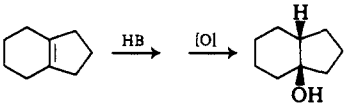
Recently, 1,3,7-octatriene (VIII) became readily available by the dimerization of 1,3-butadiene.[10] The hydroboration–carbonylation–oxidation of the triene yielded *cis*-8-hydrindanol (XI) in a yield of 33%.[11] This compound was previously obtained by Criegee and Zogel by the autoxidation–reduction of hydrindan in less than 2% yield.[12] The stereochemistry of XI was established as the *cis* isomer by its dehydration into $\Delta^{8(9)}$-hexahydroindene (XII) followed by hydroboration–oxidation to yield the original alcohol (XI).



XII XI

It is noteworthy that all of these carbonylations take place preferentially from the *cis* side of these bicyclic boranes.[13] We are exploring the stereochemistry of such carbonylations in greater detail in the hope that the study will throw additional light on the mechanism of the carbonylation reaction.

(10) E. J. Smutny, *J. Am. Chem. Soc.*, **89**, 6793 (1967). We are indebted to Dr. Smutny for a generous gift of the triene.

(11) Glpc analysis of the product revealed a minor peak which presumably is the *trans* isomer.

(12) R. Criegee and H. Zogel, *Ber.*, **84**, 215 (1951).

(13) Compare H. C. Brown and W. C. Dickason, *J. Am. Chem.Soc.*, **91**, 1226 (1969).

(14) Postdoctoral research associate on a grant provided by the National Institutes of Health (GM-10937).

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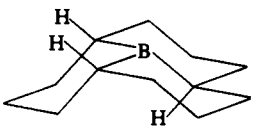
Synthesis of the *cis,cis,cis*-Perhydro-9b-phenalenol, a Very Highly Strained System, *via* the Carbonylation Reaction. A Remarkably High Rate of Solvolysis of the Corresponding *p*-Nitrobenzoate

Sir:

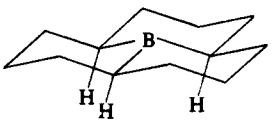
Carbonylation–oxidation of *cis,cis,cis*-perhydro-9b-boraphenalene yields the highly strained tertiary alcohol, *cis,cis,cis*-perhydro-9b-phenalenol. This requires that the carbonylation takes place predominantly from the more hindered side of the borane intermediate to give the more strained of the two possible tertiary alcohols. This strained tertiary alcohol is enormously reactive. Its *p*-nitrobenzoate undergoes solvolysis at 25° at a rate 2,000,000 times faster than the *t*-butyl derivative, and 4,000,000 times faster than the *p*-nitrobenzoate of the previously synthesized *cis,cis,trans* isomer.[1]

(1) H. C. Brown and E. Negishi, *J. Am. Chem. Soc.*, **89**, 5478 (1967).

The two possible isomers of perhydro-9b-boraphenalene have been previously prepared.[2] In an earlier publication[1] we questioned the original structural assignment[2] of these two polycyclic boranes. The accumulated evidence now fully supports our position that the assignments must be reversed.



cis,cis,trans
I



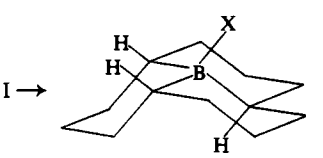
cis,cis,cis
II

Previous methods of preparation and purification of II[2] proved satisfactory. However, utilization of the published procedure for I produced a 92:8 mixture (glpc analysis) of I and an unidentified, presumably isomeric, organoborane.[3,4] However, distillation through a spinning-band column gave a much purer product, with a purity of at least 98% indicated by glpc analysis.

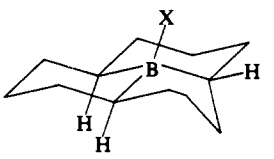
The indicated structures for organoboranes I and II are supported by a detailed pmr investigation of the free boranes and their pyridine addition compounds.

Thus the pmr of I shows a broad peak with a maximum at 1.53 ppm, a value intermediate between what may be considered the "normal" bands for equatorial and axial protons, as determined from the pmr of II. At −60° the pmr showed no evidence of conformational "freezing." Such behavior is expected on the basis of the "axial effect."[5] On the other hand, the pmr of II shows two distinct bands centered at 1.85 and 1.32 ppm, in keeping with its rigid structure and lack of axial substituents. This spectrum resembles that of *all-trans*-perhydrophenalene with two bands centered at 1.65 and 1.03 ppm.[6]

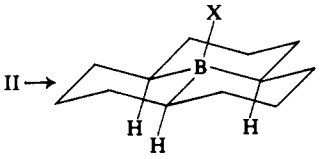
Coordination of each of these boranes with pyridine or carbon monoxide could conceivably take place from either side, producing two possible adducts from each borane.



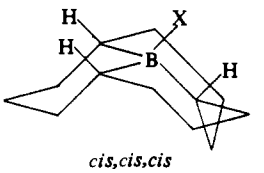
cis,cis,trans



trans,trans,cis



trans,trans,trans



cis,cis,cis

(2) G. W. Rotermund and R. Köster, *Ann. Chem.*, **686**, 153 (1965). The symbols I and II correspond to the products (but not the structures) labeled I and II by these authors.

(3) We are indebted to Professor R. Köster for the glpc conditions satisfactory for separating these boranes.

(4) Long heating at 200° did not alter this distribution.

(5) For example, *cis*-decalin, which represents part of the structure of I, shows only a broad peak even at −100°: N. Muller and W. C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962).

(6) Normal bands for rigid hydrocarbons are 1.65 ppm (equatorial) and 1.17 ppm (axial).[5] Thus these regions are shifted downfield in the borane.

Table I. Rates of Solvolysis of the *p*-Nitrobenzoates of *cis,cis,trans*- and *cis,cis,cis*-Perhydro-9b-phenalenol

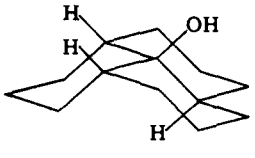
ROPNB, R	First-order rate constant, $k_1 \times 10^6$ sec^{-1} 0.0°	25.0°	100.0°	125.0°	Rel rate, 25°	ΔH^*, kcal mol^{-1}	ΔS^*, eu
t-Butyl[a]		7.45×10^{-5} [d]	1.85	23.3	1.00	29.2	−7.1
cis-9-Decalyl[b]		5.13×10^{-5} [d]	3.11	48.8	0.97	31.8	+1.0
trans-9-Decalyl[c]		1.39×10^{-5} [d]	0.822	12.9	0.19	31.7	−1.8
cis,cis,trans-III		3.88×10^{-5} [d]	1.63	23.5	0.52	30.7	−3.1
cis,cis,cis-IV	4.03	151			2,030,000	22.9	+0.7

[a] Mp 116–117°. [b] Mp 130–132°. [c] Mp 170–171°. A melting point of 106.5–107° previously reported (A. G. Davies and C. D. Hall, *J. Chem. Soc.*, 1192 (1963)) must be in error. [d] Extrapolated from data at other temperatures.

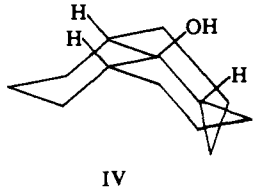
The adducts of the all-*cis* borane II can be seen to have three equivalent α protons, regardless of the side on which coordination occurs. Indeed, the pyridine adduct of II shows two completely separated bands at 1.50 and 0.67 ppm in the ratio of 18:3. The adduct from I has only two equivalent α protons. Its pmr shows two distinct, not completely separated, bands at 1.45 and 0.55 ppm in the ratio of 19:2.

Unfortunately, it is not possible to establish from the pmr data with any certainty on which side of the borane the coordination occurs. However, both examination of models and conformational analysis support the conclusion that the preferred structures should be the *cis,cis,trans* and the *trans,trans,trans* isomers.

We previously reported that carbonylation of I provides the *cis,cis,trans* alcohol III.[1] We now report that carbonylation of II provides the highly strained *cis,cis,cis* alcohol IV, mp 97–98.5° from pentane.[7] It was isomerically pure by capillary glpc. Its pmr features an extremely sharp singlet at 1.58 ppm, corresponding to 21 protons, and a singlet at 0.9 ppm, corresponding to 1 proton, exchanging with D_2O.



III



IV

The *p*-nitrobenzoate of III, mp 157–158°, was previously synthesized.[1] The PNB of IV exhibited slight melting at 108°, followed by rapid crystallization, finally melting with decomposition at 220°.[8]

Rates of solvolysis were run in 80% aqueous acetone. The rates of the *p*-nitrobenzoates of *t*-butyl alcohol, *cis*-9-decalol, and *trans*-9-decalol were run for comparison. The data are summarized in Table I.

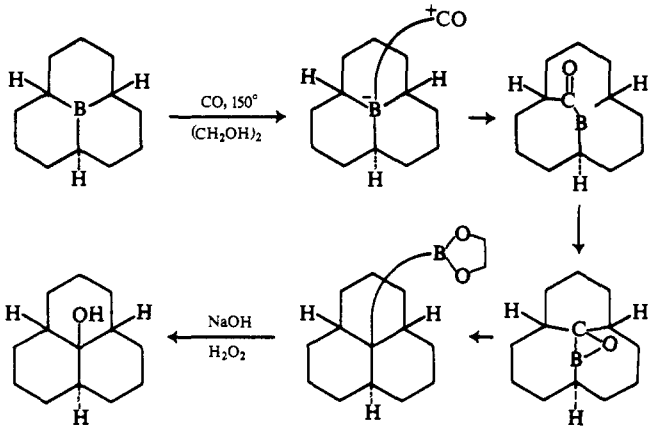
The rates for III-OPNB and for the model compounds were all relatively small and comparable. However, the rate for IV-OPNB was enormous, 2,000,000 times greater than that of *t*-butyl alcohol. The factor of 4,000,000 between III-OPNB and IV-OPNB is remarkable for two such isomeric compounds and can only reflect the driving force provided by the relief during ionization[9] engendered by the all-*cis* structure.

(7) All new compounds gave satisfactory elemental analyses and infrared and pmr spectra.

(8) This type of melting behavior is characteristic of highly branched, reactive, tertiary *p*-nitrobenzoates: P. D. Bartlett and T. T. Tidwell, *J. Am. Chem. Soc.*, **90**, 4421 (1968).

(9) H. C. Brown, *Science*, **101**, 385 (1946).

The carbonylation of borane I to give III presents no problem, since this is precisely the product to be anticipated on the basis of the proposed mechanism for the reaction.[10] Here we assume that each transfer of a bond from boron to carbon will proceed with retention.



However, the preferential carbonylation of *cis,cis,cis*-perhydro-9b-boraphenalene (II) to give *cis,cis,cis*-perhydro-9b-phenalenol (IV) apparently requires addition of the carbon monoxide molecule from the more hindered side of the borane molecule II to give the more strained of the two possible isomers. At first sight this appears most puzzling.

Nevertheless, it is possible to account for this unexpected result on the basis of two reasonable assumptions. (1) Both the all-*cis* and the all-*trans* carbonyl adducts are formed in an equilibrium mixture, with the latter greatly preferred. (2) The all-*trans* adduct is so stable that alkyl migration is relatively slow. The small amount of highly strained all-*cis* adduct undergoes migration preferentially, causing the reaction to proceed through this reactive intermediate.

In support of this last assumption we can point to our observation that the highly strained organoborane, tricyclohexylborane, undergoes carbonylation with great ease, much faster than the presumably less strained tri-*sec*-butylborane or tricyclopentylborane.[11] Also in support of this assumption is our observation that the carbonylation of II is much slower than the carbonylation of I. Whereas I undergoes complete carbonylation in only 1 hr at 150°, II requires 18 hr. Finally, the proposed explanation would also account for the preferential formation of the *cis* alcohols in the carbonylation of the

(10) H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 2737 (1967).

(11) Unpublished observations of M. W. Rathke.

9-boradecalins and 8-boraperhydroindan.[12]

Irrespective of the precise explanation of the phenomenon, this ready synthesis of highly strained systems should be exceedingly useful in obtaining these otherwise difficultly realizable structures.

(12) H. C. Brown and E. Negishi, *J. Am. Chem. Soc.*, **91**, 1224 (1969).

(13) Research assistant on grants (G 19875 and GP 6492 X) supported by the National Science Foundation.

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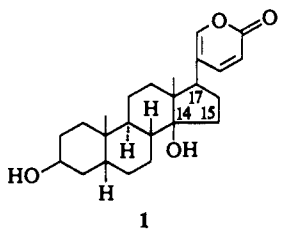
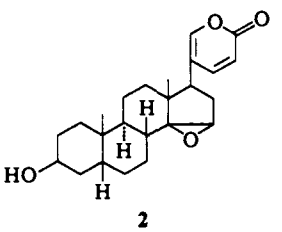
Synthesis of Bufadienolides. The Synthesis of Bufalin and Resibufogenin[1]

Sir:

The bufadienolides are a wide-spread group of heart-active steroids which occur in the poisonous secretion of the toad (in the free state or as conjugates), as well as in certain plants (as glycosides).[2] These substances all contain an α-pyrone ring at the 17β position, as well as a 14β-hydroxy group (*e.g.*, bufalin (**1**)) or a 14β,15β-oxido group (*e.g.*, resibufogenin (**2**)). Although methods have been developed for constructing the α-pyrone side chain,[3,4] as well as for preparing 14β-hydroxy (and 14β,-15β-oxido) steroids,[5] both types of grouping have not hitherto been introduced into the same molecule, and no natural bufadienolide has been synthesized previously. By comparison, several syntheses of the related cardenolides have been accomplished during recent years.[6] We now report syntheses of **1** and **2** (both constituents of Ch'an Su, a drug derived from the dried venom of the Chinese toad),[2] starting from common steroids. The work represents total syntheses of **1** and **2**, in a formal sense, since the intermediates are available by total synthesis.[7]

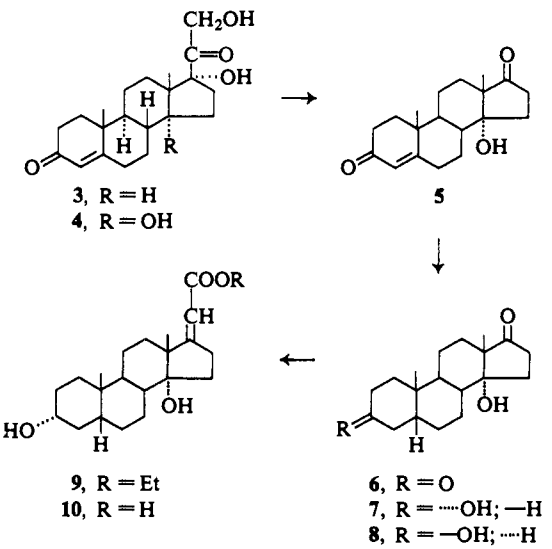


1



2

The starting material was 14α-hydroxycortexolone (**4**), available in quantity as a by-product in the commercial microbiological hydroxylation of cortexolone (**3**) to cortisol.[8,9] Side-chain degradation with sodium bismuthate, essentially as described,[10] gave 73% of 14α-hydroxy-4-androstene-3,17-dione (**5**, m.p. 256–259°). Substance **5** is also obtainable from 3β-acetoxy-5-androsten-17-one by a five-step chemical synthesis,[11] as well as from a number of 14α-hydroxy hormones derived by microbiological methods.[12] Catalytic hydrogenation of



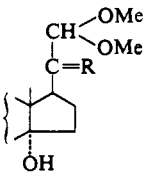
3, R = H
4, R = OH

5

9, R = Et
10, R = H

6, R = O
7, R = ····OH; —H
8, R = —OH; ····H

5 in methanol containing 1.5% of potassium hydroxide over 10% palladium–charcoal led mainly to 14α-hydroxy-5β-androstane-3,17-dione (**6**, mp 201–202°),[13] which without purification was reduced at C-3 with 1.25 equiv of sodium borohydride in 96% methanol at room temperature. Crystallization and chromatography on alumina then yielded 59% (based on **5**) of the 3α-ol **7** (mp 227–228°)[14] and 22% of the 3β-ol **8** (mp 223–225°). Only the major product **7** was used for the rest of the synthesis, but **8**



i, R = O

ii, R = CH_2

(1) Syntheses in the Cardiac Aglycone Field. VIII. For part VII, see N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **23**, 715 (1967).

(2) For a review, see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 20.

(3) D. Bertin, L. Nédélec, and J. Mathieu, *C.R. Acad. Sci., Paris*, **253**, 1219 (1961).

(4) (a) F. Sondheimer, *Chem. Brit.*, **1**, 454 (1965); (b) F. Sondheimer and E. Levy, unpublished experiments.

(5) For a review, see ref 4a.

(6) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **22**, 3189 (1966), and references given there.

(7) For reviews, see J. W. Cornforth, *Progr. Org. Chem.*, **3**, 1 (1955); I. V. Torgov, *Pure Appl. Chem.*, **6**, 525 (1963); L. Velluz, J. Valls, and G. Nominé, *Angew. Chem.*, **77**, 185 (1965).

(8) For references, see H. Iizuka and A. Naito, "Microbial Transformation of Steroids and Alkaloids," University of Tokyo Press, Tokyo, Japan, 1967.

(9) As mentioned in a lecture,[4a] **4** had previously been converted to the corresponding 21,21-dimethoxy-20-one i, and we had planned then to transform the side chain of i (after suitable reductions in ring A) to an α-pyrone by the method developed by us with a related 14-deoxy compound.[4a] A key step in this method involves conversion of the 21,21-dimethoxy-20-one to the 20-methylene-21,21-dimethoxy derivative by a Wittig reaction with methylenetriphenylphosphorane. However, all attempts to transform compounds of type i to ii with this reagent failed, and the corresponding reaction in the Δ^{14} series (derived by dehydration of i) could also not be effected.

(10) M. Tanabe and D. F. Crowe, *J. Org. Chem.*, **30**, 2776 (1965); L. Mamlok, A. Horeau, and J. Jacques, *Bull. Soc. Chim. Fr.*, 2359 (1965).

(11) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

(12) S. H. Eppstein, *et al.*, *ibid.*, **80**, 3382 (1958).

(13) K. Tsuda, H. Iizuka, Y. Sato, A. Naito, and M. Kato, *Chem. Pharm. Bull.* (Tokyo), **9**, 925 (1961).

(14) The infrared and nmr spectra of all new substances were in accord with the assigned structures. In addition, the mass spectra of most of the substances gave the appropriate molecular ions.