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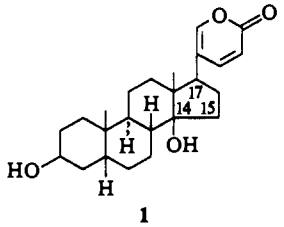
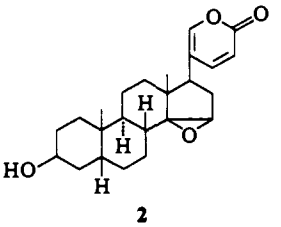
Synthesis of Bufadienolides. The Synthesis of Bufalin and Resibufogenin[1]

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]

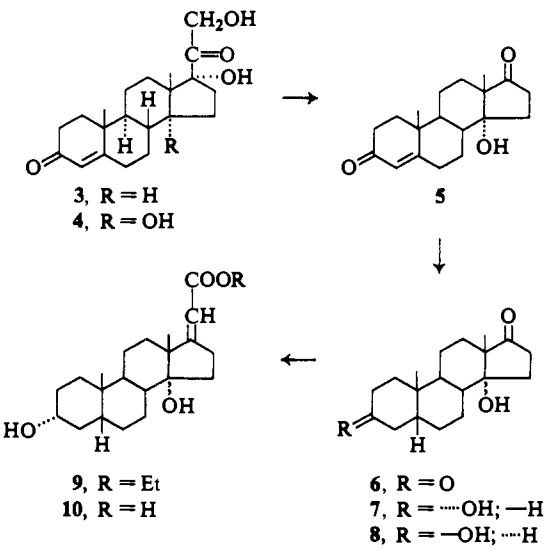


1



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



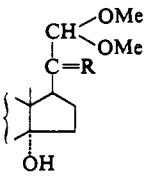
3, R = H
4, R = OH

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.

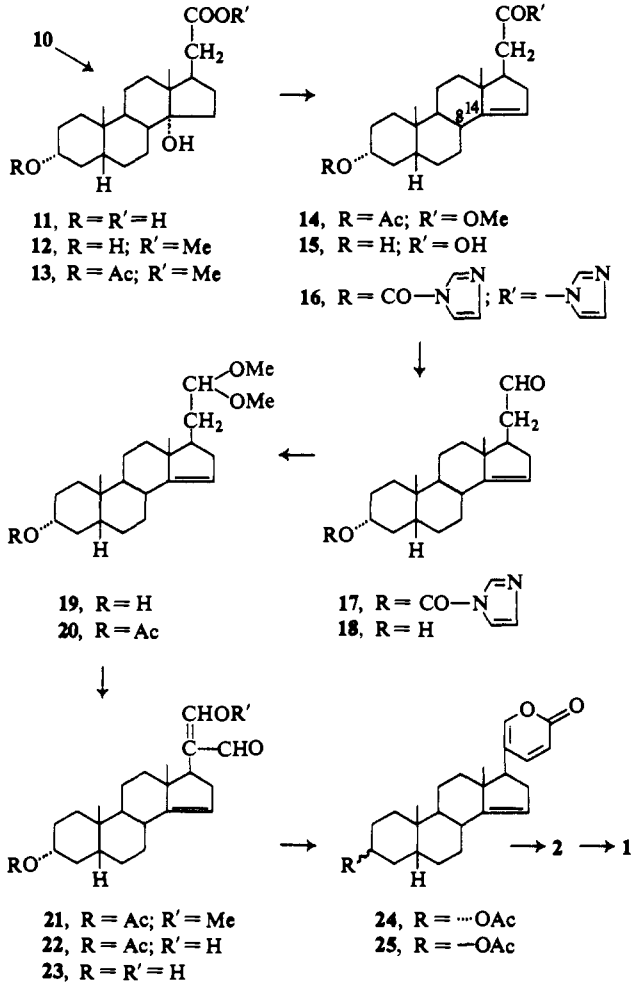
could presumably be utilized in an analogous manner.

The androstane derivative **7** was next reconverted to a pregnane through reaction with *ca.* 3.5 equiv of lithium ethoxyacetylide (from *n*-butyllithium and ethoxyacetylene) in dioxane–benzene–hexane at room temperature, followed by rearrangement of the 17-ethoxyacetylenic carbinol in dioxane with 2 *N* sulfuric acid.[15] The resulting unsaturated ester **9** on saponification with potassium carbonate in boiling aqueous methanol gave the acid **10** [mp 290–291°; λ_{max}^{EtOH} 224 mμ (ε 12,800)] in 74% yield (based on **7**). The stereochemistry of the $\Delta^{17(20)}$ double bond was not determined.

The next step, the chemical reduction of the double bond in **10**, proved to be troublesome. After some experimentation, it was found that the reaction proceeded smoothly when **10** in dioxane was added to a large excess (*ca.* 50 equiv) of potassium in liquid ammonia at −70°, followed by stirring at −50° for 16 hr. The resulting saturated acid (mp 220–222°), obtained in 95% yield, was assigned the desired 17β configuration **11** since the thermodynamically more stable isomer was expected to be formed.[16] Treatment of **11** in methanol with ethereal diazomethane led to the methyl ester **12** (mp 166–170°), which on acetylation yielded the noncrystalline acetate **13**.

Dehydration of **13** in pyridine with phosphorus oxychloride at 0–20°, followed by chromatography on silicic acid–silver nitrate (5:1), gave *ca.* 55% of the Δ^{14} compound **14** (one olefinic proton at τ 4.90 in the nmr spectrum; CCl_4, 100 MHz), as well as *ca.* 30% of the $\Delta^{8(14)}$ isomer (no olefinic protons in the nmr spectrum). Saponification of **14** with potassium carbonate in boiling aqueous methanol led to the Δ^{14}-hydroxy acid **15** (mp 218–219°) in 98% yield. The carboxylic acid function in **15** was now reduced to an aldehyde by a modification of the method of Staab,[17] through reaction with an excess of N,N'-carbonyldiimidazole in boiling tetrahydrofuran, followed by reduction of the resulting 3,21-bis derivative **16** at C-21 with excess lithium tri-*t*-butoxyaluminum hydride in tetrahydrofuran at room temperature. Hydrolysis of the product **17** at C-3 with dilute sulfuric acid in boiling *t*-butyl alcohol gave the noncrystalline hydroxy aldehyde **18** in 91% yield (based on **15**). Treatment with boiling methanol in the presence of *p*-toluenesulfonic acid led to over 90% of the dimethyl acetal **19** (mp 114–116°), which was acetylated to **20** (decomposes at *ca.* 200°).

The acetal **20** was now subjected to the Vilsmeier–Haack reaction[3] by adding a solution in dimethylformamide to a reagent prepared (at 0–50°) from equal volumes of phosphorus oxychloride and dimethylformamide and heating at 50° for 3 hr. Preparative thin layer chromatography then gave 60% of the "*cis*" isomer of the enol ether **21** (λ_{max}^{EtOH} 253 mμ) and 19% of the "*trans*" isomer (λ_{max}^{EtOH} 273 mμ).[18] Hydrolysis of the vinylogous ester "*cis*"-**21** with sodium hydroxide in aqueous ethanol at 30° for 16 hr led to a mixture of the enolized β-dialdehydes **22** and **23** (λ_{max}^{EtOH} 253 mμ, $\lambda_{max}^{EtOH+NaOH}$ 275 mμ),



which was subjected to Reformatsky reaction[3] by heating with methyl bromoacetate and zinc in dimethylformamide at 70°. Preparative thin layer chromatography resulted in the α-pyrone **24** [mp 179–181°; λ_{max}^{EtOH} 300 mμ (ε 5400)] in *ca.* 15% yield (based on "*cis*"-**21**).[19] Saponification of **24** with hydrochloric acid in aqueous methanol yielded the 3α-ol (mp 228–234°), which was converted to the *p*-toluenesulfonate (mp 156–159°) and then heated in dimethylformamide at 80° for 72 hr.[20] The resulting 3β-formate was saponified by shaking in ether with alkaline alumina to the 3β-ol, which was then acetylated. The resulting 3β-acetate **25** (mp 145–162°) proved to be identical with a sample (mp 144–161°) prepared by dehydration of bufalin acetate with thionyl chloride in pyridine at −40 to −10°.

Treatment of **25** in aqueous acetone with N-bromosuccinimide at room temperature and subsequent chromatography on basic alumina[21] gave 45% of resibufogenin acetate (mp 218–222°), identical with an authentic sample (mp 218–221°). Saponification by absorption in ether on

(15) See H. Heusser, K. Eichenberger, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 370, 1088 (1950).

(16) *Inter alia*, see G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer, and L. H. Sarett, *J. Am. Chem. Soc.*, **76**, 1715 (1954).

(17) H. A. Staab and H. Bräunling, *Ann.*, **654**, 119 (1962).

(18) "*trans*"-**21** was converted slowly to "*cis*"-**21** on standing in ethanol or ether, and more rapidly in the presence of dilute sodium hydroxide. The stereochemical assignments are based on the nmr spectra.

(19) The pure 3-hydroxy-β-dialdehyde **23** (mp 185–189°) on Reformatsky reaction gave no α-pyrone, and it appears that only the 3-acetoxy-β-dialdehyde **22** in the mixture reacted in the desired manner. An alternative synthesis of **24** was also investigated, involving condensation of the aldehyde group of "*cis*"-**21** with lithium ethoxyacetylide, followed by boiling with concentrated hydrochloric acid (see ref 4a); acetylation then led to an α-pyrone isomeric with **24**, the double bond having shifted to a tetrasubstituted (presumably the $\Delta^{8(14)}$) position.

(20) Method of F. C. Chang and R. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

(21) See H. Kondo and S. Kondo, Japanese Patent 21,779 (1965) (*Chem. Abstr.*, **64**, 3651*a* (1966)).

basic alumina for 16 hr led in high yield to **2** (mp 158–161°), identical with authentic **2** (mp 157–160°). Finally, reduction of **2** with an excess of lithium aluminum hydride in ether at −65° for 90 min[22] afforded 50% of **1** (mp 238–241°), identical with natural bufalin (mp 239–242°).

Acknowledgments. We are indebted to the Koninklijke Nederlansche Gist-en Spritusfabriek N.V. (Delft) for a generous supply of **4**, and to Professors K. Meyer (Basel), G. R. Pettit (Tempe), and T. Reichstein (Basel) for kindly providing samples of natural bufadienolides. We also thank Dr. J. Mathieu (Romainville) for valuable correspondence.

(22) See H. Kondo and S. Ohno, U. S. Patent 3,134,772 (*Chem. Abstr.*, **61**, 5736*f* (1964)).

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The Preparation of 2-Methoxypentaborane(9), a Novel Example of an Alkoxy Polyborane

Sir:

We have recently found that 1-iodopentaborane(9), 1-IB_5H_8, reacts with dimethyl ether to produce 2-methoxypentaborane(9), 2-$(CH_3O)B_5H_8$, in moderate yield. The only other examples of neutral alkoxypolyboranes have the general formula $ROB_{10}H_{13}$ and are prepared by a complex reaction between $NaB_{10}H_{13}$ and a solution of I_2 in various ethers.[1] The position of attachment of the alkoxy group is not known, but has been discussed.[2] A previous study of the reaction of 1-BrB_5H_8 with dimethyl ether resulted in the preparation of 2-BrB_5H_8 and 1-$CH_3B_5H_8$, but no tractable alkoxy derivatives of B_5H_9 were observed.[3]

In a typical preparation of 2-$(CH_3O)B_5H_8$, 1.317 g (6.97 mmoles) of 1-IB_5H_8 was allowed to react with 20.7 mmoles of liquid $(CH_3)_2O$ for 15 hr at −12°. High-vacuum fractional distillation of the pale yellow reaction mixture yielded 0.161 g (1.73 mmoles, 25%) of 2-$(CH_3O)B_5H_8$. There was 4.9 mmoles of $(CH_3)_2O$ consumed. Substantial quantities of B_5H_9, $B(OCH_3)_3$, and CH_3I, a relatively small amount of $HB(OCH_3)_2$, and traces of H_2 were also produced in the reaction. A side product of low volatility has prevented quantitative estimation of the 1-IB_5H_8 recovered from the reaction.

This new B_5H_9 derivative is a colorless liquid which freezes as a glass at −196°. Upon warming the glass begins to flow and then crystallizes. The melting point is in the vicinity of −100°. Representative vapor pressures are 4.4 ± 0.2 mm at 0° and 15.5 ± 0.2 mm at 20°. Moderately rapid decomposition occurs in the liquid phase such that the vapor pressures are of qualitative value only. In the gas phase at low pressure (~7 mm) no decomposition can be observed after 12 hr at ambient temperature (infrared).

The mass spectrum of 2-$MeOB_5H_8$, obtained using AEI MS-9 and CEC 21-103 spectrometers, is consistent with that expected for an alkoxypentaborane(9). The cutoff at *m/e* 94 corresponds to the parent ion $^{12}CH_3{}^{16}O^{11}B_5H_8{}^+$: calcd *m/e* 94.12754; found 94.12751 ± 0.00010 (estimated error range). The most intense peak in the spectrum at *m/e* 43 corresponds to $^{12}CH_3{}^{16}O^{11}BH^+$; calcd *m/e* 43.03552; found 43.03549 ± 0.00010.

The ^{11}B nmr spectrum of 2-$(CH_3O)B_5H_8$ (at 32.1 MHz) is very similar in appearance to that of 2-FB_5H_8.[4] The chemical shifts (δ in parts per million from $BF_3O(C_2H_5)_2$ ± 0.2), coupling constants (*J* in Hz ± 5), and relative areas are given in Table I. The extreme separation between the B(2) and B(4) resonances suggests that 2-$(CH_3O)B_5H_8$ is more closely related, electronically, to 2-FB_5H_8 than to any other known B(2)-substituted B_5H_9 derivative.

Table I

	δ	*J*	Area (rel)
B(2)–OCH_3	−14.1		1.00
B(3, 5)–H	+16.8	158	1.99
B(4)–H	+31.5	160	0.99
B(1)–H	+55.0	170	1.04

The ^1H nmr spectra of 2-$(CH_3O)B_5H_8$ (at 60 and 100 MHz) show the presence of two bridge hydrogen regions, as does the spectrum of 2-FB_5H_8.[4] Overlap of other areas of the spectra makes assignments for H–$B_{3,5}$, H–B_4, and H–B_1 ambiguous, but the general appearance is similar to that of 2-FB_5H_8. The methoxy resonance of 2-$(CH_3O)B_5H_8$ at −3.56 ppm is substantially shifted from that of $(MeO)_3B$ at −3.09 ppm.

The gas-phase infrared spectrum of 2-$(CH_3O)B_5H_8$ contains major bands (cm^{-1} ± 10) at 3005 (w), 2960 (w), 2870 (w), 2600 (s), 1985 (w, br), 1850 (w, br), 1475 (m), 1315 (s, br), 1005 (m), 950 (w), 875 (m), 825 (w). The two broad bands at 1985 and 1850 cm^{-1} are tentatively attributed to the two types of bridge hydrogens indicated in the ^1H nmr spectra. The band at 1475 cm^{-1} is attributed to the methoxy methyl deformation, and the band at 1005 cm^{-1} is probably due to a C–O stretch.

Boron trichloride reacts with 2-$(CH_3O)B_5H_8$ to form what appears to be a 1:1 complex. Solutions of the complex in CS_2 and BCl_3 exhibit ^{11}B nmr spectra similar to those expected for a mixture of 2-ClB_5H_8 and $ROBCl_2$ (which appears to undergo rapid exchange with excess BCl_3). Subsequent isolation of 2-ClB_5H_8, however, is not possible unless the mixture is heated to ~50°. Further studies of this behavior are in progress.

Acknowledgments. Support of this research by the National Science Foundation is gratefully acknowledged. We wish to thank Bill Stebbings for the exact *m/e* mass spectral determinations.

(1) M. F. Hawthorne and J. J. Miller, *J. Am. Chem. Soc.*, **82**, 500 (1960).

(2) R. E. Williams, *Inorg. Chem.*, **4**, 1504 (1965).

(3) A. B. Burg and J. S. Sandhu, *J. Am. Chem. Soc.*, **87**, 3787 (1965).

(4) A. B. Burg, *ibid.*, **90**, 1407 (1968).

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