membered ring such a favored transition state is possible only if the departing α-hydrogen is polar (see III). Consequently, enolization of a cyclohexanone should take place preferentially with a leaving polar hydrogen and, by the principle of microscopic reversibility, the reverse reaction, ketonization, should involve an entering electrophilic species (e.g. $H^{\delta+}$or $Br^{\delta+}$) which preferentially adopts the polar orientation.

The application of the above considerations to the assignment of configuration of a bromoketosteroid requires knowing only whether it is the product of kinetic or thermodynamic control. This is easily decided by determining whether the bromoketone is or is not subject to epimerization at $C_{(Br)}$ under the influence of hydrogen bromide.

We have found that in every case where the configuration at $C_{(Br)}$ of a bromoketosteroid has been proved, the predicted configuration agrees with that which is observed. Furthermore, we have determined that in all instances where a conflict existed between predicted and reported configurations, the previous assignment has been in error. The correct configurations have been established experimentally[1] by infrared spectroscopy and also by chemical methods in the cases where it appeared conceivable that the infrared method might be equivocal (e.g., for flexible *A*-ring ketones).

Representative examples are cited in Table III.

The approach to the stereochemistry of α-bromoketones in rigid, fused-ring systems which is presented here appears to have utility in the solution of several different types of problems, e.g. the determination of the location of carbonyl functions in steroid and triterpenoid nuclei. It is noteworthy also that one can determine whether or not a given epimer of a steroid bromoketone will be accessible by direct bromination and whether, if it is accessible, equilibrating or non-equilibrating conditions should be used for its preparation.

E. J. COREY

Division of Organic Chemistry, University of Illinois, Urbana, Ill., June 9, 1953.

Zusammenfassung

An Hand der molekularen Konfigurationen geeigneter monozyklischer Vergleichssubstanzen wurde die relative Stabilität aller epimeren Normal- und Allo-Bromoketosteroide mit der Ketogruppe im Ring *A*, *B* oder *C* abgeleitet. In gewissen Bromoketosteroiden liegt das Bromatom vorzugsweise *polar*, in anderen vorzugsweise *äquatorial*. Auf Grund dieser relativen Stabilitäten ist es möglich, die stereochemische Konfiguration am $C_{(Br)}$ in Bromoketosteroiden vorauszusagen, vorausgesetzt, dass das Bromierungsprodukt *thermodynamisch*, das heisst *durch Gleichgewicht, bestimmt* ist.

Erhielt man bei der Bromierung nicht das zu erwartende thermodynamisch bestimmte Produkt, so zeigte es sich, dass das Bromatom immer polar vorlag. Diese Tatsache zusammen mit theoretischen Überlegungen führten zur *Regel des polaren Angriffes* bei der Bromierung eines Steroidenols. Dabei lässt sich das Bromoketon am $C_{(Br)}$ epimerisieren. Das Bromatom orientiert sich offenbar immer polar, sofern das Bromierungsprodukt *kinetisch*, das heisst *durch Geschwindigkeit, bestimmt* ist.

Obige Betrachtungen erlauben, soweit wir bis jetzt ausnahmslos feststellen konnten, die eindeutige Voraussage der Stereochemie der Bromoketosteroide.

[1] E. J. COREY, J. Am. Chem. Soc., in press.

On the Constitution of Reserpine[1]

In our first publication on reserpine, isolated from *Rauwolfia serpentina* BENTH[2] some physical and chemical details were mentioned. A more detailed account of the pharmacology of this blood pressure lowering and sedative-hypnotic compound was later given by BEIN[3]. At that time, owing to difficulties with combustions, no total formula could be given for reserpine. We also found that the BARGER method[4] for the estimation of molecular weights strangely enough gave no reliable results, whereas the usual RAST methods could not be used, because reserpine easily decomposed.

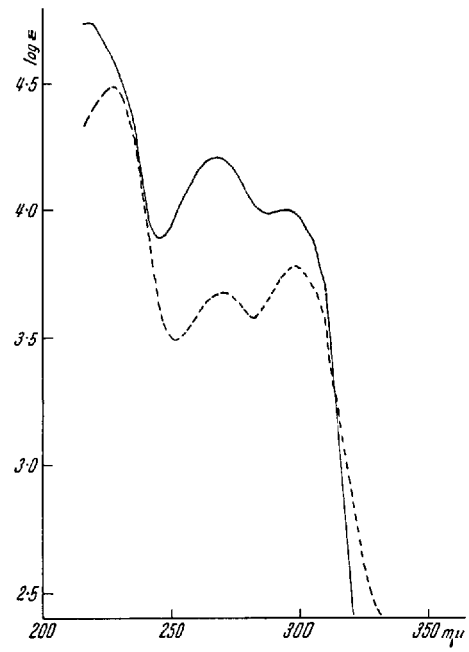


Fig. 1.

Basing on a great number of analyses in our two laboratories we have now come to the conclusion, that reserpine has the formula $C_{33}H_{40}O_9N_2$ (calculated: C = 65·11, H = 6·62, N = 4·60%; found: C = 65·07, H = 6·62, N = 4·64%). With purer samples than mentioned in our first publication, the U.V. and I.R. spectra have been measured again and they are given in Figs. 1 (straight line) and 2, and in the Table. It has been found that reserpine is an esteralkaloid, yielding on alkaline hydrolysis reserpic acid, 3,4,5-trimethoxybenzoic acid and methanol. The latter acid has been identified with an authentic sample.

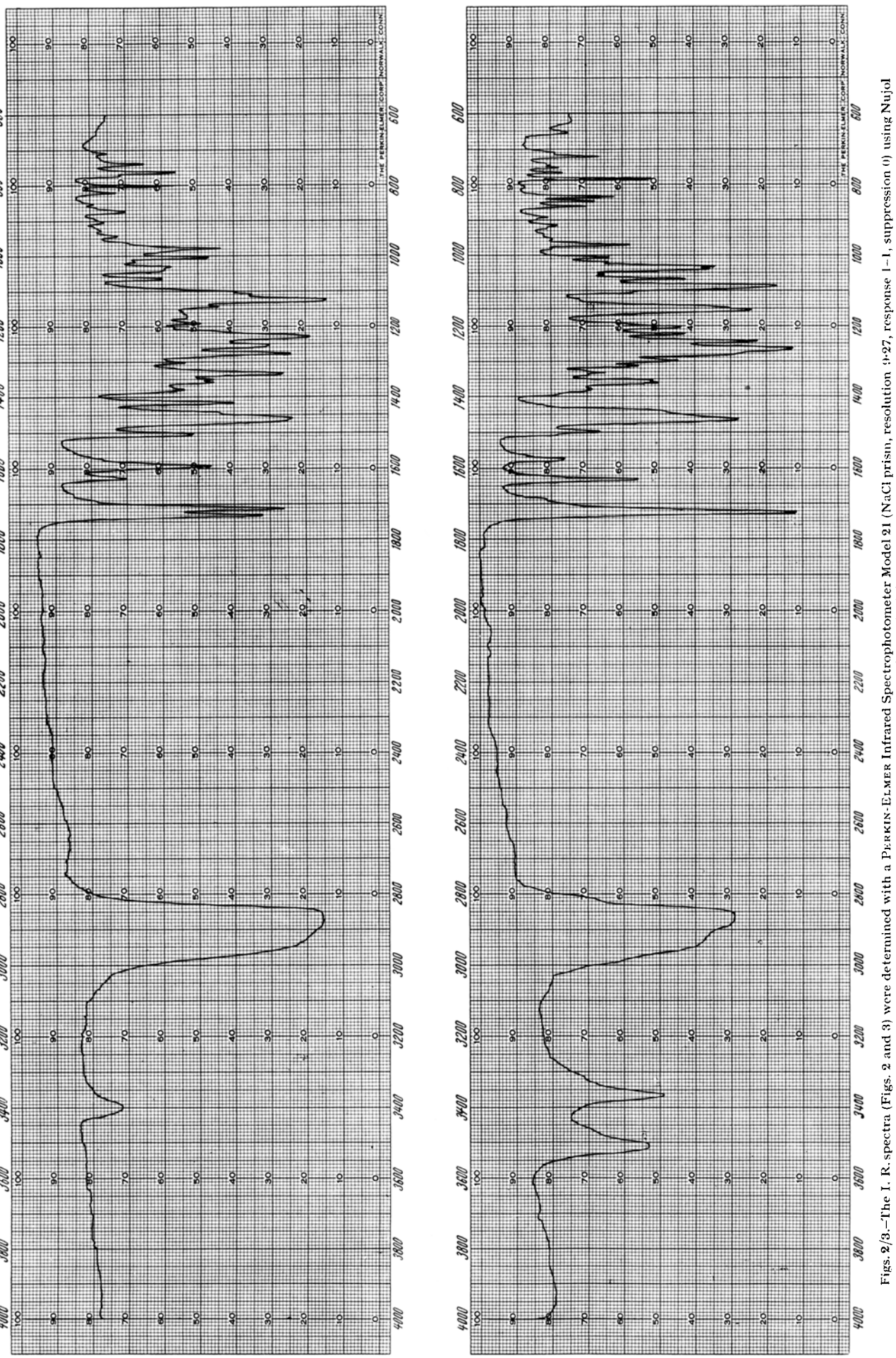
Reserpic acid is usually isolated as its hydrochloride (calculated: N = 6·41, Cl = 8·12), found: N = 6·20, Cl = 8·12%) m.p. 257–263°, $[\alpha]_D = -80 \pm 3°$ ($CHCl_3$) but by treating this compound with Ag_2CO_3 free reserpic acid ($C_{22}H_{28}O_5N_2$) m.p. 239–245° can be prepared (calculated: C = 65·98, H = 7·05, N = 7·00%; found: C = 65·66, H = 7·33, N = 6·98%). Reserpic acid shows strong hydrogen bonding in its I.R. spectrum. On esterifying reserpic acid with diazomethane methylreserpate $C_{23}H_{30}O_5N_2$ (calculated: C = 66·64, H = 7·30,

[1] Ciba's trade-mark for reserpine is "Serpasil".

[2] J. M. MÜLLER, E. SCHLITTLER, and H. J. BEIN, Exper. *8*, 338 (1952).

[3] H. J. BEIN, Exper. *9*, 107 (1953).

[4] G. BARGER, Chem. Ber. *37*, 1754 (1904); J. Chem. Soc. *85*, 286 (1904); *87*, 1756 (1905). – K. RAST, Chem. Ber. *54*, 1979 (1921).



Figs. 2/3.–The I. R. spectra (Figs. 2 and 3) were determined with a PERKIN-ELMER Infrared Spectrophotometer Model 21 (NaCl prism, resolution 0·27, response 1–1, suppression 0) using Nujol mulls compensated with Nujol.

N = 6·76%; found: C = 66·68, H = 7·30, N = 6·90%) m.p. 235–239,5°, $[\alpha]_D = -101 \pm 3°$ ($CHCl_3$) is obtained (U.V. Spectrum, Fig. 1 (dotted line); I.R. Spectrum, Fig. 3).

U.V. Spectra in ethanol.

	λ_{max}	log ε	λ_{min}	log ε
Reserpin . . .	218	4·739	246	3·889
	268	4·204	288	3·985
	294–296	3·995		
Methyl Reserpate				
	228	4·488	252	3·493
	270–272	3·667	282	3·579
	298	3·779		

This methylreserpate, which is a basic compound, on being acted upon by trimethoxybenzoylchloride yields the alkaloid reserpine back with the same physical characteristics and identical spectra as the starting material; m.p. 264–266°, mixed m.p. 263–265° (inserted into the block at 250°) (found C = 65·38, H = 6·45, N = 4·80%). Also the pharmacological activity of the synthetic material is the same as the alkaloid obtained from the plant material[1]. This sequence of reactions shows that the molecule of reserpic acid has not suffered from any rearrangements during alkaline hydrolysis and retransformation into the parent alkaloid.

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Ciba Pharmaceutical Research Laboratories, Basle, Switzerland, and Summit, N. J., June 3, 1953.

Zusammenfassung

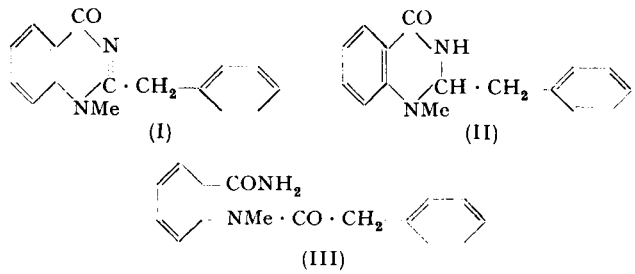
Durch alkalische Hydrolyse wird Reserpin in Reserpinsäure, 3,4,5-Trimethoxybenzoesäure und Methanol gespalten. Das Esteralkaloid liess sich aus diesen Spaltstücken wieder resynthetisieren.

[1] These experiments were carried out by Dr. A. J. Plummer and his associates.

Chemistry of Arborine

In a paper awaiting publication[1] a number of degradations of arborine, $C_{16}H_{14}ON_2$, the major alkaloid of *Glycosmis arborea*[2], has been described in detail. It has been observed that sodalime distillation of arborine affords toluene, methylaniline and ammonia and that hydrolysis of arborine with alkali affords N-methylanthranilamide, N-methylanthranilic acid, phenylacetic acid and ammonia along with a minute quantity of a weakly acidic product, arboricine, $C_{16}H_{13}O_2N$.

It has now been found that dihydroarborine, $C_{16}H_{16}ON_2$, m.p. 199–200°, is readily hydrolysed with dilute acid. N-methylanthranilamide, N-methylanthranilic acid and phenylacetaldehyde have been isolated from the product. From a consideration of these results and the general behaviour of arborine and dihydroarborine it appears that arborine is 1-methyl-2-benzyl-4(1 H)-quinazolone (I) and that dihydroarborine is (II).



The above structure for arborine has been confirmed by synthesis. For this purpose, phenylacetyl chloride has been condensed with N-methylanthranilamide to give N-methyl-N-phenylacetylanthranilamide (III), m.p. 159–160°. This on heating to 170–190° gives arborine (mixed m.p. compared).

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Zusammenfassung

Aus den Abbauprodukten von Arborin und Dihydroarborin konnte für Arborin, das Hauptalkaloid von *Glykosmis arborea*, die Formel eines 1-Methyl-2-benzyl-4-(1 H)-chinazolons erschlossen werden. Diese Formel wurde durch Synthese bestätigt.

[1] J. Chem. Soc., London.

[2] R. N. Chakravarti and S. C. Chakravarti, J. Inst. Chemists (India), *24*, 96 (1952).

Isolierung eines neuen kristallisierten Hormons aus Nebennieren mit besonders hoher Wirksamkeit auf den Mineralstoffwechsel

Nebennierenextrakte enthalten ein der Rinde entstammendes kompliziertes Gemisch von Steroiden[1]. Von diesen können drei, nämlich Corticosteron, Cortison und 17-Oxycorticosteron, sicher als Hormone bezeichnet werden, da sie im Blut in Mengen vorkommen[2], die für gewisse natürliche Funktionen der Nebennierenrinde von massgebender Bedeutung sind. Diese drei Stoffe vermögen zwar die Wirkung der Drüse auf den Kohlehydrat- und Proteinstoffwechsel weitgehend zu erklären, nicht jedoch diejenige auf den Mineralstoffwechsel (gemessen an der Na- und Wasser-Retention und K-Exkretion). Von allen bekannten reinen Steroiden besitzt Cortexon (= 11-Desoxycorticosteron) die stärkste Wirkung auf den Mineralstoffwechsel im genannten Sinn. Dieser Stoff kommt zwar in Nebennierenextrakten vor[3] und anscheinend auch im Rinderblut[4]; die darin

[1] T. Reichstein und C. W. Shoppee, *The Hormones of the Adrenal Cortex*, Vitamins and Hormones, Bd. 1, hg. v. R. S. Harris und K. V. Thimann (Academic Press Inc., New York 1943), S. 345.

[2] D. H. Nelson, H. Reich und L. T. Samuels, Science *111*, 578 (1950). – H. Reich, D. H. Nelson und A. Zaffaroni, J. Biol. Chem. *187*, 411 (1950).

[3] T. Reichstein und J. v. Euw, Helv. chim. Acta *21*, 1187 (1938). – Käufliche Extrakte für klinische Zwecke enthalten oft kein Cortexon, da dieses im Fabrikationsprozess entfernt wurde. – A. Zaffaroni und R. B. Burton, J. Biol. Chem. *193*, 719 (1951).

[4] V. Hechter, A. Zaffaroni, R. P. Jacobson, H. Levy, R. W. Jeanloz, V. Schenker und K. S. Pincus, *Recent Progress in Hormone Research*, Bd. 6 (Academic Press Inc., New York 1951), S. 215.