by epimerization of reserpine in refluxing acetic anhydride, contained less than 0·01% reserpine as indicated by paper chromatography. Refluxing 3-isoreserpine obtained in this manner in acetic acid for 24 h gave an equilibrium mixture of the C-3 epimers from which a 15% yield of reserpine could be obtained. The separation of the two alkaloids from the acetic acid equilibrium mixture was easily accomplished by treatment with limited amounts of ethyl acetate at room temperature. 3-Isoreserpine is readily soluble while only moderate amounts of reserpine dissolve. An additional 5% of reserpine can be separated from the ethyl acetate soluble fraction by chromatography on a cellulose column impregnated with formamide using benzene-cyclohexane (1:1) as the eluting agent. Because of the stability of both reserpine and 3-isoreserpine in refluxing acetic acid, especially in the absence of oxygen, and the ease of separation of the two alkaloids, the unepimerized 3-isoreserpine can be recycled to enhance the overall conversion. The reserpine obtained by this process (m. p. 265–266°, $[\alpha]_D^{26°}$–118° (chloroform); *Analysis*, Calculated for $C_{33}H_{40}N_2O_9$: C 65·11%; H 6·62%; N 4·60%; Found: C 65·29%; H 6·75%; N 4·63%) showed an identical infrared absorption spectrum and identical pharmacological activity to natural reserpine.

A 3-isoreserpine derivative has been transformed into a compound of the reserpine series by a second method. We have already reported[5] that 3-isoreserpic acid forms an O-acetyl amino acid on treatment with acetic anhydride and pyridine at room temperature, indicating its reluctance to form a lactone. Reserpic acid lactone does not epimerize at C-3 and rings *C*, *D*, and *E* must thus be locked in the *trans-anti-cis* conformation. 3-Isoreserpic acid was therefore subjected to conditions favoring acid catalyzed isomerization and subsequent lactonization. The epimerization equilibrium can thereby be displaced in the desired direction. Treatment of isoreserpic acid hydrochloride (m.p. 277–279°C [dec.]; *Analysis*, Calculated for $C_{22}H_{28}O_5N_2 \cdot HCl \cdot \frac{1}{2}H_2O$; C59·24%; H6·78%; N6·28%; Found: C59·13%; H6·85%; N6·28%) obtained by potassium hydroxide-methanol hydrolysis of methyl isoreserpate (m.p. 220°C)[4] with refluxing acetic anhydride containing a small amount of acetic acid gave reserpic acid lactone (m.p. 310–314°C). The material was identified by comparison of melting point, mixed melting point and infrared spectrum with a sample of reserpic acid lactone.[6] Similarly this transformation could be effected in better yield in refluxing collidine containing *p*-toluenesulfonic acid and phosphorus pentoxide. Reserpic acid lactone has been converted previously to reserpine in these laboratories[6].

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Research Laboratories, CIBA Pharmaceutical Products Inc., Summit, New Jersey, April 12, 1956.

Zusammenfassung

Es konnte gezeigt werden, dass das Gleichgewichtsgemisch Reserpin/3-Isoreserpin, das beim Kochen in Essigsäure erhalten wird, beträchtliche Mengen Reserpin enthält. Durch Abtrennung der beiden Komponenten dieses Systems ist die Umwandlung von 3-Isoreserpin in Reserpin ermöglicht.

3-Isoreserpsäure-hydrochlorid erfuhr in Acetanhydrid eine Isomerisation mit anschliessender Bildung des Lactons der Reserpsäure.

[5] C. F. HUEBNER, H. B. MACPHILLAMY, E. SCHLITTLER, and A. F. ST. ANDRÉ, Exper. *11*, 303 (1955).

[6] L. DORFMAN, A. FURLENMEIER, C. F. HUEBNER, R. LUCAS, H. B. MACPHILLAMY, J. M. MUELLER, E. SCHLITTLER, R. SCHWYZER, and A. F. ST. ANDRÉ, Helv. chim. Acta *37*, 59 (1953).

Rauwolfia Alkaloids XXVI. Stereochemistry at C-17

Reserpine and deserpidine have been formulated with the C-17 methoxyl *trans* to the groups at C-16 and C-18 (α-oriented in the absolute sense)[1], as best evidenced by the postulated neighboring group participation of the C-17 methoxyl in the internal quaternization of methyl reserpate tosylate[2]. This complex reaction occurs only under the comparatively rigorous conditions of refluxing collidine or dimethylformamide. In addition to the 30% yield of the inner quaternary salt and a smaller quantity of methyl anhydroreserpate, at least two other as yet unidentified crystalline products are formed. Therefore, corroboration for the assigned configuration of the C-17 methoxyl is desirable. This confirmation comes from two independent lines of evidence.

The previously reported product obtained from 3-*epi*-α-yohimbine in 70% yield by the action of *p*-toluenesulfonyl chloride in pyridine at 5°[3] has been reexamined and found to be the quaternary tosylate I. It is soluble in hot water, is neutral, shows the infrared absorption bands characteristic of the *p*-tosylate ion at 1168, 1118, 1029, and 1007 cm^{-1} [4], and lacks the band in the 2632–2500 cm^{-1} region indicative of a $>NH^{\oplus}$ group. Since compound I must almost certainly result from a concerted displacement of tosylate by N-4 with inversion at C-17, its ready formation under mild conditions and in good yield establishes the *trans* relationship of the groups at C-16 and C-17 in 3-*epi*-α-yohimbine. We have reported that deserpidinol yields α-yohimbyl alcohol on treatment with 48% hydrobromic acid by demethylation at C-17 and inversion at C-3[5]. Since under these conditions inversion at C-17 during the demethylation is very unlikely, the α-orientation of the C-17 methoxyl in deserpidine is also established.

The formation of internal quaternary ammonium salts during the tosylation of reserpinol and 3-*iso*reserpinol and the conversion to their crystalline iodides, II*a* (m.p. 345–350° (dec.)[6], $[\alpha]_D^{24°}$ + 122° (dimethylformamide); Analysis calculated for $C_{22}H_{29}N_2OI$: C 54·98%; H 6·10%; N 5·83%; Found: C 54·99%; H 6·30%;

[1] C. F. HUEBNER, H. B. MACPHILLAMY, E. SCHLITTLER, and A. F. ST. ANDRÉ, Exper. *11*, 303 (1955). – E. WENKERT and L. H. LIU, Exper. *11*, 302 (1955). – E. E. VAN TAMELEN and P. D. HANCE, J. Amer. chem. Soc. *77*, 4692 (1955).

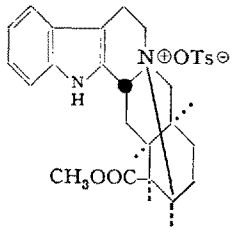
[2] E. WENKERT and L. H. LIU, Exper. *11*, 302 (1955). – E. E. VAN TAMELEN and P. D. HANCE, J. Amer. chem. Soc. *77*, 4692 (1955).

[3] F. E. BADER, D. F. DICKEL, C. F. HUEBNER, R. A. LUCAS, and E. SCHLITTLER, J. Amer. chem Soc. *77*, 3547 (1955).

[4] F. L. WEISENBORN and D. BURN, J. Amer. chem. Soc. *75*, 259 (1953).

[5] H. B. MACPHILLAMY, C. F. HUEBNER, E. SCHLITTLER, A. F. ST. ANDRÉ, and P. R. ULSHAFER, J. Amer. chem. Soc. *77*, 4335 (1955).

[6] Erroneously reported as m.p. 315–316° (dec.) in paper C. F. HUEBNER and E. WENKERT, J. Amer. chem. Soc. *77*, 4180 (1955).



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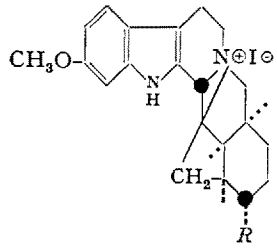
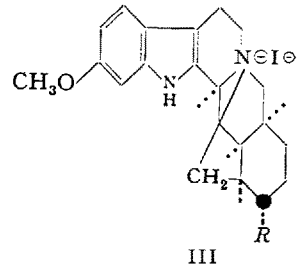


II

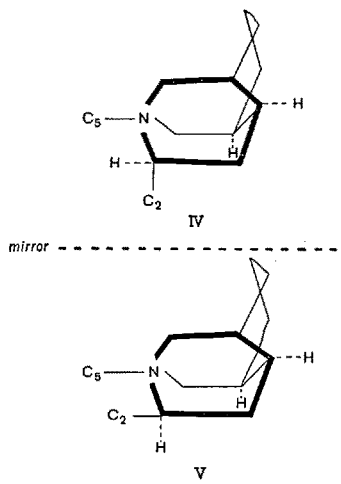
a: $R = OCH_3$
b: $R = H$



III

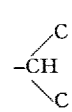
a: $R = OCH_3$
b: $R = H$

N 5·93%) and III*a* ($[\alpha]_D^{24°} - 95°$ in dimethylformamide)[8], respectively, have already been reported[7]. An inspection of the three dimensional formulas, IV and V, corresponding to II*b* and III*b* reveals that these structures which lack the C-17 methoxyl are mirror images. This is the result of a new element of symmetry introduced into the molecule by the quinuclidine ring system. This is most clearly seen by rotation of V 120° toward the observer. The contribution of the C-17 methoxyl to the molecular rotation of II*a* and III*a* may be estimated as follows: Remembering that $[M]_D$ of II*b* and $[M]_D$ of III*b*, must be of equal magnitude and opposite in sign,



IV V

the equations $\Delta(OCH_3)$ in II*a* = $[M]_D$ of II*a* − $[M]_D$ of II*b* and $\Delta(OCH_3)$ in III*a* = $[M]_D$ of III*a* − $[M]_D$ of III*b* may be solved for $\Delta(OCH_3)$ since the molecular rotational contribution of the C-17 methoxyl in both II*a* and III*a* can be assumed to be similar. Thus $\Delta(OCH_3) = (+5960 - 4560) \times 0{\cdot}5 = +700$. Further, many examples drawn from the steroids indicate that the sign and magnitude of rotational contribution of hydroxyl and methoxyl groups are similar[9]. KLYNE and STOKES[10] have proposed general rules regarding the contribution of hydroxyl in cyclic systems in which the –CHOH-grouping is flanked on one side by $-CH_2-$ and on the other by



Such a system is present in II*a*. It is an α-oriented substituent at C-17 which would, according to these rules, have a positive rotational contribution.

We wish to acknowledge the invaluable contributions to this problem made by Dr. E. WENKERT, Iowa State College.

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Research Laboratories CIBA Pharmaceutical Products Inc. Summit, New Jersey, April 25, 1956.

Zusammenfassung

Bei der Behandlung von 3-*epi*-α-Yohimbin mit *p*-Toluol-sulfochlorid in Pyridin bei 5° wird mit grosser Leichtigkeit und ausgezeichneter Ausbeute ein quaternäres Tosylat erhalten. Dieser Befund, zusammen mit der bekannten sterischen Beziehung zwischen 3-*epi*-α-Yohimbin und Deserpidin, stützt die Annahme der *trans*-Konfiguration der Substituenten in 16- und 17-Stellung auch im Deserpidin. Ein Vergleich der optischen Drehungen von Reserpinderivaten spricht für analogen räumlichen Bau des Kohlenstoffatoms 17 im Reserpin.

The Biogenesis of the Morphine Alkaloids and Related Topics

Several theories have been advanced for the formation in nature of the typical skeleton of the morphine alkaloids. ROBINSON and SUGASAWA[1] suggested that sinomenine (I) is formed from a protosinomenine (II, $R = H$) by cyclisation; they synthesised the protosinomenine but obtained insufficient for further study. For the production of thebaine (III) ROBINSON[1] suggested closure of the 4:5-oxide bridge by the dehydration of a 4:5-dihydroxy-compound. The necessary intermediate for this (IV) would, however, have to be produced by the cyclisation of an oddly substituted *iso*quinoline, and the suggestion was accordingly made[1] that base (V) (obtained from the same intermediates as protosinomenine by closure of the *iso*quinoline ring *ortho* instead of *para* to the hydroxyl group) cyclises to (VI), which then undergoes reversal of the substituents at $C_{(14)}$ and $C_{(13)}$ giving the base (IV).

More recently SCHÖPF[2], on the basis of the presumed oxidation of *p*-cresol to the ketone (VII)[3], suggested

[7] C. F. HUEBNER and E. WENKERT, J. Amer. chem. Soc. *77*, 4180 (1955).

[8] Analysis reported in paper C. F. HUEBNER and E. WENKERT, J. Amer. chem. Soc. *77*, 4180 (1955).

[9] D. K. FUKUSHIMA and T. F. GALLAGHER, J. Amer. chem. Soc. *73*, 196 (1951).

[10] W. KLYNE and W. M. STOKES, J. chem. Soc. *1954*, 1979.

[1] R. ROBINSON and S. SUGASAWA, J. chem. Soc. 3163 (1931); 280 (1933). – R. ROBINSON, J. chem. Soc. 1079 (1936); Nature *160*, 815 (1947).

[2] C. SCHÖPF, Naturwissenschaften *11*, 241 (1952).

[3] R. PUMMERER, D. MELAMED, and H. PUTTFARCKEN, Ber. dtsch. chem. Ges. *55*, 3116 (1922). – R. PUMMERER, H. PUTTFARCKEN, and P. SCHOPFLOCHER, Ber. dtsch. chem. Ges. *58*, 1808 (1925).