Synthetic Intermediates Potentially Useful for the Synthesis of Tetrodotoxin and Derivatives. II.[1] Reaction of Diazomethane with Some Shikimic Acid Derivatives

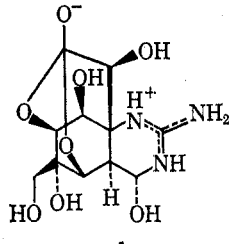
JOHN F. W. KEANA AND CHOUNG U. KIM

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

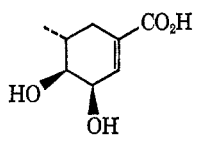
Received September 22, 1969

The reaction of diazomethane with three readily available derivatives, **3–5**, of natural shikimic acid has led to a series of new pyrazolines, the stereochemical assignments of which are discussed herein.

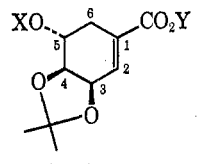
Our continuing interest in the synthesis of the Japanese puffer fish (*Fugu*)[2] and California newt (*Taricha Torosa*)[3] neuropoison tetrodotoxin (**1**) and closely related derivatives has led us to examine the reaction of diazomethane with alcohol **3**,[4] acetate **4**, and mesylate **5**, three readily available derivatives of natural shikimic acid (**2**). The pyrazolines which resulted, together with some of their chemistry, are described herein.



1



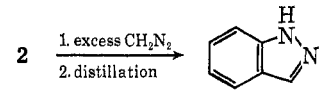
2



3, X = Y = H
4, X = Ac; Y = H
5, X = Ms; Y = H
6, X = Ac; Y = CH_3

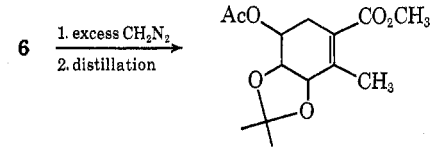
The pyrazolines were prepared with the idea that it should be possible to reduce them to the corresponding substituted 1,3-diaminopropane,[5] condensation of which with either cyanogen bromide[6] or nitroguanidine[7] should lead to a cyclic guanidine, a structural moiety present in tetrodotoxin. Subsequent elaboration of the carbocyclic ring would then lead to a toxin derivative.

The action of diazomethane on shikimic acid itself has been reported by Grewe[8] to afford an oil, presumably a mixture of stereoisomeric pyrazolines, which was not characterized but instead was distilled, affording indazole **7**. Grewe[8] also reported that addition of diazomethane to ester **6** gave an oil which could be



7

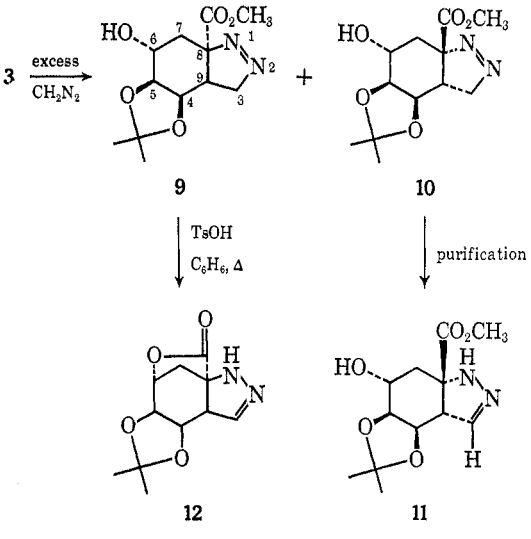
pyrolyzed to a mixture from which ester **8** could be isolated.



8

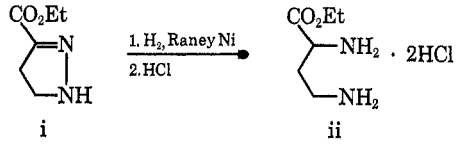
When hydroxy acid **3** (Chart I) was allowed to react with excess diazomethane in methanol–ether, a colorless oil was produced which, after chromatography over silica gel, afforded pyrazoline **9**, mp 108–109°, in 23% yield and pyrazoline **11**, mp 82–84°, in 75% yield.

CHART I



9 **10** **12** **11**

Presumably the Δ^1 isomer **10** was produced initially and then this substance suffered rearrangement during the purification process to the more stable[9] Δ^2 isomer **11** (see below). That pyrazoline **11** was indeed a Δ^2



i **ii**

(1) Part I: J. F. W. Keana, F. P. Mason, and J. S. Bland, *J. Org. Chem.*, **34**, 3705 (1969).

(2) K. Tsuda, *Naturwissenschaften*, **53**, 171 (1966); C. Y. Kao, *Pharmacol. Rev.*, **18**, 997 (1966); R. B. Woodward and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **86**, 5030 (1964); K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, K. Sakai, C. Tamura, and O. Amakasu, *Chem. Pharm. Bull.* (Tokyo), **12**, 1357 (1964); T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron*, **21**, 2059 (1965); C. Tamura, O. Amakasu, Y. Sassada, and K. Tsuda, *Acta Crystallogr.*, **21**, 219, 226 (1966).

(3) H. S. Mosher, F. A. Fuhrman, H. D. Buchwald, and H. G. Fischer, *Science*, **144**, 1100 (1964).

(4) H. O. L. Fischer and G. Dangschat, *Helv. Chim. Acta*, **18**, 1206 (1935).

(5) For example, pyrazoline i has been reduced in high yield with Raney nickel and hydrogen in ethanol to the diamine ii, isolated as the dihydrochloride after treatment of the reduction product with hot hydrochloric acid: H. E. Carter, F. R. Van Abeele, and J. W. Rothrock, *J. Biol. Chem.*, **178**, 325 (1949). For the reduction of hydrazones to amines with platinum and hydrogen, see, *inter alia*, F. W. Lichtenthaler, H. Leinert, and T. Suami, *Chem. Ber.*, **100**, 2383 (1967).

(6) P. Pierron, *Ann. Chim.* (Paris), **11**(9), 361 (1919).

(7) A. F. McKay, *Chem. Rev.*, **51**, 301 (1952).

(8) R. Grewe and A. Bokranz, *Chem. Ber.*, **88**, 49 (1955).

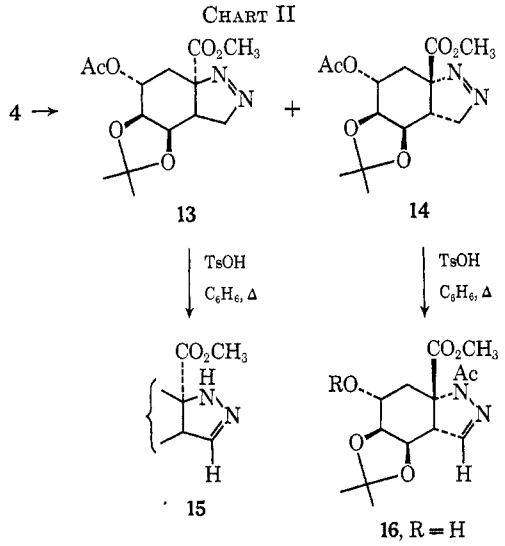
(9) See, *inter alia*, R. J. Crawford, A. Mishra, and R. J. Dummel, *J. Amer. Chem. Soc.*, **88**, 3959 (1966).

pyrazoline was clearly shown by its nmr spectrum,[10] which displayed a one-proton doublet (J = 1.5 Hz) at δ 6.9 owing to the proton at C-3 together with a broad NH absorption at δ 6.0–6.5. Pyrazoline **9** showed no absorption in this region. The two singlets which were due to the nonequivalent acetonide methyl groups of **9** were separated from one another by 4 Hz, whereas in **11** the separation was 9 Hz. This latter observation proved to be general for several stereoisomeric pyrazoline pairs resulting from the addition of diazomethane to various shikimic acid derivatives (see below and unpublished results).

Rinehart[11] has shown that diazomethane adds in a stereospecific *cis* manner to methyl angelate and methyl tiglate, leading to the corresponding Δ^1 pyrazolines. It is reasonable to assume that diazomethane will likewise add in a sterospecific *cis* manner to the rather analogous shikimic acid derivatives. Two Δ^1 pyrazolines, therefore, should be produced from **3**, and to the extent that the approach of diazomethane to **3** is sensitive to steric bulk, one would expect pyrazoline **10**, resulting from approach of diazomethane from the side opposite the bulky acetonide residue, to predominate. The stereochemistry of **9** was secured by reaction of this substance with a trace of *p*-toluenesulfonic acid in refluxing benzene, whereupon lactone **12**, mp 200–201°, was produced in moderate yield. Lactonization was accompanied by isomerization to a Δ^2 pyrazoline, as seen from the nmr spectrum of **12**, which displayed a one-proton doublet (J = 1.5 Hz) at δ 6.80 corresponding to the proton at C-3. The ir spectrum of **12** displayed a strong absorption at 1770 cm^{-1}, expected for a γ lactone. In order for lactone formation to occur with **9**, the C-6 α-hydroxy group and the C-8 carbomethoxy group must be *cis* to one another. Treatment of ester **11** under identical lactone-forming conditions led only to recovered starting material.

In another series of experiments, the acetylated derivative **4** (Chart II) was converted by excess diazomethane into an oily mixture of pyrazolines **13** and **14**.

CHART II

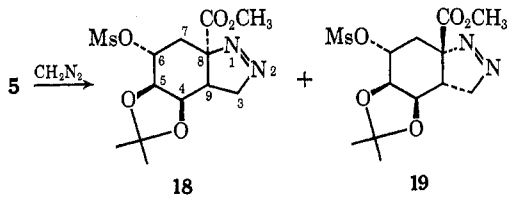


Chromatography over silica gel afforded **13** as a crystalline solid, mp 84–85°, in 27% yield and **14** as a homogeneous oil in 65% yield. It was expected that the preponderant isomer should have structure **14** (steric reasons, see above). Consistent with this formulation, the difference (see above) between the two singlets which were due to the methyl groups of the acetonide ring in **14** was 9 Hz, whereas this difference was 5 Hz in the case of **13**. Chemical proof of the stereochemical assignment was provided by the observation that **14** underwent a smooth *p*-toluenesulfonic acid catalyzed isomerization in refluxing benzene to Δ^2-pyrazoline **16**, mp 197–198°, in 78% yield, a process accompanied by migration of the acetyl group from oxygen to nitrogen.

This rather unusual *acid-catalyzed*[12] OAc → NAc migration was revealed by the nmr spectrum of pyrazoline **16**, which displayed the acetyl group as a sharp three-proton singlet at δ 2.25 rather than at δ 1.9–2.0, where it appeared with substances **13**–**15**, and by the ir spectrum of **16**, which showed a new strong band at 1620 cm^{-1} ascribed to the –HC=N– linkage. This band was not observed in the ir spectra of pyrazolines **11**, **12**, and **15**. Apparently the presence of the acetyl group on N-1 of pyrazoline **16** greatly enhanced the –HC=N– double bond absorption.

Pyrazoline **16**, upon treatment with acetic anhydride in pyridine, smoothly afforded diacetate **17**, mp 113–114°, the nmr spectrum of which displayed two three-proton acetyl singlets at δ 1.98 (OAc) and 2.23 (NAc). A strong band at 1620 cm^{-1} (–HC=N–) was present in the ir spectrum of this last substance. Treatment of pyrazoline **13** with *p*-toluenesulfonic acid in refluxing benzene led only to Δ^2-pyrazoline **15** (by nmr). From the above transformations, it follows that in pyrazoline **14** the C-6 acetoxy group and the pyrazoline ring are *cis* to one another.

Since it was important for later planned synthetic transformations to have a good leaving group attached to the 6 position, the mesylate acid **5** was prepared and subsequently treated with diazomethane. Again, two pyrazolines were isolated by silica gel chromatography of the reaction mixture. The preponderant isomer, an oil obtained in 36% yield, was assigned the stereochemistry embodied in structure **19**. The nmr spectrum of this substance showed a chemical-shift difference of 9 Hz between the two acetonide methyl singlets. The minor crystalline pyrazoline, mp 115–116°, was obtained in 21% yield and was assigned structure **18**. This last substance showed a corresponding chemical-shift difference of 4 Hz, in accord with differences shown by the pyrazoline pairs discussed above in which the stereochemistry was proven by chemical means.



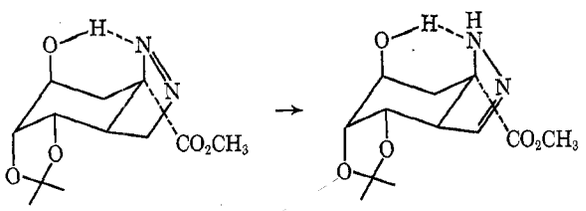
It is interesting that only in the case of the hydroxy-

(10) Complete spectral data for pertinent compounds are found in the Experimental Section.

(11) T. V. Van Auken and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **84**, 3736 (1962).

(12) OAc → NAc migrations are normally base catalyzed, whereas NAc → OAc migrations are normally acid catalyzed. See, *inter alia*, T. Posternak, "The Cyclitols," Holden-Day, Inc., San Francisco, Calif., 1965, p 31.

Δ^1-pyrazoline **10** was the Δ^1 isomer too easily isomerized to permit ready isolation. Quite possibly the hydroxy group assisted the isomerization in an intramolecular manner.



Experimental Section

Infrared spectra were recorded with a Beckman IR-5 spectrophotometer. Ultraviolet spectra were recorded with a Cary Model 15 spectrophotometer. Nmr spectra were determined on a Varian Associates Model A-60 high-resolution spectrometer. Chemical shifts are recorded in parts per million (δ) downfield from internal TMS, employing deuteriochloroform as solvent unless otherwise stated. Elemental analyses were performed by either Alfred Bernhard Laboratories, Mullheim, Germany, or Chemalytics, Inc., Tempe, Ariz. Mass spectra (70 eV) were determined on a CEC-110 spectrometer equipped with a direct inlet attachment. Melting points were determined in a stirred oil bath and are uncorrected. All chemicals were reagent grade. Solvents were routinely distilled prior to use.

Shikimic Acid 3,4-Acetonide (3).—The procedure of Fischer[4] was followed exactly. From 2.00 g of shikimic acid (Aldrich Chemical Co., mp 185–186°) there was obtained 2.17 g (87%) of **3**, mp 184.5–185.5° (lit.[4] mp 184°).

Diazomethane.—Diazomethane was prepared from Diazald[13] (Aldrich Chemical Co.). The resulting ether solution of diazomethane was distilled and the diazomethane content was estimated by portionwise addition of benzoic acid to an aliquot until the yellow color of the solution was discharged.

4β,5β,6α-Trihydroxy-8α-carbomethoxy-4,5,6,7,8,9α-hexahydro-3(H)-indazole 4,5-Acetonide (9) and 4β,5β,6α-Trihydroxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-1(H)-indazole 4,5-Acetonide (11).—A solution of 1.06 g (4.95 mmol) of acetonide **3** in 3 ml of methanol was added to a stirred solution of 1.5 g (36 mmol) of diazomethane in 60 ml of ether at 0°. After addition was complete, the resulting solution, protected from light by aluminum foil, was stirred at 0° for 1 hr and then at 25° for 12 hr. Removal of the solvent at reduced pressure afforded 1.64 g of a colorless oil which was chromatographed over 30 g of silica gel. Elution with 1% methanol in chloroform afforded first, crystalline minor pyrazoline **9**. Recrystallization of combined fractions from ether gave 320 mg (23%) of **9** as white needles: mp 108–109°; nmr δ 1.24 (s, 3, acetonide methyl), 1.30 (s, 3, acetonide methyl), 2.13 (q, 1, H-9), 2.6–3.2 (m, 2, H-7), 3.70 (s, 3, methyl ester protons), and 3.8–5.3 (m, 5, H-3–6); ir ($CHCl_3$) 3500 (w) and 1740 cm^{-1} (s); uv max (EtOH) 322 mμ (ϵ 182);[9] mass spectrum *m/e* 255 (loss of a methyl from the acetonide moiety[14]), 228 (loss of diazomethane or ketene), 167, 153, 135, 123, and 107.

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.92; H, 6.98; N, 10.27.

Continued elution with the same solvent system afforded oily pyrazoline **11**, which slowly crystallized in the cold room, probably picking up water (see analysis). Recrystallization from ether–hexane afforded 950 mg (75%) of **11** as white needles: mp 82–84°; nmr δ 1.38 (s, 3, acetonide methyl), 1.52 (s, 3, acetonide methyl), 1.7–2.5 (m, 2, H-7), 3.45–3.70 (m, 1, H-9), 3.80 (s, 3, methyl ester protons), 3.8–4.4 (m, 3, H-4–6), *ca.* 5.0–6.0 (broad, 1, H-1), and 6.90 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3400 (m) and 1740 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{18}N_2O_5 \cdot H_2O$: C, 49.99; H, 6.99; N, 9.72. Found: C, 50.25; H, 6.93; N, 9.76.

4β,5β,6α-Trihydroxy-8α-carboxy-4,5,6,7,8,9α-hexahydro-1(H)-indazole 4,5-Acetonide 8α→6α-Lactone (12).—A solution of 100 mg of pyrazoline **9** and 2 mg of *p*-toluenesulfonic acid monohydrate in 3 ml of dry benzene was heated at reflux under nitrogen for 12 hr. Removal of the benzene under reduced pressure afforded 84 mg of a reddish, crystalline solid. Recrystallization from ether–chloroform gave 35 mg (34%) of **12** as white needles: mp 200–201°; nmr δ 1.37 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 1.8–3.0 (m, 2, H-7), 3.4–5.0 (m, 4, H-4–6, -9), 5.6–6.0 (broad, 1, NH), and 6.80 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3300 (w) and 1770 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.32; H, 5.83; N, 11.88.

5-Acetylshikimic Acid 3,4-Acetonide (4).—To a solution of 2.66 g (12.4 mmol) of acetonide **3** in 10 ml of pyridine at 25° was added 1.3 ml (18 mmol) of acetic anhydride. The solution was allowed to stand under nitrogen for 24 hr at 25° and then the volatile solvents were removed under high vacuum at 25°, affording a slightly orange, viscous oil. The oil was dissolved in 50 ml of chloroform, washed with several portions of ice-cold 2% hydrochloric acid, dried ($MgSO_4$), and evaporated, affording 3.2 g (100%) of a viscous, colorless oil which slowly crystallized upon standing in the cold room. Because of its low melting point, recrystallization was not attempted. Molecular distillation at *ca.* 10^{-5} mm in a 100° oil bath afforded the analytical specimen as a colorless, hard oil: nmr δ 1.42 (s, 6, acetonide methyl) 2.10 (s, 3, acetyl protons), 2.1–2.8 (m, 2, H-6), 4.1–5.3 (m, 3, H-3–5), 6.9–7.2 (m, 1, H-2), and 8.7 (s, 1, acid proton); ir ($CHCl_3$) 2400–3000 (broad), 1750 (m), 1730 (s), 1670 (s), and 1650 cm^{-1} (w).

Anal. Calcd for $C_{12}H_{16}O_6 \cdot {}^1/_2H_2O$: C, 54.34; H, 6.41. Found: C, 54.51; H, 6.21.

4β,5β-Dihydroxy-6α-acetoxy-8α-carbomethoxy-4,5,6,7,8,9α-hexahydro-3(H)-indazole 4,5-Acetonide (13) and 4β,5β-Dihydroxy-6α-acetoxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-3-(H)-indazole 4,5-Acetonide (14).—To a solution of 1.5 g (36 mmol) of diazomethane in 60 ml of ether was added with stirring at 0° a solution of 2.1 g (8.2 mmol) of acetate **4** (sticky glass) in 20 ml of ether. The solution was allowed to stir protected from light for 12 hr at 25° and then the ether was evaporated, affording 2.3 g of a colorless oil. Chromatography over 45 g of silica gel and elution with 0.5% methanol in chloroform afforded first 700 mg (27%) of crude, crystalline **13**, mp 84–85°, suitable for further reactions. Recrystallization of a 500-mg portion from ether–hexane produced 200 mg of the analytical specimen as white prisms: mp 85–86°; nmr δ 1.26 (s, 3, acetonide methyl), 1.35 (s, 3, acetonide methyl), 1.8–2.8 (m, 1, H-9), 1.93 (s, 3, acetyl protons), 2.5–3.0 (m, 2, H-7), 3.0–5.3 (m, 5, H-3–6), and 3.72 (s, 3, methyl ester protons); ir (CCl_4) 3000 (m) and 1745 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.96. Found: C, 53.84; H, 6.19; N, 9.17.

Continued elution with the same solvent system afforded 1.6 g (65%) of **14** as a homogeneous (tlc), colorless oil. Molecular distillation at *ca.* 10^{-5} mm in a 110° oil bath afforded the analytical specimen as a colorless, hard oil: nmr (CCl_4) δ 1.28 (s, 3, acetonide methyl), 1.40 (s, 3, acetonide methyl), 1.7–2.2 (m, 1, H-9), 1.90 (s, 3, acetyl protons), 2.3–3.0 (m, 2, H-7), 3.5–5.3 (m, 5, H-3–6), and 3.80 (s, 3, methyl ester protons); ir (CCl_4) 3000 (m) and 1745 cm^{-1} (s); mass spectrum *m/e* 312 (parent ion), 298, 297 (loss of methyl), 270 (loss of diazomethane or ketene), and 269.

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.96. Found: C, 53.25; H, 6.19; N, 8.97.

1-Acetyl-4β,5β,6α-trihydroxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-1(H)-indazole 4,5-Acetonide (16).—A solution of 700 mg of **14** (hard oil), 2 mg of *p*-toluenesulfonic acid monohydrate, and 10 ml of benzene was heated at reflux under nitrogen for 60 min. Evaporation of the benzene produced a reddish glass which was chromatographed over 10 g of silica gel. Elution with 2% methanol in chloroform gave 550 mg (78%) of crystalline **16**, mp 197–198°. Two further recrystallizations from chloroform–hexane afforded the analytical specimen as white needles: mp 197–198°; nmr δ 1.32 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 2.25 (s, 3, N acetate), 2.5–3.2 (m, 2, H-7), 3.4–4.6 (m, 4, H-4–6, -9), and 6.86 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3400 (m), 3000 (m), 1750 (s), 1670 (s), and 1620 cm^{-1} (s); mass spectrum *m/e* 312 (parent ion), 297 (loss of methyl), 256, 255, and 254.

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.96. Found: C, 54.04; H, 6.48; N, 9.00.

1-Acetyl-4β,5β-dihydroxy-6α-acetoxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-1(H)-indazole 4,5-Acetonide (17).—To a

(13) T. J. DeBoer and H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **73**, 229 (1954).

(14) Acetonides frequently do not show a parent ion. See J. A. McCloskey and M. J. McClelland, *J. Amer. Chem. Soc.*, **87**, 5090 (1965).

solution of 200 mg (0.670 mmol) of **16** in 1.5 ml of pyridine at 0° was added under nitrogen 135 mg (1.33 mmol) of acetic anhydride. The solution was stirred for 12 hr at 25°, after which time the pyridine and excess acetic anhydride were removed by high vacuum distillation at 25°, affording 251 mg of a yellow, viscous oil. The oil was dissolved in 10 ml of chloroform and washed with ice-cold 2% hydrochloric acid. The chloroform layer was dried ($MgSO_4$) and then evaporated, affording 230 mg of pale yellow crystals. Recrystallization from ether–hexane gave 150 mg (65%) of **17** as white needles: mp 113–114°; nmr δ 1.32 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 1.98 (s, 3, O-acetate), 2.23 (s, 3, N-acetate), 2.3–2.8 (m, 2, H-7), 3.80 (s, 3, methyl ester protons), 3.8–5.2 (m, 4, H-4–6, -9), and 6.78 (broadened singlet, 1, H-3); ir ($CHCl_3$) 3000 (m), 1740 (s), 1670 (s), and 1620 cm^{-1} (s); mass spectrum *m/e* 354 (parent ion), 339 (loss of methyl), and 237.

Anal. Calcd for $C_{16}H_{22}N_2O_7$: C, 54.23; H, 6.26; N, 7.91. Found: C, 53.87; H, 6.07; N, 7.95.

4β,5β-Dihydroxy-6α-acetoxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-3(H)-indazole 4,5-Acetonide (15).—A solution of 1.7 g of the original mixture of Δ¹-pyrazolines **13** and **14** formed by the addition of diazomethane to acetate **4** (see above) and 15 mg of *p*-toluenesulfonic acid monohydrate in 15 ml of benzene was heated at reflux for 60 min under nitrogen and then the solvent was evaporated, leaving a reddish oil. Chromatography over 30 g of silica gel and elution with 0.5% methanol in chloroform afforded *ca.* 600 mg (24%, based on starting **4**) of **15** as a colorless, homogeneous (tlc) oil suitable for further reactions. The oil decomposed on attempted molecular distillation at *ca.* 10^{-5} mm in a 110° oil bath, forming a yellow oil, the elemental analysis of which showed <1% nitrogen (calcd: 8.98). An acceptable mass spectrum could not be obtained. Nevertheless, the nmr and ir spectra were completely consistent with those expected for **15**: nmr δ 1.32 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 2.00 (s, 3, acetate), 1.9–2.4 (m, 2, H-7), 3.7–5.1 (m, 4, H-4–6, -9), 3.75 (s, 3, methyl ester protons), 5.0–5.8 (broad, 1, NH), and 6.80 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3400 (m), 3000 (m), and 1747 cm^{-1} (s). Another experiment utilizing crystalline **13** as starting material for the isomerization also afforded an oil identical with **15** above by nmr.

Continued elution with 2% methanol in chloroform afforded 564 mg (23%, based on starting **4**) of crystalline **16** (see above), suitable for further reactions.

5-Mesylshikimic Acid 3,4-Acetonide (5).—To a solution of 500 mg (2.34 mmol) of acetonide **3**, 500 mg (4.95 mmol) of triethylamine, and 20 ml of benzene was added dropwise with stirring at 5° under nitrogen 570 mg (5.0 mmol) of methanesulfonyl chloride. After addition was complete the triethylamine hydrochloride was removed by filtration and the solvent was removed at 25° under vacuum, affording a viscous, reddish oil. This was dissolved in 30 ml of chloroform and washed with ice-cold 3% hydrochloric acid. The chloroform layer was dried ($MgSO_4$) and evaporated, producing 626 mg of a yellow oil. This oil contained some of the corresponding acid chloride and was therefore treated with a solution of 3 ml of acetone and 3 ml of 2% aqueous sodium bicarbonate at 25° for 12 hr. The solution was then acidified with 2% hydrochloric acid at 0° and then extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated, producing 488 mg (72%) of **5** as a colorless foam. Molecular distillation at 120° and *ca.* 10^{-5} mm afforded the analytical specimen as a colorless, hard oil: nmr δ 1.43 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 2.5–3.0 (m, 2, H-6), 3.17 (s, 3, mesylate), 4.1–5.1 (m, 3, H-3–5), and 6.9–7.2 (m, 1, H-2); ir ($CHCl_3$) 3600–2400 (broad), 3000 (m), 1780 (s), and 1725 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{16}O_7S$: C, 45.20; H, 5.49. Found: C, 44.69; H, 5.37. Analytically pure **5** acquired a deep red-brown coloration while standing for several days.

4β,5β-Dihydroxy-6α-mesyloxy-8α-carbomethoxy-4,5,6,7,8,9α-hexahydro-3(H)-indazole 4,5-Acetonide (18) and 4β,5β-Dihydroxy-6α-mesyloxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-3(H)-indazole 4,5-Acetonide (19).—To a solution of *ca.* 50 mg (1.2 mmol) of diazomethane in ether was added at 0° with stirring a solution of 100 mg (0.34 mmol) of crude mesylate **5** (yellow oil) in 1 ml of methanol. The solution was stirred for 12 hr at 25° and then the solvent was evaporated, affording 130 mg of a reddish oil. Chromatography over 10 g of silica gel and elution with chloroform afforded first 25 mg (21%) of crystalline **18**. Recrystallization of the combined fractions from ether–hexane afforded 20 mg of **18** as white needles: mp 115–116°; nmr δ 1.28 (s, 3, acetonide methyl), 1.35 (s, 3, acetonide methyl), 1.5–3.5 (m, 3, H-7, -9), 3.05 (s, 3, mesylate), 3.75 (s, 3, methyl ester protons), and 4.0–5.3 (m, 5, H-3–6); ir ($CHCl_3$) 3000 (m) and 1745 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{20}N_2O_7S$: C, 44.83; H, 5.75; N, 8.05. Found: C, 44.87; H, 5.78; N, 8.03.

Continued elution with chloroform afforded 45 mg (36%) of **19** as a homogeneous (tlc) oil which resisted attempts at crystallization. Molecular distillation at *ca.* 10^{-5} mm in a 110° oil bath produced the analytical specimen of **19** as a colorless, hard oil: nmr δ 1.30 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 1.5–3.5 (m, 3, H-7, -9), 3.05 (s, 3, mesylate), 3.83 (s, 3, methyl ester protons), and 4.0–5.4 (m, 5, H-3–6); ir ($CHCl_3$) 3000 (m) and 1745 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{20}N_2O_7S$: C, 44.83; H, 5.75; N, 8.05. Found: C, 44.50; H, 5.63; N, 8.12.

Registry No.—**1**, 4368-28-9; **4**, 23330-72-5; **5**, 23367-55-7; **9**, 23367-56-8; **11**, 23330-73-6; **12**, 23367-57-9; **13**, 23328-30-5; **14**, 23328-31-6; **15**, 23367-58-0; **16**, 23367-59-1; **17**, 23328-32-7; **18**, 23328-33-8; **19**, 23328-34-9; diazomethane, 334-88-3.

Acknowledgment.—The authors thank the National Science Foundation (GP 10736) and the National Institutes of Health (5-R01-NB07586-02) for generous financial support of this work, and Hoffman-LaRoche for a generous gift of shikimic acid.