Reaction of Santonin with Hydroxylamine[1]

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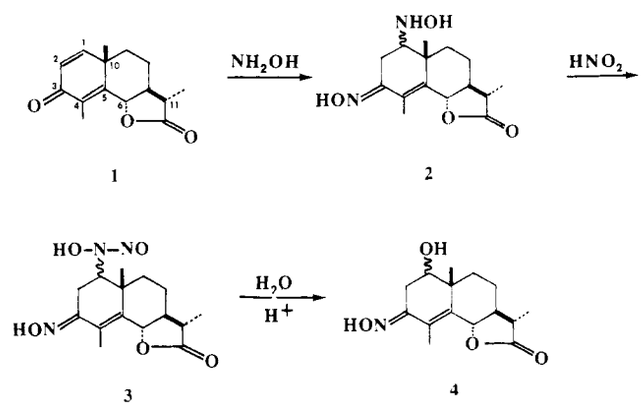
Structures are assigned on the basis of UV, IR, and NMR spectra to the products obtained by Francesconi and Cusmano[2] from the reaction of santonin with excess hydroxylamine. Reaction under approximately neutral conditions affords, in addition to santonin oxime, (1*S*,4*S*,5*R*)-5,1-(epoxyimino)tetrahydrosantonin (*E*)- and (*Z*)-oximes (**6**); under strongly alkaline conditions it affords the 4*R*-*Z*-isomer **5**. These react with benzaldehyde to give isomeric (1*S*, 5*R*)-5,1-[epoxy(phenylmetheno)nitrilo]tetrahydrosantonin (*E*)- and (*Z*)-oximes (**23**), and with nitrous acid to give *N*-nitroso derivatives. The latter decompose in aqueous acetic acid and form (1*R*,4*R*,5*S*,10*S*)- and (1*R*,4*S*,5*S*,10*S*)-3-(*E*)- and -(*Z*)-oximino-5,10-epoxyhexahydrohyposantonin (**9, 10**).

Francesconi and Cusmano[2] observed that (−)-α-santonin (**1**)[3] reacted with an excess of hydroxylamine to give, besides the expected oxime, two isomeric products ("α- and β-hydroxylaminosantonin oximes") containing an additional molecule of hydroxylamine. Many years later, it was suggested[4] that these two compounds had structures (possibly stereoisomeric) represented by **2**, produced by Michael-type addition for which there is ample precedent.[5] On the basis of these structures, the further reactions observed by Francesconi and Cusmano were rationalized as shown in Scheme I. Thus, the nitroso derivatives **3**, on digestion with 50% acetic acid, gave two isomeric compounds ("hydroxysantonin oximes") which could be formulated as **4**; again, a reaction with ample precedent.[6] However, dehydration of either of the hydroxysantonin oximes was reported to give, not the expected santonin oxime, but a product isomeric with it. This pointed to the possibility of skeletal rearrangement, and so we undertook the reexamination of Francesconi and Cusmano's compounds by the physical techniques (UV, IR, NMR) not available in their day. This work showed that the structures of Scheme I must be revised to those of Scheme II.

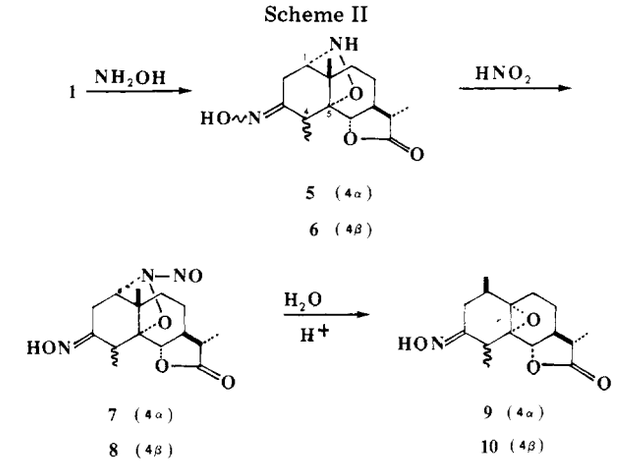
Our preliminary attempts to obtain other bridged epoxyimino compounds from cyclic dienones such as 4-trichloromethylcyclohexa-2,5-dienone and cholesta-1,4-dien-3-one were unsuccessful;[1] however, more recently Rice and Weiss[7] have observed a double Michael-type addition of the OH and NH of hydroxylamine across the double bonds of phorone to give an oxazepine, and the generality of this reaction remains yet to be explored.

Scheme I



1 2 3 4

Scheme II



5 (4α)
6 (4β)
7 (4α)
8 (4β)
9 (4α)
10 (4β)

Results and Discussion

We now review the spectroscopic properties of these compounds which necessitated the reformulations of Scheme II.

Epoxyaminosantonin Oximes 5 and 6. The isomeric α- and β-hydroxylaminosantonin oximes of Francesconi and Cusmano were obtained by reaction of santonin with an excess of hydroxylamine, the α compound under strongly basic conditions and the β compound under the approximately neutral conditions provided by 4 molar equiv of hydroxylamine and 0.4 molar equiv of hydroxylamine hydrochloride. These compounds had the correct analyses and had physical properties (mp, $[\alpha]_D$) in good agreement with those reported.[2] However, while the α compound gave single spot on TLC, the β compound gave two spots and is probably a mixture of (*E*)- and (*Z*)-oximes (see below).

The UV, IR (see Experimental Section for details), and ^1H NMR spectra (discussed below) excluded α,β-unsaturated oxime structures such as **2** and pointed to the saturation of the 4,5-double bond as in **5**/**6** (Scheme II). Such a bridged structure also accounted for the presence of only two exchangeable hydrogen atoms and not three as required by **2**. This was shown by treatment of both α and β isomers with excess D_2O, which caused the disappearance of a sharp NMR singlet at δ 10.42 (oxime OH) and a broad peak (NH; δ 7.07 for α and 7.10 for β compound). The two *O*,*N*-dibenzoyl derivatives had no exchangeable hydrogens.

Accepting a bridged structure, four isomers appear plausible on mechanistic grounds, according to whether the bridge is below (α) or above (β) the molecule and whether nitrogen is attached to C_1 or C_5. The evidence for the particular structures **5** and **6** comes from the decomposition products of the nitroso derivatives discussed below.

Stereochemical Difference between Hydroxylaminosantonin Oximes α and β. Santonin forms two isomeric oximes (α, mp 230 °C; β, mp 218 °C),[4] presumably geometrical isomers, and the difference between the hydroxylaminosantonin oximes α and β could be due to a similar difference of oxime configuration. Consequently, the oxime grouping was removed under conditions mild enough not to affect the rest of the molecule.[8] Reaction of the α isomer with sodium bi-

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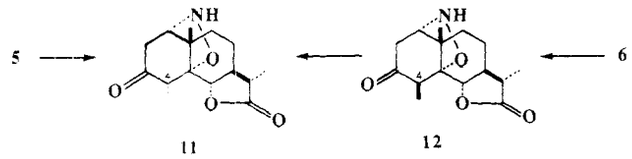
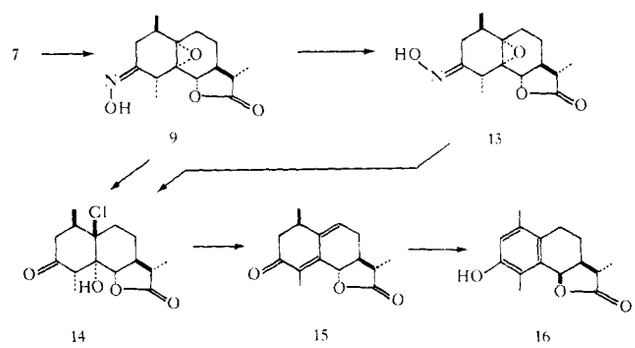
Scheme III



Scheme IV



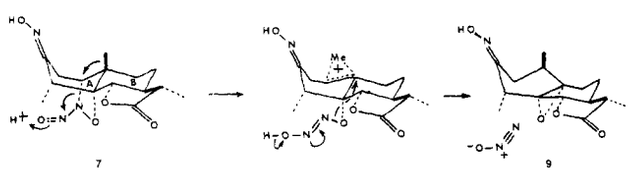
sulfinte in aqueous ethanol, followed by decomposition of the intermediate bisulfite complex with dilute hydrochloric acid,[10] gave a little santonin and a good yield of an epoxyimino ketone, $C_{15}H_{21}NO_3$, which we can formulate as **11** (Scheme III), because of the disappearance from the IR spectrum of the oxime O–H band and the appearance of a ketone band (IR, 1710 cm^{-1}; UV, λ_{max} 294 nm, ϵ_{max} 17).

The reaction of the β isomer gave initially a more complex mixture, as shown by TLC. However, on workup the major product turned out to be the same epoxyimino ketone (formulated above as **11**) accompanied by some santonin. Thin-layer chromatography of the mother liquors showed the presence of another compound in addition to **11**; when a small amount of sodium methoxide was added to the mother liquors, this compound disappeared and the amount of **11** increased. This is most easily interpreted as the epimerization of an axial C_4 methyl in **12** to an equatorial C_4 methyl in **11** (Scheme III); such alkali-catlayzed epimerization cannot take place until the oximino has been converted into a carbonyl group.

This evidence would require α and β isomers to have the epoxyimino bridge attached in the same way to the santonin skeleton so that the difference between them resides in the configuration at C_4 (and possibly also in the oxime configuration). It also indicates the probable genesis of α and β compounds. The latter is formed under approximately neutral conditions and requires the formation first of **12** by attack of hydroxylamine on the underside of the molecule, followed by rapid reaction of **12** with the large excess of hydroxylamine to give the stable β-compound **6** before epimerization at C_4 can take place. On the other hand, when the reaction is carried out in strongly alkaline solution, the intermediate **12** first formed epimerizes to **11**, which then reacts with excess hydroxylamine to give the α-compound **5**. This route is supported by the observation that **5** was obtained by the reaction of hydroxylamine with **11** but not with santonin oxime.

Reactions of the α-Nitroso Derivative 7. (Scheme IV). Hydroxylaminosantonin oxime α reacted with nitrous acid to give a nitroso compound having properties in general agreement with those described by Francesconi and Cusmano. The UV spectral data indicated a nitrosamine[11] (e.g., **7**) and not a nitrimine.[12]

When heated in 50% aqueous acetic acid, the nitroso compound formed nitrous oxide and the compound $C_{15}H_{21}NO_4$, for which the hydroxy structure **4** had been advanced[4] (Scheme I). This structure can be eliminated, because of the absence of a UV peak above 200 nm and because the NMR spectrum shows only one exchangeable proton (oxime, δ 8.75). The rearranged structure **9** is indicated by the fact that all methyl peaks in the NMR spectrum are now doublets and is further confirmed by the reactions of Scheme IV, discussed below. First, however, we should note that the formation of **9** supports, in turn, the structure **7** for the nitroso compound,



with the nitrosamine group axial and trans to the 10-methyl group, so that a facile rearrangement can be envisaged. Accepting such a mechanism requires the epoxyimino bridge to be attached to the underside (α) of the molecule, with the nitrogen linked to C_1 rather than C_5.

Treatment of the epoxy oxime **9** with levulinic acid–hydrochloric acid at room temperature to remove the oxime grouping[8] gave crystalline material, shown by TLC to be a mixture of two compounds. These were separated by preparative TLC. One proved to be a compound isomeric with **9** to which we assign the structure **13.** The epoxide ring forces rings A and B in both compounds to adopt half-chair conformations (if we choose to ignore boat conformations). That of ring B is fixed by the trans-fused lactone ring. However, ring A can adopt two half-chair conformations. In one (shown in **9**), the C_1 methyl group is in a quasiaxial position, involving an interaction energy of ca. 0.7 kcal/mol; in the other, the C_4 methyl group and the oxime hydroxyl are involved in an $A^{(1,3)}$ interaction (ca. 3.7 kcal/mol).[13] In acid solution, isomerization of the oxime group[14] to the configuration shown in **13** permits a half-chair conformation in which both C_1 and C_4 methyl groups avoid these interactions.

The second compound was rather unstable, but its analysis and spectral properties pointed to the chlorohydrin structure **14.**

Treatment of **9** with levulinic acid–hydrochloric acid at a higher temperature (100 °C) gave a crystalline compound $C_{15}H_{18}O_3$ whose ultraviolet[15] and NMR spectrum indicated a diunsaturated ketone structure as in **15.** More prolonged treatment of **9** at 100 °C gave (−)-α-desmotroposantonin (**16**).[4] This compound is known to have the β conformation at C_6.[3] The work of Cocker and McMurry[16] makes it likely that isomerization of **15** first affords the C_6 epimer of **15,** which then epimerizes to the more stable **16,** and this accords with NMR data discussed below.

Reactions of the β-Nitroso Compound 8 (Scheme V). When the β-nitroso compound **8** was heated in 50% acetic acid, nitrous oxide was again evolved and three compounds were obtained. One proved to be the oxime **19,** converted by treatment with sodium bisulfite into **15** in quantitative yield.

The other two compounds were separated by column and

Scheme V

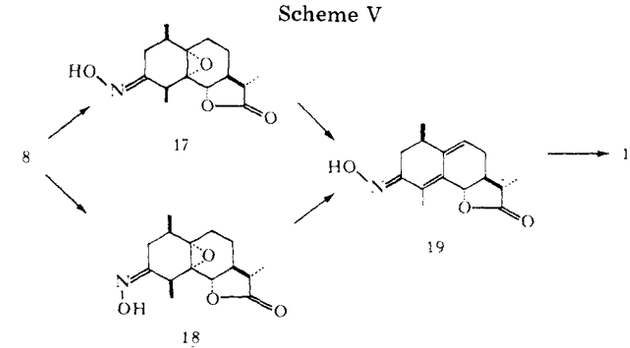


Table I. Chemical Shifts (δ) of Compounds [a] Having a 10-Methyl Group

Compound	Registry no.	4-CH_3[c]	6-H[d]	10-CH_3[e]	11-CH_3[f]
1	481-06-1	2.13[g]	4.88	1.34	1.27
Santonin oxime	1618-82-2	2.16[g]	4.80	1.27	1.25
5[b]	64201-45-2	1.24[h]	4.10	1.07	1.07
O,N-Dibz-**5**	64201-46-3	1.62[i]	4.07	1.31	1.15
6		1.23[h]	4.22	1.12	1.06
O,N-Dibz-**6**		1.60[j]	4.14	1.28	1.13
11	64201-47-4	1.33[h]	3.98	1.27	1.21
23-α		1.42[h]	4.12	1.23	1.24
23-β		1.35[k]	4.22	1.32	1.18

[a] Dissolved in $CDCl_3$ except **5**. [b] Dissolved in Me_2SO-d_6. [c] d, 3 H. [d] d, J = 10 Hz, 1 H. [e] s, 3 H. [f] d, J = 7 Hz, 3 H. [g] J, 1 Hz. [h] J = 7 Hz. [i] J = 6 Hz. [j] J = 8 Hz. [k] J = 10 Hz.

Table II. Chemical Shifts (δ) of Compounds [a] Having the 10-Methyl Group Shifted to the 1 Position

Compound	Registry no.	4-CH_3	6-H[b]	1-CH_3	11-CH_3[c]
9	64201-48-5	1.36[d]	4.19	1.24[e]	1.08
O-Bz-**9**	64201-49-6	1.45[d]	4.12	1.17[e]	1.07
13	64234-76-0	1.35[d]	4.16	1.24[e]	1.05
14	64201-50-9	1.12[d]	4.50	1.12[e]	0.99
17	64234-77-1	1.38[d]	4.34	1.10[e]	1.05
18	64234-78-2	1.45[d]	4.30	1.20[e]	1.12
15	64201-51-0	1.93[f]	4.58	1.15[e]	1.02
19	64201-52-1	2.15[f]	4.69	1.23[e]	1.00
16	13743-88-9	2.20[f]	5.72	2.20[f]	1.28

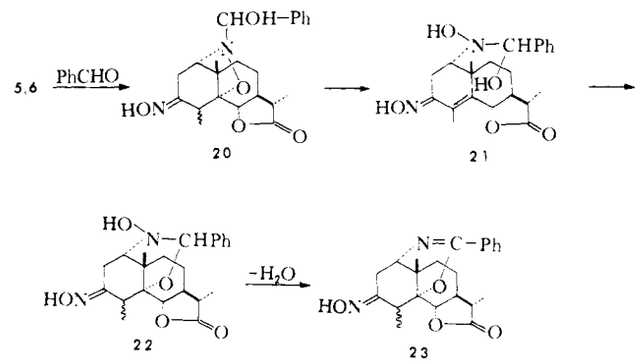
[a] Dissolved in $CDCl_3$. [b] d, J = 8.5–10 Hz, 1 H, except for **16** (see text). [c] d, J = 6–8 Hz, 3 H. [d] d, J = 7 Hz, 3 H. [e] d, J = 6 Hz, 3 H. [f] s, 3 H.

plate chromatography and proved to be isomeric with the epoxy oximes **9** and **13** already described (Scheme IV). They were assigned the structures **17** and **18** from arguments similar to those outlined above for **9** and **13** and based on NMR spectra. A mixture of **17** and **18** in refluxing 50% acetic acid after 1 h was converted into **19.**

Since the epoxy oxime **9** is the sole product from the decomposition of the nitroso compound **7** in 50% acetic acid, we may conclude that **7** and its precursor **5** (Scheme II) have the oxime hydroxyl syn to C_4. On the other hand, the simultaneous formation of the syn (**18**) and anti (**17**) compounds from decomposition of the nitroso compound **8** in 50% acetic acid indicates that **6** and **8** are probably each a mixture of geometrical isomers, as concluded earlier from TLC studies. However, the mixture is probably made up mostly of the anti isomer, because alkaline treatment of **8** (which we have not studied) was reported by Francesconi and Cusmano[2] to eliminate the bridge and give santonin oxime β, mp 218 °C, while similar treatment of **7** gave santonin oxime α, mp 230 °C (dec). These compounds can differ only in the configuration of the oximino group; on the basis of the arguments advanced above, the first oxime would be *E* containing some *Z* and the second *Z*.

Reaction of Hydroxylaminosantonin Oximes α and β with Benzaldehyde. Francesconi and Cusmano[2] found that both hydroxylaminosantonin oxime α and β reacted with benzaldehyde in refluxing ethanol to give "benzal" derivatives $C_{22}H_{26}N_2O_4$. Following their procedure, we obtained a product from **5** having properties agreeing well with those reported. From **6** we obtained a compound having almost the same melting point as the compound from **5;** however, a mixture melting point showed the two compounds to be different.[17] The IR and NMR spectra of these compounds again indicated the absence of both olefinic double bonds and hence the presence of bridged structures; the NMR spectra also showed the disappearances of the bridge NH groups of **5** and **6.** The only reasonable structure permitted by the empirical

Scheme VI



formulas is **23,** which accords with the UV spectra of the compounds in neutral and acid solution and with their p*K*s (α, 4.65; β, 4.70) all close to the values expected from that of methyl benzimidate.[18,19]

A possible route to the phenylimino ether structure **23** is advanced very tentatively in Scheme VI.[20] We have already noted above the elimination of the epoxyimino bridge from **5** and **6** under strongly basic or acidic conditions and the regeneration of the two olefinic double bonds; the elimination step **20** → **21** under near-neutral conditions represents the first stage of a similar elimination and the ring-closure **21** → **22** a reversal in which a less-strained ring system is formed. Dehydration of **22** to yield **23** would be favored by the resonance stabilization of the phenylimino ether product. The reaction sequence of Scheme VI would require the elimination of the stereochemical distinction between α and β compounds at C_4, so that the two products **23** would differ only in the configuration of the oxime function, that form **5** being *Z* and that from **6** being *E* with some *Z*. Unfortunately, we were unable to study further this remarkable reaction, which clearly merits further work.

In deriving the structures **5–23,** the information obtained from ^1H NMR was vital. The peaks at high field due to the three methyl groups and the doublet at low field due to the hydrogen at the 6-position were most easily recognized; their chemical-shift values are given in Tables I and II. The coupling constant of the 6-hydrogen doublet remained constant for all compounds until (−)-α-desmotroposantonin (**16**) was reached, when it decreased from 10 to 5 Hz as expected from the change at this stage from a trans to a cis-fused lactone. The peak of the 11-methyl group remained as a doublet ($J \approx 7$ Hz) in all compounds. On the other hand, the 4-methyl peak in santonin was barely split ($J \approx 1$ Hz) because of long-range coupling, but became a well defined doublet (J = 6–8 Hz) when the Δ^4 double bond was saturated on bridge formation to give **5** and **6** and only became a singlet when the double bond reappeared in **15, 16,** and **19.** Similarly, the angular methyl at the 10-position gave rise to a singlet in all the

compounds of unrearranged carbon skeleton in Table I, but to a doublet (J = 6 Hz) when it had migrated to the 1-position to afford the compounds of Table II (with the exception only of **16**, where aromatization of the ring had removed the vicinal hydrogen responsible for the splitting).

Other NMR peaks important in establishing structures are given earlier or in the Experimental Section.

Experimental Section

General Methods. Melting points are corrected. IR spectra were obtained with Perkin-Elmer Model 337 and 521 spectrophotometers. UV spectra were obtained using a Unicam Model S.P.-800 recording spectrophotometer and are for ethanol solutions, unless otherwise noted. NMR spectra were obtained with a Varian Associates A-60 instrument. Optical rotations were determined with a Carl Zeiss automatic polarimeter at 25 °C, using a 1.0-dm cell and solute concentrations of about 8% in EtOH. Silica gel G and calcium sulfate were used for preparative thick-layer chromatography and for TLC, and silical gel (Grace Davison Chemical, grade 923) was used for column chromatography. Unless otherwise noted, three solvent mixtures were used to elute TLC plates: (a) 50% benzene, 50% ether; (b) 45% benzene, 45% ether–10% ethanol; (c) a mixture of chloroform (15 mL), ether (10 mL), methylene chloride (15 mL), methanol (2 mL). R_f values quoted below indicate the solvent mixture used.

(1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*Z*)-Oxime (5). (a) From Reaction of Santonin with Hydroxylamine. The following method achieved somewhat better yields than that of Francesconi and Cusmano.[2] A solution of sodium methoxide, prepared from 46.6 g (2 mol) of sodium and 1 L of methanol, was mixed with a solution of 140 g (2 mol) of hydroxylamine hydrochloride in methanol. After removing sodium chloride by filtration, more sodium methoxide [from 7 g (0.3 mol) of sodium] was added, and the solution was concentrated to 1 L. Santonin (120 g) was added, and the solution was refluxed under nitrogen until no santonin was shown by TLC (about 24 h). The solution was concentrated to a volume of 150 mL under reduced pressure, and 100 mL of water was added. The clear solution at room temperature deposited a first crop of 30 g of fine white needles, shown by TLC to be a mixture of santonin oxime and of **5**. The solid was extracted with 50 mL of hot methanol. The residue (15 g) was almost pure **5**.

Evaporation of the mother liquor from the first crop gave a second crop of **5** (15 g, total 20%); further concentration of the filtrate gave only santonin oxime. The compound **5** crystallized from methanol in fine white prisms, giving a single spot on TLC, turning brown at ca. 200 °C: mp with evolution of gas 230 °C; $[\alpha]^{25}_D$ +46.5° (lit.[2] mp 229–230 °C; $[\alpha]^{12}_D$ +47.44°); IR (KBr) ν_{max} 3550 (s) (oxime OH), 3250 (s) (N–H), 1750 (s) (lactone C=O), 1650 (w) (oxime C=N) cm^{-1}; UV, end absorption only.

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52; mol wt 294.34. Found: C, 60.66; H, 7.28; N, 9.40; mol wt 297 (osmometry), 294 (mass spectrum).

The *N,O*-dibenzoyl derivative, prepared by reaction with benzoyl chloride in pyridine, had mp 175–178 °C; IR (KBr) ν_{max} 1785, 1750, 1640, 1600, and 1505 cm^{-1}.

Anal. Calcd for $C_{29}H_{30}N_2O_6$: C, 69.30; H, 6.02; N, 5.57. Found: C, 68.10; H, 6.05; N, 6.01.

(b) From Reaction of (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (11) with Hydroxylamine. The ketone **11** (0.192 g) (see below) was heated with hydroxylamine in 5 mL of methanol. TLC showed the reaction to be complete in 3 h; the solution when cooled deposited colorless prisms identical with **5** obtained above (mp, mmp, TLC, IR, $[\alpha]^{25}_D$ +46.5°).

(1*S*,4*S*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*E*)- and (*Z*)-Oximes (6). The following procedure is an improvement over that of Francesconi and Cusmano.[2] Santonin, hydroxylamine hydrochloride, and sodium methoxide were allowed to react under the conditions used in the preparation of the α isomer, the mole ratio of hydroxylamine hydrochloride to sodium methoxide now being 1.15:1.00. After 24 h of refluxing, the solution was concentrated to about 200 mL. On cooling, 30 g of santonin oxime crystallized out. On addition of 300 mL of water, a further 35 g of santonin oxime precipitated. After being extracted several times with chloroform to remove more santonin oxime, the aqueous solution was boiled for 15 min. On cooling, 25 g (16.5%) of **6** separated as colorless needles. After crystallization from aqueous dimethyl sulfoxide, this still showed two overlapping spots [R_f (b) 0.50] on TLC: turning brown at ca. 200 °C; mp (evolution of gas) 232–233 °C; mmp with α isomer (**5**) 210 °C; $[\alpha]^{25}_D$ 0.0° (lit.[2] mp 232–233 °C; $[\alpha]^{12}_D$ −3.0°). The IR and UV spectra were similar to those of the α isomer.

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52. Found: C, 60.54; H, 7.14; N, 10.07.

The *N,O*-dibenzoyl derivative, prepared as above, crystallized from methanol as needles: mp 185–186 °C (lit.[2] mp 184 °C); UV λ_{max} 233.5 nm, ϵ_{max} 25 000, λ_{max} 273 nm, ϵ_{max} 4780 (MeOH); IR ν_{max} (KBr) 1785, 1750, 1640, 1615, 1582, and 1505 cm^{-1}.

Anal. Calcd for $C_{29}H_{30}N_2O_6$: C, 69.30; H, 6.02; N, 5.57. Found: C, 69.42; H, 6.13; N, 5.96.

Levulinic Acid Treatment of (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)-tetrahydrosantonin (*Z*)-Oxime (5). One gram of **5** was heated at 100 °C with 15 mL of levulinic acid reagent[10] for 4 h. Neutralization ($NaHCO_3$) and extraction with chloroform removed 0.78 g of white crystalline product found by mp, IR, and NMR to be identical with santonin oxime.[2,4] The same result was obtained with the β isomer **6**.

(1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (11). (a) From (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin Oximes (6). The β compound **6** (1.5 g) in 20 mL of ethanol was treated with a solution of 2.8 g of sodium bisulfite in 10 mL of water. Partial precipitation of both reagents occurred. The mixture was heated under reflux on a steam bath while nitrogen was bubbled through to keep the solids in suspension. After 30 min the solids had dissolved, and TLC showed starting material [R_f (a) 0.35] and three other spots: one (feeble) with the same R_f (a) as santonin (0.70); a second (ca. 40% of reaction mixture) R_f (a) 0.24; and a third R_f (a) 0.00 (50% of reaction mixture). After 4 h, starting material was gone and TLC showed a new spot [R_f (a) 0.55]. The solution was concentrated to 10 mL, acidified with 50 mL of cold dilute hydrochloric acid, and extracted with chloroform (2 × 50 mL). Evaporation of the chloroform gave 0.25 g of a yellow oil, which crystallized after addition of ether and cooling as white platelets, mp 171 °C, identified by IR and UV as santonin.

The aqueous layer from the extraction was neutralized ($NaHCO_3$) and extracted with 2 × 50 mL of chloroform. Evaporation of the chloroform gave 0.5 g of a yellow crystalline product. Two crystallizations from 96% ethanol gave 0.2 g of colorless needles of **11**: R_f (a) 0.24; mp 190.5 °C; $[\alpha]^{25}_D$ +13.9°; UV λ_{max} 294 nm, ϵ_{max} 17; IR (KBr) ν_{max} 3260 (s) (NH), 1775 (s) (lactone C=O), 1710 cm^{-1} (s) (ketone C=O).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.39; H, 7.55; N, 5.10.

The mother liquor showed a spot [R_f (a) 0.55] (attributed to **12**) as well as santonin [R_f (a) 0.70] and **11** [R_f (a) 0.24]. When the mother liquor was made alkaline with sodium methoxide and allowed to stand at room temperature for 3 min, the spot [R_f (a) 0.55] was shown by TLC to have disappeared and the spot R_f (a) 0.24 to have been strengthened.

(b) From (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*Z*)-Oxime (5). The α isomer **5** (0.5 g) was allowed to react under the conditions described above for the β isomer. Santonin (0.125 g) was recovered by chloroform extraction of the acidified reaction mixture. After neutralization of this ($NaHCO_3$), chloroform extraction gave 0.225 g of a crystalline product, mp 190 °C, identical by mmp, IR, UV, and NMR with the product **11** from **6**. The mother liquors from which this compound separated showed only santonin and **11** [R_f (a) 0.24], but no spot with R_f (a) 0.55.

(1*S*,5*R*)-5,1-[Epoxy(phenylmetheno)nitrilo]tetrahydrosantonin (*E*)- and (*Z*)-Oximes (23). A solution of 1 g of **5** and 1 mL of benzaldehyde in 10 mL ethanol was refluxed for 26 h, concentrated, and cooled. The precipitate was washed with cold ether and crystallized from aqueous methanol, giving 0.75 g of colorless needles: mp 215–217 °C (lit.[2] mp 217 °C); UV λ_{max} 235 nm, ϵ_{max} 11 200; IR (KBr) ν_{max} 3550 (w) (oxime OH), 3200 (s), 3080 (s), 1790 (s) (lactone C=O), 1662 (s) (oxime C=N), 1615 (w), 1600 (w), 1510 (m), and 1490 (m) cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.08; H, 6.85; N, 7.33. Found: C, 69.36; H, 6.89; N, 7.54.

The same procedure, applied to the β isomer **6**, gave 0.75 g of colorless needles: mp 219–220 °C; mmp with product from **5** 190–200 °C; UV λ_{max} 235 nm, ϵ_{max} 10 600; IR ν_{max} (KBr) 3450 (w), 3250 (s), 1787 (s), 1655 (s), 1613 (w), 1592 (m), and 1505 (m) cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.08; H, 6.85; N, 7.33. Found: C, 68.86; H, 7.05; N, 7.12.

In acid solution both compounds had λ_{max} 252 nm. A series of spectra in solutions of pH 8.9, 6.6, 4.5, 3.7, 1.0, and −1.0 (H_0) passed through an isobestic point at 239 nm, and analyzed by the usual method[21] gave pK values of 4.65 and 4.70 for α and β compounds, respectively.

(1*S*,4*R*,5*R*)-5,1-(Epoxynitrosoimino)tetrahydrosantonin (*Z*)-Oxime (7). (1*S*,4*R*,5*R*)-5,1-(Epoxyimino)tetrahydrosantonin (*Z*)-Oxime (**5**) (5.0 g) in 50 mL of water containing 0.65 g of hydrochloric acid was treated with 1.15 g of sodium nitrite in 5 mL of water. A pale yellow precipitate formed, which was digested in 25 mL of hot ethanol, and then **7** was filtered off. A portion was recrystallized from methanol and obtained as minute needles, very faintly yellow, giving a single spot on TLC analysis. The needles turned brown at 160 °C and melted at 164–165 °C with evolution of gas: $[\alpha]^{25}_D$ −112.9° (lit.[2] mp 164 °C; $[\alpha]^{12}_D$ −112.8°); UV λ_{max} 246 nm, ϵ_{max} 7650; IR (KBr) ν_{max} 3425 (s), (oxime OH), 1775 (s) (lactone C=O), 1630 (w), (oxime C=N), 1570 (w), and 1350 (s) cm^{-1} (N=O).

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.89; H, 6.29; N, 12.86.

No NMR spectrum could be obtained because of the compound's low solubility at ordinary temperatures and facile decomposition in solution when warmed.

(1*S*,4*S*,5*R*)-5,1-(Epoxynitrosoimino)tetrahydrosantonin (*E*)- and (*Z*)-Oximes (8). This product was prepared in the same way from the β isomer **6** except that glacial acetic acid was used as solvent. It crystallized from methanol in large yellow needles: R_f (b) 0.30 and 0.45; turning brown at 160 °C; evolved gas at 168 °C; mp 172 °C (lit.[2] mp 172 °C); mmp with α isomer 152–154 °C; UV λ_{max} 245 nm, ϵ_{max} 7300; IR (KBr) ν_{max} 3425 (s), 1775 (s), 1630 (w), 1570 (w), and 1360 (m) cm^{-1}.

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 56.85; H, 6.71; N, 12.37.

On standing the material decomposed slowly, and after a few days TLC showed the presence of another, less polar compound, R_f (b) 0.70, the same R_f (b) as shown by **17** and **18**. The poor analysis was probably due to partial decomposition to the compounds **17** and **18**; a 12% decomposition would lead to the analytical figures shown above.

(1*R*,4*R*,5*S*,10*S*)-3-(*Z*)-Oximino-5,10-epoxyhexahydrohyposantonin (9). The 4α-nitroso compound **7** (1.025 g) was suspended in 10 mL of 50% aqueous acetic acid in a round-bottom flask connected via a reflux condenser to a trap cooled in liquid air. The apparatus was flushed with nitrogen and the flask was heated on a water bath. The evolved gas condensed in the trap as a white solid. The trap was warmed to room temperature and the gas taken into a previously evacuated IR cell: ν_{max} 3840 (w), 3487 (s), 3460 (s), 3370 (w), 3340 (w), 2790 (m), 2470 (s), 2450 (m), 2210 (s), 1300 (s), 1270 (s), and 1265 (m) cm^{-1}, identical to spectrum reported for nitrous oxide.[22]

The yellow solution from the flask, on addition of water, gave 0.683 g of white precipitate, which crystallized from methanol as prisms, giving a single spot on TLC: R_f (a) 0.50; mp 199–200 °C; $[\alpha]^{25}_D$ +220° (lit.[2] mp 199–200 °C; $[\alpha]^{25}_D$ +219°); IR (KBr) ν_{max} 3440 (s) (oxime OH), 1760 (s) (lactone C=O), and 1653 (w) cm^{-1} (oxime C=N).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.78; H, 7.32; N, 5.05.

The benzoyl derivative, prepared in the usual way, crystallized from methanol/ether in plates: R_f (a) 0.75; mp 134–138 °C (dec); IR (KBr) ν_{max} 1775 (s), 1738 (s), 1620 (m), 1595 (m), and 1250 (s) cm^{-1}.

Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.71; H, 6.10; N, 3.81.

Levulinic Acid Treatment of (9). (a) At Room Temperature. The oxime **9** (0.5 g) was stirred for 15 h at room temperature in a mixture of 18 mL of levulinic acid and 2 mL of 1.0 N hydrochloric acid. TLC showed one spot having the same R_f (a) 0.50 as the starting material and a second of R_f (a) 0.60. The mixture was poured into 50 mL of water, filtered from resinous material, and neutralized ($NaHCO_3$). The precipitate was taken up in ether, washed with sodium bicarbonate solution, and evaporated to yield 0.33 g of a white crystalline product. This was chromatographed on five silica gel plates using solvent a. (1*R*,4*R*,5*S*,10*S*)-3-(*E*)-Oximino-5,10-epoxyhexahydrohyposantonin (**13**), R_f (a) 0.50, was recovered as a white crystalline solid (0.119 g). Recrystallization from aqueous methanol gave colorless prisms: mp 187–190 °C; mmp with **9**, 173 °C; IR (KBr) 3450 (s), 1750 (s), and 1636 (m) cm^{-1}.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.66; H, 7.42; N, 5.04.

The second compound of R_f (a) 0.60 was obtained as 0.084 g of white crystals from cold ether. It showed a single spot on TLC, but decomposed to a brown solid at ca. 130 °C (depending on rate of heating). The compound (14?) on sodium fusion gave a positive test for halogen and negative test for nitrogen; IR ν_{max} (KBr) 3425 (s) (OH), 1763 (s) (lactone C=O), 1705 (s), (ketone C=O), and 682 (s) cm^{-1} (CCl).

Anal. Calcd for $C_{15}H_{21}O_4Cl$: C, 59.99; H, 7.03. Found: C, 59.55; H, 6.83.

(b) At 100 °C for 4 h. The oxime **9** (1.17 g) was heated with 30 mL of the levulinic acid reagent on the steam bath for 4 h. The product, worked up as above, gave white crystals of (1*R*)-3-oxo-$\Delta^{4,9}$-dihydrohyposantonin (**15**), R_f (a) 0.75. On recrystallization from aqueous methanol, mp 108–109 °C, UV λ_{max} 288 nm, ϵ_{max} 11 100, and λ_{max} 232.5 nm, ϵ_{max} 3800; IR (KBr) ν_{max} 1780 (s) (lactone C=O), 1660 (s) (conjugated C=O), and 1620 (m) cm^{-1} (C=C); NMR δ 5.32 (olefinic H).

Anal. Calcd for $C_{15}H_{21}O_3$: C, 73.14; H, 7.37. Found: C, 73.60; H, 7.12.

(c) At 100 °C for 15 h. More prolonged treatment of 1.0 g of the oxime **9** with 30 mL of levulinic acid reagent gave 0.44 g of a different white crystalline compound: R_f (a) 0.65; mp 194 °C. Its UV (λ_{max} 289 nm, ϵ_{max} 3800), IR, and NMR spectra were identical with those of an authentic sample of (−)-α-desmotroposantonin (**16**).[16]

Acid Treatment of 8. The 4β-nitroso compound **8** (0.95 g) was treated with 50% aqueous acetic acid and then worked up as described above for the α isomer **7**. Evolution of nitrous oxide was again observed, and a crystalline product was isolated in two crops. The first crop was shown by TLC to consist of three compounds [R_f (a) 0.50, 0.58, 0.80] and the second of only one [R_f (a) 0.80]. This compound was readily separated from the other two in the first crop by crystallization from methanol, in which it was much more soluble. After two crystallizations from methanol, white crystals of (1*R*)-$\Delta^{4,9}$-dihydrohyposantonin (*E*)-oxime (**19**) were obtained, mp 255 °C (dec); UV λ_{max} 276 nm, ϵ_{max} 24 870; IR (KBr) 3400 (s) (oxime OH), 3035 (w) (olefinic CH), 1750 (s) (lactone C=O), 1602 (w) (C=C), and 1590 (w) cm^{-1} (oxime C=N); NMR δ 5.65 (olefinic H).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.06; H, 7.59; N, 5.34.

The other two compounds [R_f (a) 0.50, 0.58] were partially separated on a silica gel column and finally purified by TLC plates. One [R_f (a) 0.50] crystallized from aqueous ethanol as fine white needles of (1*R*,4*S*,5*S*,10*S*)-3-oximino-5,10-epoxyhexahydrohyposantonin (**17** or **18**): mp 186.5 °C; IR (KBr) ν_{max} 3560 (s) (oxime OH), 3200 (s, br) (H-bonded OH), 1760 (s) lactone (C=O), and 1660 (m) cm^{-1} (oxime C=N); UV, end absorption only; NMR δ 9.87, exchangeable with D_2O (oxime OH).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.73; H, 7.65; N, 5.21.

The second compound [R_f (a) 0.58] crystallized from aqueous ethanol as white platelets of isomeric (1*R*,4*S*,5*S*,10*S*)-3-oximino-5,10-epoxyhexahydrohyposantonin (**17** or **18**): mp 196.5 °C; IR (KBr) 3500–3450 (s), 1760 (s), and 1630 (w) cm^{-1}; UV, end absorption only.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.63; H, 7.83; N, 4.90.

Registry No.—(*E*)-**6**, 64234-79-3; (*E*)-**6** *O*,*N*-dibenzoyl derivative, 64234-81-7; (*Z*)-**6**, 64234-80-6; (*Z*)-**6** *O*,*N*-dibenzoyl derivative, 64234-82-8; **7**, 64201-53-2; (*E*)-**8**, 64234-83-9; (*Z*)-**8**, 64234-84-0; **12**, 64234-85-1; (*E*)-**23a**, 64201-54-3; (*Z*)-**23a**, 64234-86-2; (*E*)-**23b**, 64234-87-3; (*Z*)-**23b**, 64234-88-4; hydroxylamine hydrochloride, 5470-11-1; hydroxylamine, 7803-49-8; benzaldehyde, 100-52-7.

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Isonucleosides. 2. Purine and Pyrimidine Derivatives of 1,4-Anhydro-2-deoxy-D-arabinitol

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1,4-Anhydro-D-xylitol (1), prepared from sorbose by three steps, was converted into 1,2:3,4-dianhydro-D-ribitol (7) by a sequence of six high-yield reactions. Reaction of 7 with concentrated ammonium hydroxide resulted in exclusive attack at C-2 to give 2-amino-1,4-anhydro-D-arabinitol (8), which was converted in three steps to the adenosine analogue 2-(6-amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (11). It was also converted to the uridine analogue 15.

The naturally occurring nucleosides and nucleotides are those in which the purine or pyrimidine base is attached to C-1 of ribose or 2-deoxyribose. This linkage is part of an aminal structure that is quite susceptive to both hydrolytic and enzymatic cleavage. For many years, the design of congeners of these compounds was based on the assumption that only analogues with bases attached in the β configuration to C-1 of D-furanoses were likely to fit the active sites of the anabolic enzymes necessary for activation of the enzymes whose inhibition by the resultant nucleotides results in cell death. The same requirements were assumed to apply also to the incorporation of analogues into cofactors or macromolecules. However, the discovery of the biologic activity of α-2′-deoxythioguanosine,[1] of the *α-arabino* nucleosides,[2] and of the carbocyclic analogues of nucleosides[3] has made it necessary to revise these concepts about structural requirements. Thus, it seemed worthwhile to investigate the biologic potential of isonucleosides—compounds in which the base is attached to the sugar at positions other than the normal C-1 position.

Previous work in this laboratory resulted in the preparation of purine isonucleosides by the reaction of methyl 2,3-anhydro-α-D-arabinofuranoside with ammonium hydroxide to give a mixture of methyl 2-amino-2-deoxy-α-D-arabinofuranoside and methyl 3-amino-3-deoxy-α-D-xylofuranoside.[4] The reaction of each of these compounds with 2,6-dichloro-5-aminopyrimidine followed by ring closure gave the isonucleosides, methyl 2-(6-chloro-9-purinyl)-2-deoxy-α-D-arabinofuranoside and methyl 3-(6-chloro-9-purinyl)-3-deoxy-α-D-xylofuranoside. In this manner, a number of purine isonucleosides were prepared by nucleophilic displacement of the 6-chloro group.[5,6]

We have now extended this work by the synthesis of compounds lacking the 1-*O*-methyl group of the sugar moiety in the hope that such compounds might be substrates for the anabolic enzymes such as adenosine kinase, and that they might therefore be activated to forms capable of interfering with vital cellular metabolism, such as the biosynthesis or function of nucleic acids.

The success of the reaction of methyl 2,3-anhydro-α-D-arabinofuranoside with ammonium hydroxide[4] led us to undertake the preparation of 1,2:3,4-dianhydro-D-ribitol (7). Preparation of 7 was initially attempted by reaction of 1,2-di-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylofuranose[7] with ethereal HCl (saturated at 0 °C) to give 2-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-β-D-xylofuranosyl chloride.[8] Reduction of this chloride followed by ring closure should give the corresponding epoxide; however, all attempts to reduce the glycosyl chloride, either catalytically or chemically, were unsuccessful, giving in most cases unchanged starting material. Attempts were made to displace the 1-chloro group with sodium ethylmercaptide[9] and at the same time effect ring closure to the epoxide to give ethyl 2,3-anhydro-1-deoxy-1-thio-β-D-ribofuranose, which could then be reduced to give **7.** The reaction to prepare the thio sugar was unsuccessful, giving an intractable mixture.

An alternative approach to **7** involved the anhydridizing of sorbitol with sulfuric acid catalyst to give arlitan (1,4-sorbitan).[10] When the reaction was carried out as described in the literature (i.e., 135–145 °C for 30 min), we obtained, in addition to the product, a large amount of a by-product tentatively identified as isosorbide, since it is known that further treatment of arlitan with sulfuric acid results in the formation of isosorbide in high yield.[11] When the reaction was carried out at a lower temperature, 130 °C for 45 min, a cleaner product was obtained free of isosorbide. The method of Kjølberg for shortening the chain length of glycosides was used for the synthesis of 1,4-anhydro-D-xylitol (1).[12] Cleavage of the C^5–C^6 bond of arlitan with periodate gave the aldehyde, which was reduced with sodium borohydride to **1.**[13] (For the syntheses of compounds **2–16,** see Scheme I.) The 1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (**2**), a white crystalline solid, was prepared by the reaction of **1** with acetone containing 2,2-dimethoxypropane and 60% perchloric acid. Acetylation of **2** with pyridine–acetic anhydride furnished 2-*O*-acetyl-1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (**3**), a crystalline solid. By deacetonation of **3** in 1 N ethanolic HCl, 2-*O*-acetyl-1,4-

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