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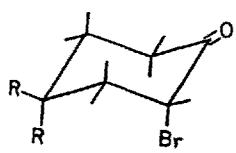
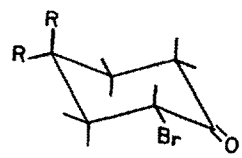
Prediction of the Stereochemistry of α-Brominated Ketosteroids

Previous work[1] has shown that the orientation of bromine in the most stable conformation of a monocyclic α-bromocyclohexanone is sometimes polar and sometimes equatorial. For example, the stable conformation of 2-bromocyclohexanone is that chair form in which the bromine is *polar* (I *A*), while the stable form of 2-bromo-4,4-dimethylcyclohexanone is that chair form in which bromine is *equatorial* (II *B*) (Table I). This dichotomy is due to the fact that both steric and electrical repulsions[2] between ring substituents are important in determining the preferred molecular configuration. When the bromine substituent in an α-bromocyclohexanone is equatorial electrical repulsions are at a maximum and steric repulsions are at a minimum; however, when the bromine is polar the reverse is true.

Thus, when electrical repulsions due to equatorial bromine are much more important than steric repulsions due to polar bromine, the stable molecular configuration will be that in which bromine is polar. This is the situation with 2-bromocyclohexanone, as has been confirmed by calculations[1]. Electrical interaction between the C–O and C–Br dipoles destabilize form I *B* of 2-bromocyclohexanone by at least 2·7 kcal./mole relative to form I *A*, while steric interactions destabilize form I *A* by only *ca.* 0·4 kcal./mole relative to form I *B*. In the case of 2-bromo-4,4-dimethylcyclohexanone, however, the steric interaction in II *A* between polar bromine and a polar, *cis*-methyl group at C_4 completely overshadows the electrical interactions in II *B* involving equatorial bromine and, consequently, the stable form is II *B*.



I *A*, R = H
II *A*, R = CH_3



I *B*, R = H
II *B*, R = CH_3

From a knowledge of the stable molecular configuration of non-rigid α-bromocyclohexanones[3], which is easily obtained by infrared spectroscopy[4], one can evaluate the relative importance of the electrical and steric interactions between substituents in any type of cyclohexane ring systems, rigid or non-rigid. Consequently, the preferred molecular configurations of suitable non-rigid reference systems can be used to derive the preferred configuration at an asymmetric carbon atom in a rigid system.

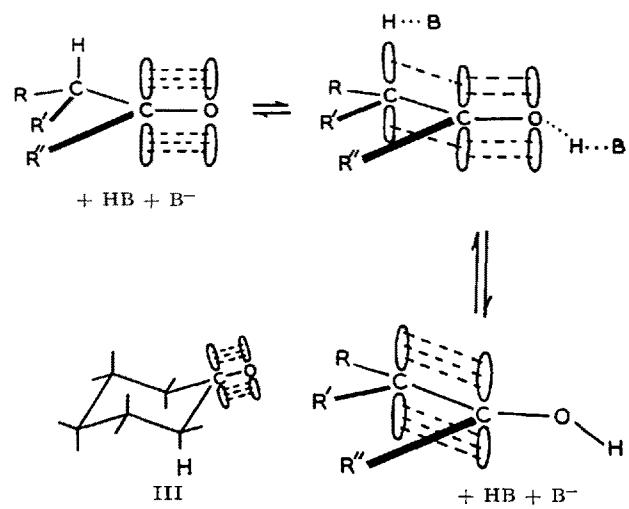
Table I

Relative stabilities of chair-formed conformations of α-bromocyclohexanones

Ketone	Approx. Keq., (Br polar)* / (Br equatorial)
2-bromocyclohexanone-1	> 50
2-bromo-3,3-dimethyl-cyclohexanone-1	> 40
2-bromo-4,4-dimethyl-cyclohexanone-1	< 0·01
2-bromo-6,6-dimethyl-cyclohexanone-1	~ 0·4
7-bromo-spiro[4·5]decane-6-one. . . .	~ 0·4
cis-2,6-dibromocyclohexanone-1 . . .	< 0·05

* In carbon tetrachloride solution at 25°. Data obtained by infrared spectroscopy [ref. 1; E. J. Corey and T. Topie, to be published].

Thus, from the data in Table I on preferred molecular configurations we have deduced the relative stabilities of the epimeric bromination products of any ketosteroid with ketone function in ring *A*, *B* or *C* and *A*/*B* *cis* or trans. The results are recorded in Table II. Since the stable epimer predominates when the product of bromination is *thermodynamically* (*equilibrium*) *controlled*, it is possible by means of these data to *predict* the configuration at $C_{(Br)}$ of any bromoketone thus formed.



+ HB + B^-

III

+ HB + B^-

We also have found a rule, which has a theoretical basis, for predicting the stereochemistry of the *kineti-*

[1] E. J. Corey, J. Amer. Chem. Soc. *75*, 2301 (1953).

[2] By electrical repulsions we mean the inverse-square field effect associated with the proximity of non-bonded atoms of like net charge; by steric repulsions we mean the inverse-exponential field effect due to interaction between the outer valence-shell electrons of non-bonded atoms.

[3] The term non-rigid is used to mean that both possible chair forms of the cyclohexane ring can exist. A rigid chair-formed six-membered ring is one which is prevented from assuming the other possible chair form.

[4] E. J. Corey, J. Amer. Chem. Soc. *75*, 2301 (1953). – R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, J. Amer. Chem. Soc. *74*, 2828 (1952).

Table II
Stability of epimeric α-bromoketosteroids

A/B trans:		*A/B cis:*	
Position of ketone function	Configuration of Br in stable epimer	Position of ketone function	Configuration of Br in stable epimer
C (1)	C (2):α (e)*	C (1)	C (2):β (e)*
C (2)	C (1):α (p) C (3):α (p)	C (2)	C (1):β (p) C (3):β (p)
C (3)	C (2):α (e) C (4):α (e)	C (3)	C (2):β (e) C (4):β (e)
C (4)	C (3):α (p) C (5):α (p)	C (4)	C (3):β (p) C (5):α (p)
C (6)	C (5):α (p) C (7):α (p)	C (6)	C (5):α (p) C (7):β (e)
C (7)	C (6):α (e) C (8):β (p)	C (7)	C (6):α (e) C (8):β (p)
C (11)	C (9):α (p) C (12):α (p)	C (11)	C (9):α (p) C (12):α (p)
C (12)	C (11):α (e)	C (12)	C (11):α

* The isomer with bromine polar should be only slightly less stable, and the equilibrium mixture of C(2) epimers should contain *ca.* 75% of the epimer with bromine equatorial and 25% of the epimer with bromine polar.

cally (rate) controlled bromination products of ketosteroids. This rule which, as far as we are aware, leads invariably to the correct assignment of configuration is as follows: *the epimer which is formed faster in the bromination of a ketosteroid is always that in which bromine is polar.*

The theoretical basis which we set forth for this rule depends on the recognition of both the enolization of a ketone and the ketonization of an enol as *stereoselective* processes. In general, the energy of the transition state for enolization will be minimized when there is maximum overlap between the $sp^3 \rightarrow p$ orbital made available by the leaving α-hydrogen and the p orpital of the carbonly carbon, as shown[1]. In the case of a chair-formed, six-

[1] Thus, there is a striking parallelism between enolization and β-elimination. β-Elimination proceeds most readily when the four atoms involved in bond-making and bond-breaking are coplanar. [E. D. HUGHES and C. K. INGOLD *et al.*, J. Chem. Soc. *1948*, 2117; D. H. R. BARTON and E. MILLER, J. Amer. Chem. Soc. *72*, 1066 (1950)]. This stereoselectivity probably is due to the fact that the incipient p orbitals can overlap most effectively in a planar transition state.

Table III

Ketone brominated	Observed and predicted Configuration at C(Br)
Cholestanone-3[1]	2α-bromo (*a, c, t*)
Coprostanone-3[2]	4β-bromo (*a, t*)
5α,6β-dibromocholestanone-3[3]	4β-bromo (m.p. 106°) (*b, k, d*)
5α,6β-dibromocholestanone-3[3]	4α-bromo (m.p. 138°) (*a, t, d*)
3-acetoxycholestanone-6[4]	5α-bromo (m.p. 162°) (*d, k*)
3-acetoxycholestanone-6[4]	7α-bromo (m.p. 145°) (*a, c, t* or *k*)
3-acetoxycholestanone-6[4]	5α, 7α-dibromo (m. p. 152°) (*b, k, d*)
3-acetoxycholestanone-6[4]	5α, 7β-dibromo (m. p. 129°) (*a, c, t*)
3-acetoxycholestanone-7[4]	6β-bromo (m. p. 175°) (*b, k*)
3-acetoxycholestanone-7[5]	6α-bromo (m. p. 143°) (*a, t*)
Methyl 7-keto-3α,12α-diacetoxycholanate[6]	6α-bromo (*a, t*)
Methyl 11-keto-3α-acetoxycholanate[7]	12α-bromo (*a, k* or *t*)
Methyl 12-keto-3α-acetoxycholanate[8]	11β-bromo (m. p. 222°) (*b, k*)
Methyl 12-keto-3α-acetoxycholanate[8]	11α-bromo (m.p. 182°) (*a, t*)

(*a*) Cannot be epimerized. (*b*) Can be epimerized. (*c*) Previously assigned structure incorrect. (*d*) No conclusive assignment of structure previously made. (*k*) Product of kinetic control. (*t*) Product of thermodynamic control.

[1] R. N. JONES, D. A. RAMSAY, F. HERLING, and K. DOBRINER, J. Amer. Chem. Soc. *74*, 2828 (1952). – See. E. J. COREY, J. Amer. Chem. Soc. In press for proof of this configuration and a correction of the recent article of L. F. FIESER and X. A. DOMINGUEZ, J. Amer. Chem. Soc. *75*, 1704 (1953).

[2] R. N. JONES, D. A. RAMSAY, F. HERLING, and K. DOBRINER, J. Amer. Chem. Soc. *74*, 2828 (1952). – L. F. FIESER and R. ETTORE, J. Amer. Chem. Soc. *75*, 1700 (1953).

[3] A. BUTENANDT and J. SCHMIDT-THOMÉ, Ber. dtsch. chem. Ges. *69*, 882 (1936). – A. BUTENDANDT and G. SCHRAMM, Ber. dtsch. chem. Ges. *69*, 2289 (1936). – H. H. INHOFFEN, Ber. dtsch. chem. Ges. *69*, 1134 (1936). – D. H. R. BARTON and E. MILLER, J. Amer. Chem. Soc. *72*, 1066 (1950).

[4] I. M. HEILBRON, E. R. H. JONES, and F. S. SPRING, J. Chem. Soc. *1937*, 801. – I. M. HEILBRON, H. JACKSON, E. R. H. JONES, and F. S. SPRING, J. Chem. Soc. *1938*, 102.

[5] T. BARR, I. M. HEILBRON, E. R. H. JONES, and F. S. SPRING, J. Chem. Soc. *1938*, 334.

[6] W. M. HOEHN and J. LINSK, J. Amer. Chem. Soc. *67*, 312 (1945).

[7] E. BORGSTROM and T. F. GALLAGHER, J. Biol. Chem. *162*, 707 (1946). – V. R. MATTOX, R. B. TURNER, B. F. MCKENZIE, L. L. ENGEL, and E. C. KENDALL, J. Biol. Chem. *173*, 283 (1948).

[8] T. F. GALLAGHER and W. P. LONG, J. Biol. Chem. *162*, 495 (1946).

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.

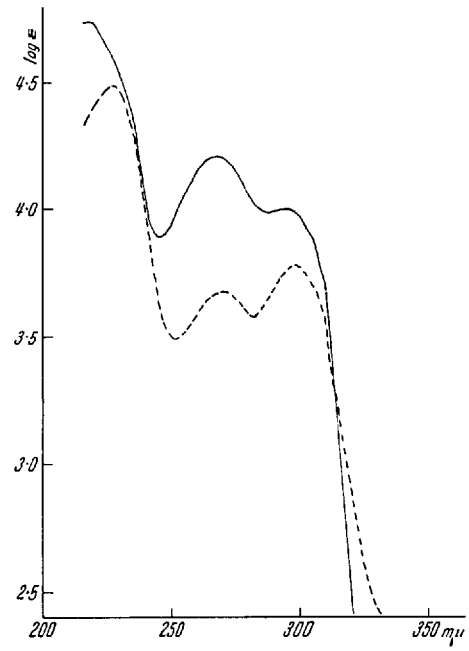


Fig. 1.

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).