Application of the Hofmann Elimination Reaction to α-, β-, γ-, and δ-Skytanthine[1a]

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Received November 25, 1968

The four isomers of skytanthine (1α, 1β, 1γ, and 1δ) were converted into quaternary ammonium salts and these were subjected to Hofmann β-elimination reactions. The pronounced differences in product composition are correlated with differences in stereochemistry of the reactants. Conformational differences appear to be important in determining the extent and direction of elimination *vs.* regeneration of tertiary amine. Gas chromatography using on-column reactions permitted study of a few milligrams of sample.

Of the *Skytanthus* alkaloids, β-skytanthine was the first to be subjected to the Hofmann degradation.[2] Later, α-, β-, γ-, and δ-skytanthine were prepared from the corresponding nepetalinic acids, and at least three skytanthine isomers were shown to be present in natural *Skytanthus* oil.[3]

Each quaternary salt derived from a skytanthine isomer can undergo either β elimination to form two possible methines or regeneration of the original amine. The double bond of the methine may appear in an isopropenyl group (*cf.* **3** and **5**) or in the junction of the methylene group to the cyclopentane ring (*cf.* **4** and **6**). However, only four methines result as shown in Scheme I. These studies were greatly facilitated by effecting the elimination reaction directly on a glpc column on a milligram scale.[4a] A second-stage Hofmann degradation readily removes nitrogen from these methines and provides dienes.[4a]

Scheme I shows a dramatic difference between 2α and 2β in direction of elimination. For 2α, only 5% 2-(*S*)-isopropenyl-N,N,5-(*S*)-trimethylcyclopentane-1-(*R*)-methylamine (**3**) resulted, and the main reaction product was N,N-dimethyl-2-*R*-[3-(*S*)-methyl-2-methylene-1-(*R*)-cyclopentane]propylamine (**4**), but 1α was also found. Care was taken to remove any 1α from the starting material 2′α by extraction with ether before conversion to the quaternary hydroxide for pyrolysis. When the Hofmann reaction was applied to 2β, a complete change in olefin proportions to favor an isopropenyl group rather than a methylene group was observed in the formation of 2-(*S*)-isopropenyl-N,N,5-(*S*)-trimethylcyclopentane-1-(*S*)-methylamine (**5**) and N,N-dimethyl-2-(*S*)-[3-(*S*)-methyl-2-methylene-1-(*R*)-cyclopentane]propylamine (**6**). The change in ratio was 65:0.2 (**5**:**6**) compared with 5:72 (**3**:**4**).

These changes in product composition prompted our including γ- and δ-skytanthine (1γ and 1δ) in the study. Pure α- and β-skytanthine (1α and 1β) were obtained from the natural oil. The γ and δ isomers were not available and were synthesized, along with a further supply of 1α, by reducing the appropriate nepetalinic acid to the diol, converting the diol to the ditosylate, and cyclizing this to the corresponding skytanthine isomer by heating with excess methylamine at 100° for 18 hr.[3a] The presence of δ-skytanthine in the natural oil was confirmed by glpc and mass spectroscopic studies, but the γ isomer was absent.[3,4b] These findings are of interest in the biogenesis of the methylcyclopentane monoterpenoid alkaloids.[4a]

The drastic change in methine yield in comparing 2α and 2β with 2γ and 2δ is notable. Regeneration of the starting skytanthine is the major outcome of the Hofmann reaction with 2γ and 2δ; the consequent scarcity of methines **3** and **6** necessitated study of these products exclusively by instrumental methods. Pyrolysis of methiodides 2′γ and 2′δ also led to low yields of methines and high yields of regenerated 1γ and 1δ. Other attempts to suppress regeneration of skytanthine isomers by substitution of other strong bases (NaH, $NaOCH_3$) and varying the pyrolysis temperature failed to alter the yield and ratio of products from 2γ and 2δ, even though it is known (and currently confirmed) that, in the Hofmann reaction of 1,2,3,4-tetrahydroquinoline, β elimination *vs.* regeneration of the tertiary amine can be altered by changing the reaction temperature.[5]

The different outcome of the pyrolysis of quaternary hydroxides 2α, 2β, 2γ, and 2δ may be rationalized with the aid of Dreiding models which show differences in both the preferred conformations and the resulting torsional angles of protons β to nitrogen. Newman projections are shown in Table I.

The chair models for 2α with *cis* ring junctions show both A_1 and B_1 to be reasonable ground-state conformations. Form A_1, with an equatorial C-4 methyl group and axial C-4 proton, does not present a favorable torsional angle for *anti* elimination[6a] to **3**. In contrast,

(1) (a) Supported by NIH Grant GM-11144 and NSF Grant GB-5607. (b) In part.

(2) (a) C. Djerassi, J. P. Kutney, and M. Shamma, *Chem. Ind.* (London), 210 (1961); (b) *Tetrahedron*, **18**, 183 (1962); (c) C. G. Casinovi, J. A. Garbarino, and G. B. Marini-Bettòlo, *ibid.*, **17**, 253 (1961).

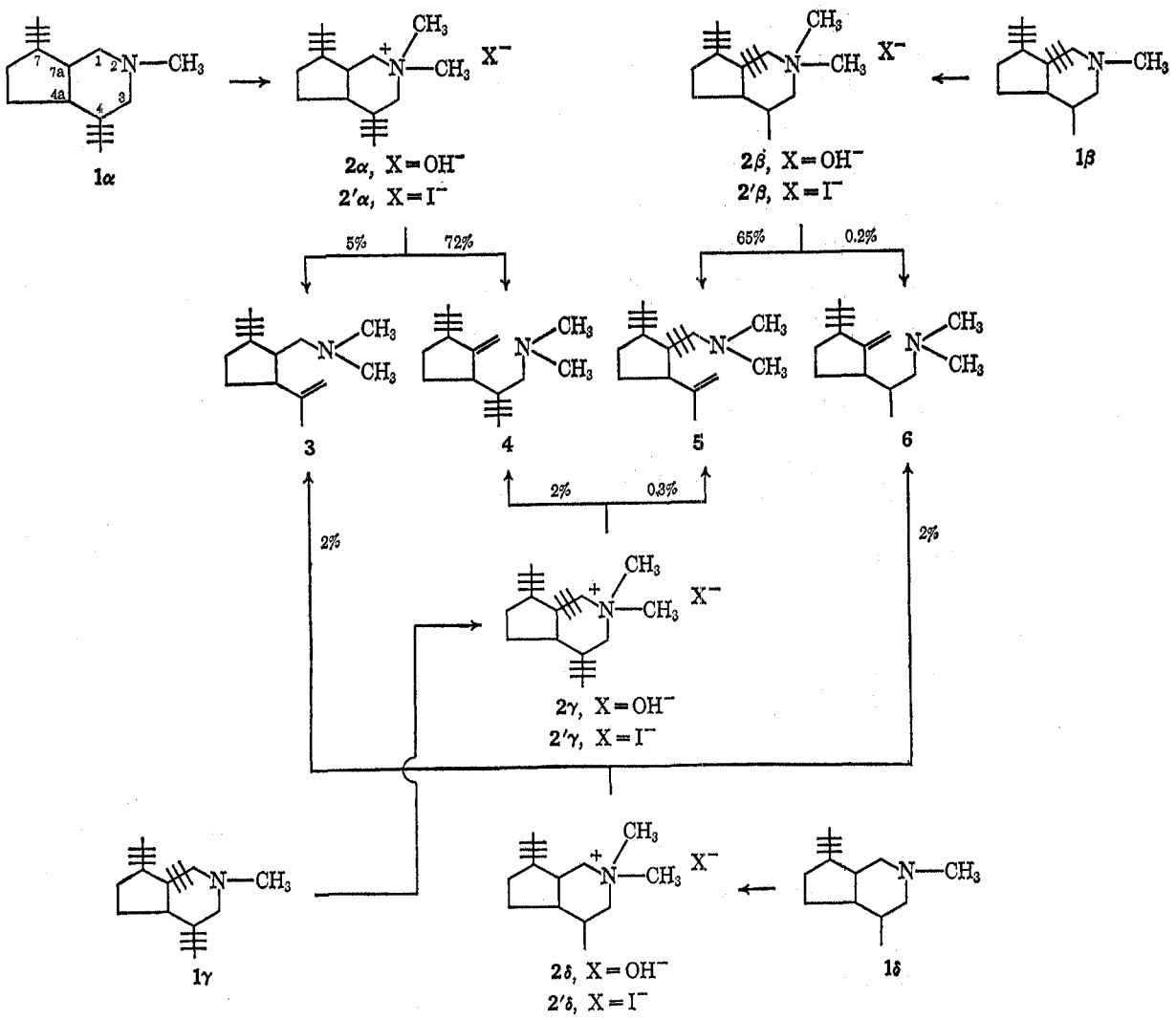
(3) (a) E. J. Eisenbraun, A. Bright, and H. H. Appel, *Chem. Ind.* (London), 1242 (1962). (b) C. G. Casinovi, F. Delle Monache, G. B. Marini-Bettòlo, E. Bianchi, and J. A. Garbarino, *Rend. Ist. Super. Sanita* (Ital. Ed.), **25**, 487 (1962).

(4) (a) H. Auda, H. R. Juneja, E. J. Eisenbraun, G. R. Waller, W. R. Kays, and H. H. Appel, *J. Amer. Chem. Soc.*, **89**, 2476 (1967). (b) Comparison of gas chromatography records for synthetic 1δ, the natural oil, and this oil enriched with 1δ showed the 1δ isomer as a small peak immediately following that for 1β in the gas chromatogram of the natural oil. The mass spectrum of natural 1δ was identical with that of synthetic 1δ.

(5) (a) A. C. Cope, *Org. React.*, **11**, 317 (1960); (b) J. F. Bunnett, *Angew. Chem. Int. Ed. Engl.*, **1**, 225 (1962); (c) D. J. Cram, F. D. Greene, and C. H. Depuy, *J. Amer. Chem. Soc.*, **78**, 790 (1956).

(6) (a) The most favorable situation for *anti*-elimination reactions is a planar four-center transition state with an 180° torsional angle between the β proton and the departing nitrogen atom. (b) For favorable *syn*-elimination reactions, this torsional angle should be near zero. (c) J. Závoda and J. Sicher, *Collect. Czech. Chem. Commun.* **32**, 3701 (1967); (d) M. Pankova, J. Závoda, and J. Sicher, *Chem. Commun.*, 1142 (1968); (e) J. L. Coke, M. P. Cooke, Jr., and M. C. Mourning, *Tetrahedron Lett.*, 2247 (1968); (f) D. S. Bailey and W. H. Saunders, Jr., *Chem. Commun.*, 1598 (1968); (g) D. H. Froemsdorf and H. R. Pinnick, Jr., *ibid.*, 1600 (1968); (h) G. G. Ayerst and K. Schofield, *J. Chem. Soc.*, 3445 (1960).

SCHEME I



the equatorial C-7 a proton of form A_1 provides an *anti* orientation to yield **4** as the observed major product. Yields of methine products are shown in Scheme I. Since **4** is the major product from 2α, form A_1 apparently resembles the most likely transition-state conformation for β elimination despite the unfavorable 1,3 interaction between the N-methyl and C-7 proton. A transition state leading from form B_1 to **3** would suffer from a severe *syn*-axial interaction of the methyl groups at C-4 and on nitrogen, and, in fact, **3** is found only to the extent of 5%. Form B_1, with an axial methyl group and equatorial proton at C-4, has a favorable (near 180°) torsional angle for β elimination from *cis*-2α to give methine **3**. The C-7a proton is considerably more hindered in form B_1 compared with form A_1.

It is pertinent that Hofmann degradation was reported to yield the methines **7a**, **7b**, **7c**, and **7d** from the corresponding piperidines and none of the isomeric methine with a methylene group attached to the ring.[6h] These results emphasize the importance of steric effects introduced by the presence of C-methyl substituents in the examples of Scheme I and Table I.

Similar analysis of the boat forms for 2α shows unfavorable torsional angles or severe steric hindrance so that these conformations are less likely.

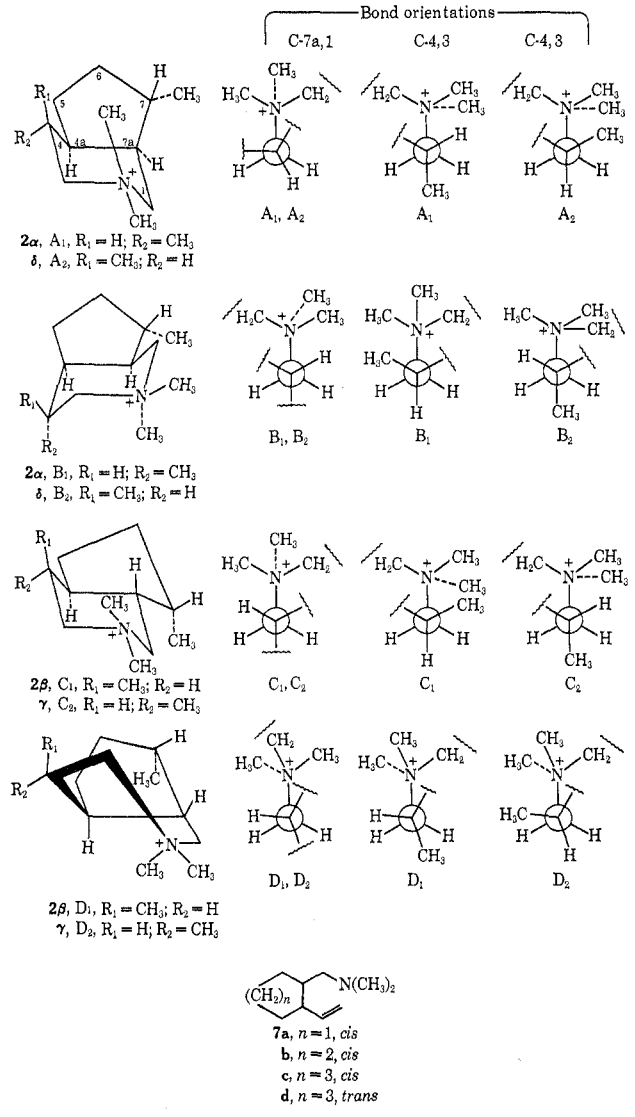
In 2β, form C_1 represents a chair model with a *trans* ring junction, and since a favorable torsional angle (180°)[6a] is observed for the equatorial C-4, a high yield (65%) of β elimination to **5** seems reasonable. *syn* elimination of the C-7a proton is considered unlikely owing to an unfavorable (*ca.* 60°) torsional angle,[6b] whereas relief of the 1,3-*syn*-axial C-4 methyl and N-methyl interaction in form C_1 facilitates formation of **5**.

Form D_1, a twisted boat, represents another model of 2β and shows a *ca.* 90° torsional angle for C–4 proton and approximately the same angle for the C-7a proton. Neither of these is favorable for β elimination.[6a,b]

The 2γ isomer with a *trans* ring junction is shown as the chair form C_2. This form may be compared to form C_1 of 2β, the two differing only in the configurations of C-4. However, inversion at this point destroys the stereochemistry favorable for *anti* elimination toward **5**. There results a change in ratio of products 2:0.3 (**4**:**5**) from 2γ compared with that of 0.2:65 (**6**:**5**) from 2β. Even more marked is the large drop in yield (to 2.3%) of *both* elimination products **4** and **5**, the formation of neither of which is now conformationally favored as an *anti* elimination, so that the major product from 2γ is the regenerated tertiary amine 1γ. A boat model (form D_2) does not appear to give better torsional angles[6a] for the elimination of a proton from C-4 or C-7a.

TABLE I

CONFORMATIONS AND NEWMAN PROJECTIONS FOR HYDROXIDES 2α, 2β, 2γ, AND 2δ



7a, $n = 1$, *cis*
b, $n = 2$, *cis*
c, $n = 3$, *cis*
d, $n = 3$, *trans*

The 2δ isomer is related to 2α by inversion of the methyl group at C-4 to give form A_2 or B_2. The model for form A_2 shows severe *syn*-axial interactions between N-methyl and axial C-4 methyl as well as the C-7 methine group. Thus, though the torsional angles for the equatorial C-4 proton (*ca.* 180°) and the C-7a proton in form A_2 are favorable and would be expected to give the observed 1:1 ratio (**3**:**6**) of olefins, the total yield of olefins is understandably low because a transition state corresponding in conformation to A_2 is disfavored by steric interactions. An arrangement with equatorial C-4 methyl (form B_2) is stable but for this conformation the torsional angles for both β-protons become unfavorable for elimination (*ca.* 80–120°),[6a,b] and the corresponding transition state leads to regeneration of tertiary amine **1**δ, which is, in fact, the main product of the reaction, olefins **3** and **6** being obtained in only 2% yield each.

Several eliminations from quaternary ammonium salts previously thought to proceed exclusively through an *anti* mechanism are now known to yield products which must arise through a *syn* mechanism.[6c-g] However, no studies demonstrating that a hetero quaternary nitrogen participates in *syn*-β elimination have appeared, and our results appear to favor the *anti* process. A *syn* process cannot be conclusively ruled out, but it would require acceptance of considerable deviation from the necessary eclipsing to permit elimination to olefin.

Experimental Section

Preparation of α-, β-, γ-, and δ-Skytanthine (1α, 1β, 1γ, and 1δ). A.—Isolation of 1α and 1β.—These were isolated by preparative gas chromatography of the steam-volatile oil from *Skytanthus acutus*[3] on a 15 ft × 0.5 in. column containing base-washed 80–100 mesh Chromosorb W coated with 15% Carbowax 20M heated at 130°. The retention times were 10 and 15 min, respectively, and the peak ratio was 1:9.

B.—Preparation of 1γ and 1δ.—These were prepared as previously reported.[3a] Their retention times were 26 min for **1**γ and 25 min for **1**δ.[7] The mass spectra[8] for **1**α, **1**β, **1**γ, and **1**δ are represented in Table II.

TABLE II

MASS FRAGMENTATIONS[a] OF 1α, 1β, 1γ, 1δ, 3, 4, 5, AND 6

	% ionization							
m/e	**1**α	**1**β	**1**γ	**1**δ	**3**	**4**	**5**	**6**
43	18	19	3	19				
44					10	12	24	6
58[b]	81	100	75	72	100	100	100	100
67	10	13	6	11				
81	9	13	5	1				
82					4	2	4	6
84	13	14	6	18				
98					6	1	16	13
110	1	12	15	12	4	1	3	8
124					3	2	2	2
138					3	1	2	1
152	20	22	20	23	3	1	5	1
166	100	100	100	100	6	3	11	3
167[c]	50	50	85	47				
181[c]					8	2	5	4

[a] See ref 8. [b] $[CH_2 \cdots N(CH_3)_2]^+$. [c] Parent ion.

α-, β-, γ-, and δ-Skytanthine Methiodides (2′α, 2′β, 2′γ, and 2′δ).—These were prepared in yields comparable to those previously reported[2a,b,4] and were purified by crystallization from ethanol and washed with ether before further use (Table III).

TABLE III

		Found[a]	
	Mp, °C	% C	% H
2′α	237–239	46.42	7.84
2′β	...[b,c]	46.23[d]	7.68[d]
2′γ	308–310	46.90	8.02
2′δ	303–305	46.84	8.25

[a] Calcd for $C_{12}H_{24}NI$: C, 46.60; H, 7.82; N, 4.56. [b] Lit.[2a,b] 296–298°. [c] Lit.[4] 293–295°. [d] Found: N, 4.45.

Conversion of 2′α, 2′β, 2′γ, and 2′δ to the Hydroxides 2α, 2β, 2γ, and 2δ.—The methiodides 2′α, 2′β, 2′γ, and 2′δ were converted to 2α, 2β, 2γ, and 2δ as described[2a,b,4a] except that water was removed by lyophilization. The methohydroxide concentrates were used as such.

Pyrolysis of 2α, 2β, 2γ, and 2δ to Methines 3, 4, 5, and 6.—The concentrates of 2α, 2β, 2γ, and 2δ were pyrolyzed at 180°

(7) A 0.25 in. × 10 ft glass column packed with base-washed 60–80 mesh Chromosorb P coated with 15% Carbowax 20M was used. The temperatures of the column, injector, and detector were 130, 210, and 280°, respectively.

(8) (a) The column,[7] separator, injector, and ion source of a prototype of the LKB-900 mass spectrometer–gas chromatograph were kept at 130–140, 250, 210, and 290°, respectively. (b) For the mass spectrum of **1**β, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, "Alkaloids," Holden-Day, Inc., San Francisco, Calif., 1964, pp 225, 226.

(1 mm) in small round-bottomed flasks[2a,b] or inside the injection port of the gas chromatograph.[4] Relative yields of **3**, **4**, **5**, and **6** were determined by planimeter measurement of glpc peak areas and are reported in Scheme I. The yields of recovered **1α**, **1β**, **1γ**, and **1δ** relative to total methine were 23, 35, 98, and 96%, respectively, and their retention times were 19, 25, 25, and 26 min on the 10 ft × 0.25 in. Carbowax 20M column.[7] Under the same conditions, **3**, **4**, **5**, and **6** showed 18, 22, 20, and 19 min retention, respectively. Samples of **4** and **5** were purified by preparative gas chromatography.[7] Some spectral properties follow.

Methine **4**: ir (liquid film) 2950, 2850, 2775, 2750, 1460, 1380, 1260, 1040, 880, 845 cm^{-1}; $[\alpha]^{23}D$ +139° (*c* 0.2, $CHCl_3$); nmr[9] (neat) δ 4.8 (m, 2), 2.1 (s, 6), 2.0 (s, 2), 1.0 (d, 3, J = 6 Hz), and 0.7 (d, 3, J = 6 Hz). *Anal.* Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79. Found: C, 79.17; H, 12.82.

(9) The nmr spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as internal standard. The infrared spectra were determined with a Beckman IR-5a spectrometer.

5:[2a,b] ir (liquid film) 2950, 2850, 2775, 2750, 1650 (6.05 μ),[2b,4a] 1460, 1380, 1270, 1050, 1030, 885 (11.30 μ);[2b,4a] nmr (CCl_4) δ 4.7 (m, 2), 2.1 (s, 6), 1.65 (m, 3), 0.85 (d, 3, J = 6 Hz).[10]

Peaks from the mass spectra of **3**, **4**, **5**, and **6** are reported in Table II.

Registry No.—**1α**, 2065-32-9; **1β**, 2232-27-1; **1γ**, 23912-39-2; **1δ**, 2883-89-8; **2′α**, 23912-41-6; **2′γ**, 23912-42-7; **2′δ**, 23912-43-8; **3**, 23912-44-9; **4**, 23912-45-0; **5**, 23912-46-1; **6**, 23912-47-2.

Acknowledgment.—We thank Dr. E. L. Eliel for his advice and many helpful suggestions, and Dr. O. C. Dermer, who also read the manuscript. The partial support of the National Research Foundation through GB-5607 and the American Petroleum Institute through API Research Project 58A is gratefully acknowledged.

(10) We acknowledge a prior nmr determination by H. R. Juneja.

Bufadienolides. 1. Introduction and Base-Catalyzed Condensation of Methyl Ketones with Glyoxylic Acid[1]

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Received February 11, 1969

Introduction to a series of contributions pertaining to syntheses of isocardenolides, cardenolides, isobufadienolides, and bufadienolides is presented. A comprehensive study of an aldol condensation between glyoxylic acid and various methyl ketones is described. At high hydroxyl ion concentration, methyl β-naphthyl ketone gives bis(β-naphthacyl)acetic acid (**11a**), but by careful control of pH the condensation can be directed to yield the γ-ketoacrylic acid **16a** and/or a mixture of α-hydroxy-γ-oxobutyric acid (**15a**) and α-methoxy-γ-oxobutyric acid (**17a**). The reaction is applied to methyl cyclopentyl ketone, 2,5-dimethoxyacetophenone, 2,4-dimethylacetophenone, pinonic acid (**18**), and the steroidal ketones, 3β-hydroxy-20-oxo-5-pregnene (**7a**) and 3β-hydroxy-20-oxo-5α-pregnane (**24a**).

Ch'an su, the dried venom of a common Chinese toad, and extracts of the Mediterranean plant *Scilla maritima* (white squill) have received varied application in primitive medical practice for at least several millennia. The latter has been used from *ca.* 3500 B.C.[3] in the form of active glycoside extracts, principally for its diuretic and heart effects, but by the middle ages applications of the drug had gradually subsided. The heart effects were rediscovered in the early 18th century, but, with introduction of digitalis glycosides about 1785,[4] the plant was again gradually abandoned. The pioneering chemical investigations of Stoll[5] with the squill glycosides and Wieland[6] with extracts from the European toad *Bufo vulgaris* led, respectively, to structures for scillaren A,[7] bufotalin[8] (**1a**), and bufalin[9] (**1b**). The aglycones proved to be steroids bearing an α-pyrone ring at position 17 (*cf.* **1a**).[10,11]

Characteristic chemical and physiological[12] features of the plant and toad steroidal α-pyrones appear in bufalin (**1b**). In 1957, when the present study was initiated, neither bufalin nor any naturally occurring bufadienolide had yielded to total synthesis, and indeed no method was available for preparing even simpler 5-substituted 2-pyrones, such as **3**. Since then a preliminary account of the synthesis of a steroidal α-pyrone of the bufadienolide type has been reported,[13] and recently Sondheimer described a synthesis of

(1) Steroids and Related Natural Products. XLVIII. For the preceding contribution, see J. C. Knight and G. R. Pettit, *Phytochemistry*, **8**, 477 (1969). This investigation was supported by Public Health Service Research Grants CY-4074 (C3) to CA-04074-06 and CA-10115-01 to CA-10115-02 from the National Cancer Institute, and is based, in part, on the Ph.D. dissertation submitted in June 1962 by G. L. Dunn to the University of Maine.

(2) To whom correspondence should be addressed.

(3) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., 1963.

(4) A. Stoll, *Chem. Ind.* (London), 1558 (1959).

(5) A. Stoll, E. Suter, W. Kreis, B. B. Bussemaker, and A. Hofmann, *Helv. Chim. Acta*, **16**, 703 (1933).

(6) H. Wieland and F. J. Weil, *Chem. Ber.*, **46**, 3315 (1913).

(7) A. Stoll and J. Renz, *Helv. Chim. Acta*, **24**, 1380 (1941).

(8) For leading references, see K. Meyer, *ibid.*, **32**, 1993 (1949).

(9) Isolation and structural determination of bufalin was reported by K. Kuwada [*J. Chem. Soc. Jap.*, **60**, 335 (1939); *Chem. Abstr.*, **34**, 1031 (1940)] and was confirmed by K. Meyer [*Helv. Chim. Acta*, **32**, 1238 (1949)].

(10) In the case of hellebrigenin, the same aglycone has been found in both a plant extract and toad venom. For this and other interesting facets of bufadienolide chemistry, see ref 3 and other reviews cited therein.

(11) Subsequent extensive studies of Ch'an su, particularly by K. Meyer and colleagues, has led to location and identification of a number of related bufadienolides in this material, the most recent being 19-oxocinobufagin and 19-oxocinobufotalin: K. Meyer, *ibid.*, **52**, 1097 (1969).

(12) The cardiac action of bufalin has been found almost equal to that of digitoxigenin (**2**) and in respect to local anesthetic potency on the rabbit cornea, *ca.* 90 times that of cocaine; see M. Okada, F. Sakai, and T. Suga, *Itsuu Kenkyusho Nempo*, **67**, 75 (1960); *Chem. Abstr.*, **55**, 16798 (1961). The bufadienolides generally display digitalis-like activity; *e.g.*, see K. K. Chen and A. Kovařikova, *J. Pharm. Sci.*, **56**, 1535 (1967); H. Murase, *Jap. J. Pharmacol.*, **15**, 72 (1965); *Chem. Abstr.*, **63**, 7517 (1965); W. Foerster, *Acta Biol. Med. Ger.*, **9**, 341 (1962); *Chem. Abstr.*, **58**, 11846 (1963).

(13) D. Bertin, L. Nedelec, and J. Mathieu, *Compt. Rend.*, **253**, 1219 (1961).