.

(11) Yields were calculated from areas under vapor phase chromatography peaks; each component which was identified was characterized by n.m.r. and infrared. *III* and *XI* were not well resolved by vapor phase chromatography, and thus are included together; careful vapor phase chromatography of a sample of the mixture isolated after 14 hours indicated it to contain nearly equal amounts of III and XI.

(12) K. Takeda, H. Minato and S. Nosaka, *Tetrahedron*, **13**, 308 (1961).

(13) Private communication with Dr. G. Büchi and Mr. W. MacLeod.

(14) We gratefully acknowledge the financial support of the Public Health Service (RG-7689).

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MAGNETIC ANISOTROPY OF FERROCENE

Sir:

The anisotropy measurements were made by the method of maximum torque originally developed by Krishnan, in which a number of modifications, including those suggested by Gordon,[1] were inincluded. The torsion fibers used in the measurements on the ferrocene crystals were calibrated by means of the known principal susceptibilities and crystal structure of naphthalene and acenaphthene. The field strength of the electromagnet ranged from about 4,000 to 9,000 oersteds.

(1) D. A. Gordon, *Rev. Sci. Instruments*, **29**, 929 (1958).