Table II. ^{13}C NMR Chemical Shifts (δ) for Hispidols A (1) and B (2), Sapelin A (3), and Hispidol B Acetate (2a)

atom	3 [a]	1 [b]	2 [b]	2a [a]
C-1	31.3 (t)	31.9	37.6	36.8
C-2	25.4 (t)	26.6	28.6	24.2
C-3	76.3 (d)	75.3	78.3	81.2
C-4	37.6 (s)	38.0	39.5	37.9
C-5	44.6 (d)	44.9	51.2	50.8
C-6	23.9 (t)	24.4	24.4	23.8
C-7	118.2 (d)	118.6	118.5	117.8
C-8	145.9 (s)	146.4	146.1	145.7
C-9	48.6 (d)	49.2	49.3	48.8
C-10	34.8 (s)	35.2	35.2	34.8
C-11	17.9 (t)	18.4	18.4	18.1
C-12	33.1 (t)	34.4	34.3	33.2
C-13	43.3 (s)	43.8	43.8	43.6
C-14	51.4 (s)	51.6	51.4	51.1
C-15	33.9 (t)	34.4	34.3	33.9
C-16	27.3 (t)	28.7	28.6	27.9
C-17	44.8 (d)	54.4	54.4	53.6
C-18	13.0 (q)	13.5	13.5	13.2
C-19	21.9 (q)	22.0	22.1	21.9
C-20	37.6 (d)	34.4	34.3	33.9
C-21	70.2 (t)	19.5 (q)	19.6 (q)	21.4 (q)
C-22	36.5 (t)	42.4	42.3	38.0
C-23	64.7 (d)	69.5	69.5	70.4
C-24	86.5 (d)	76.8	76.8	76.8
C-25	74.2 (s)	73.8	73.8	72.5
C-26, C-27	23.9, 28.5 (q)	27.3, 27.8	27.2, 27.8	26.3, 27.2 [c]
C-28	27.8 (q)	28.7	28.3	27.2 [c]
C-29	22.2 (q)	22.2	15.5	15.9
C-30	27.4 (q)	27.6	27.4	27.6 [c]
C=O				170.5, 170.7, 171.0 (s)
MeC=O				18.4, 20.9, 21.4 (q)

[a] In $CDCl_3$. [b] In pyridine-d_5. [c] May be reversed.

– (15 + 58) peaks. That the losses of 72 mass units gave isobutyraldehyde was supported by strong peaks at m/e 72 (87%) and 71 (71%); these compositions were verified by exact measurements.

Hispidols **A** (1) and **B** (2) are probably derived in nature by acid-catalyzed addition of water to the epoxide group in a side chain like that of **11**, synthesized from bourjotinolone C (**7**) with base; though **11** has not been found in nature, it was suggested that **7** is an artifact formed from natural **11** during workup with HCl.[4] Epoxide **11** can serve as a precursor to epoxide **12**,[4] which can give the other tirucallane derivatives **3**–**6** found in the same plant as well as many other tirucallanes found in different plants.[4,6,10]

Experimental Section

The high-resolution mass spectral data were obtained at a resolution of 7000 by scanning the mass range from m/e 100 to 500 repetitively at 25 s/dec, using PFK as the internal standard. Metastable ion spectra were recorded by either scanning the magnetic (B) and electrostatic (E) fields at constant accelerating voltage with the B/E ratio constant to obtain the daughters of parents or by scanning the accelerating voltage at constant B and E for determining parents of daughters. Samples were introduced by using a direct probe. The normal ionizing voltage was 70 eV with a source temperature of 250 °C. All other experimental conditions specified in ref 2 and 3 apply.

Hispidols A (1) and B (2). The fraction containing these alcohols, which had R_f values slightly lower than sapelin B (**4**), was isolated following the procedure outlined earlier for the isolation of **5** and **6**.[2] Rechromatography of this fraction (EM SiO_2-60; CH_2Cl_2 with increasing concentration of EtOAc) yielded two sets of fractions, A and B. Fraction A, when rechromatographed (EM SiO_2-60; CH_2Cl_2 with increasing concentrations of MeCN), yielded hispidol A (**1**), which crystallized from MeOH–CH_2Cl_2 as colorless needles: mp 118 °C, $[\alpha]^{25}_D$ –80° (pyridine); NMR and mass spectral parameters are given in Tables I and II and Scheme I; IR (KBr) 3340, 1370, 820 cm^{-1}.

Anal. Calcd for $C_{30}H_{52}O_4$: C, 75.6; H, 10.9. Found: C, 75.3; H, 11.1.

Fraction B (foam), after being washed with CH_2Cl_2–EtOAc (1:1) and after addition of MeOH–CH_2Cl_2, gave hispidol B (**2**) as lustrous rectangular prisims: mp 252–253 °C, $[\alpha]^{25}_D$ –57° (pyridine; NMR and mass spectral parameters are given in Tables I and II and Scheme I; IR (KBr) superimposable with hispidol A (**1**).

Anal. Calcd for $C_{30}H_{52}O_4$: C, 75.6; H, 10.9. Found: C, 75.4; H, 11.2.

Hispidol A Triacetate (1a). Acetylation of hispidol A (**1**) overnight at room temperature with excess Ac_2O–pyridine gave **1a** as colorless foam, homogeneous on TLC. The IR [($CHCl_3$) 3600, 1735, 1380, 1240, 820 cm^{-1}] and ^1H NMR (Table I) spectra were in accord with structure **1a**.

Hispidol B Triacetate (2a). Similar treatment of hispidol B (**2**) with Ac_2O–pyridine followed by crystallization from ether–hexane gave **2a**, mp 146–148 °C, identical R_f value with that of **1a**. The IR [($CHCl_3$) superimposable with **1a**], NMR (Tables I and II), and mass [m/e 602 (M^+, 19.6), 587 (14.4), 569 (62.7), 542 (4.7), 528 (34.4), 527 (91.7), 510 (12), 509 (31.6), 484 (6.8), 467 (32.6), 449 (29.7), 425 (7.3), 409 (16.8), 407 (16.9), 389 (33.3), 369 (39.2), 367 (10.6), 353 (25.6), 335 (15.4), 309 (48.4)] spectra were in accord with structure **2a**.

Anal. Calcd for $C_{36}H_{58}O_7$: C, 71.76; H, 9.63. Found: C, 71.73; H, 9.85.

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Registry No. 1, 78739-37-4; **1a**, 78739-38-5; **2**, 78739-39-6; **2a**, 78739-40-9; **3**, 26790-93-2.

Convenient Laboratory Preparation of Glyoxal-d_2 and 2,4,6,8-Tetrakis(methoxycarbonyl)bicyclo[3.3.0]octane-3,7-dione-1,5-d_2

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Glyoxal-d_2 has been prepared in low yield by the oxidation of ethylene-d_4 with a mixture of selenium dioxide and phosphorus pentoxide at 200 °C[1,2] and by the ozonization of acetylene-d_2 in a special apparatus.[3,4] While these may serve to make small amounts of glyoxal-d_2 for spectroscopic studies, they do not constitute bench-scale preparations suitable for organic synthesis. The strategy conceived to guide the development of such a procedure was to use a derivative of glyoxal which would contain C–H bonds sufficiently acidic to exchange with D_2O. Because it is an established source of glyoxal for further reactions,[5] glyoxal bis(sodium bisulfite) was chosen for study.

Results

Although both heat and base (sodium carbonate) were found to facilitate the exchange, heat was found to give better results than base catalysis, as the latter caused more decomposition. The best procedure proved to be the gentle refluxing of a saturated D_2O solution of glyoxal bis(sodium

† Abstracted from Bertz, S. H. Dissertation, Harvard University, 1978. Current address: Bell Laboratories, Murray Hill, NJ 07974.

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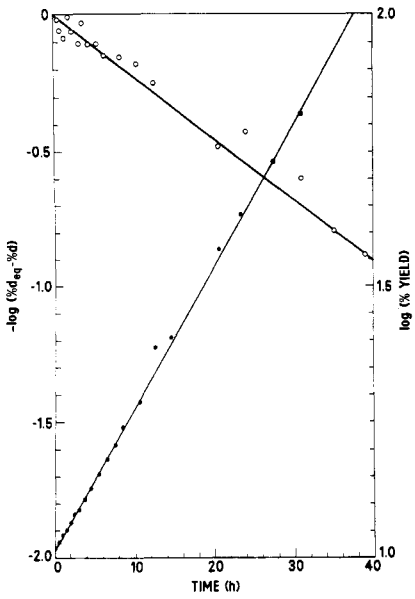
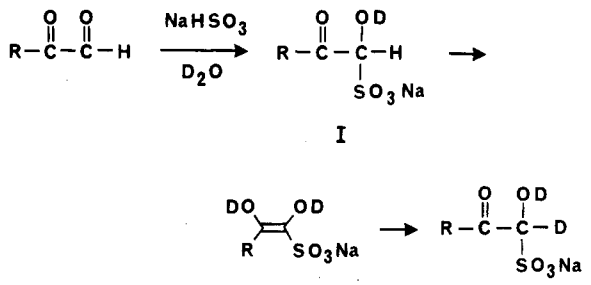


Figure 1. Deuteration of glyoxal bisulfite (correlation coefficient 0.9996) and its decomposition (correlation coefficient −0.9875) at 100 °C. The slopes are 0.0523 and −0.0107 h^{-1}, respectively.

bisulfite) under nitrogen for two days. Cooling gave a 50% yield of crystalline glyoxal-d_2 bis(sodium bisulfite)-*O*-d_2, 99% pure based upon conversion to the phenylosazone, which mass spectrometry showed to be 96% deuterated when 99.8% D_2O was used. Resubjecting this material to the deuteration procedure gave 98% deuterated product. Further, less pure crops were obtained by again reducing the volume and cooling. The graphs plotted in Figure 1 show the smooth incorporation of deuterium as a function of time ($t_{1/2}$ = 13 h, 100 °C) and the slow attrition in yield as some glyoxal is destroyed ($t_{1/2}$ = 65 h). The extent of deuteration was monitored by mass spectrometric examination of the phenylosazone derivative after exchanging N–D groups back to N–H with boiling ethanol. The yields in Figure 1 were calculated from the weights of the crude osazones. The phenyl osazone proved to be an excellent derivative for mass spectrometric measurement because of its smooth volatilization and prominent molecular ion.

The condensation of this deuterated glyoxal bisulfite with dimethyl 3-oxoglutarate was investigated in order to prepare labeled starting materials for a study of the mechanism of the Weiss reaction.[6] Surprisingly, it proved possible to obtain 2,4,6,8-tetrakis(methoxycarbonyl)bicyclo[3.3.0]octane-3,7-dione-*1,5*-d_2 by using glyoxal-d_2 bisulfite as the only deuterium-containing substance. Initially, the labeled glyoxal bisulfite (96% deuterated) was treated with dimethyl 3-oxoglutarate-*2,2,4,4*-d_4 (95% deuterated by ^1H NMR; prepared by Na_2CO_3-catalyzed exchange with D_2O) in 99% CH_3OD containing NaOD

Scheme I



(prepared by dissolving Na in D_2O). The bicyclo[3.3.0]-octane-3,7-dione-*1,5*-d_2 produced after hydrolysis–decarboxylation was found to be 96% deuterated by mass spectrometry. In spite of the higher deuterium content of the medium, the product had the same deuterium content as the glyoxal bisulfite! Therefore 95% labeled glyoxal bisulfite was condensed with unlabeled dimethyl 3-oxoglutarate in ordinary methanolic sodium hydroxide to give 93% deuterated product. For most purposes it is not important whether the product be 93% or 95% deuterated.

Discussion

If the sodium bisulfite is omitted or replaced by sodium dihydrogen phosphate (to give a solution with the same pH) 1% or less deuterium incorporation results, in agreement with Whipple's ^1H NMR results.[7] A mechanism which accounts for the requirement that an aldehyde be activated by a strongly electron-withdrawing group in order for its hydrogen to undergo rapid exchange involves the intermediacy of a species such as I (Scheme I), in which the aldehyde is present in the form of its bisulfite adduct whereas the neighboring carbonyl group is not. The enolization is undoubtedly acid catalyzed, as bisulfite solutions are acidic (pH 4). In an experiment using glycolaldehyde in place of glyoxal, 19% deuterium incorporation was observed after 2 days in refluxing D_2O containing 1 equiv of sodium bisulfite. The glycolaldehyde was converted to the same osazone[8] for mass spectral analysis, so that the results are directly comparable. A control experiment without the sodium bisulfite gave 13% deuterated material. An 80% deuterium incorporation was obtained by substituting 10 mol % sodium dihydrogen phosphate for the sodium bisulfite; however, extensive charring also resulted. Therefore, in the case of glycolaldehyde, the sodium bisulfite acts as an acid catalyst for the exchange reaction of the free glycolaldehyde in equilibrium with the bisulfite adduct. The base-catalyzed exchange has been studied and an enediol intermediate proposed.[9]

The condensation of the glyoxal-d_2 bisulfite with dimethyl sodio-3-oxoglutarate in refluxing methanol is a modification of the method perfected for aqueous glyoxal.[10] For achievement of optimal yields with glyoxal bisulfite, the reaction solution must be much more dilute than with aqueous glyoxal, 0.2 vs. 1 M, respectively. The use of 4 equiv of dimethyl sodio-3-oxoglutarate, two to free and two to react with the glyoxal-d_2, resulted in higher yields than the use of 2 equiv of it and 2 equiv of sodium hydroxide.

(1) Riley, H. L.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 2342.
(2) For a recent example see: Küttner, H. G.; Selzle, H. L.; Schlag, E. W. *Chem. Phys.* **1978**, *28*, 1.
(3) Erlenmeyer, E.; Bitterlin, O.; Weber, H. M. *Helv. Chim. Acta* **1939**, *22*, 701.
(4) Inspired by this method, an attempt was made to ozonize benzene-d_6 to 3 equiv of glyoxal-d_2. A violent detonation resulted when the procedure for benzene was followed: Harries, C.; Weiss, V. *Ber.* **1904**, *37*, 3431.
(5) Ronzio, A. R; Waugh, T. D. "Organic Syntheses"; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 438. Jones, R. G.; McLaughlin, K. C. *Ibid.* Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 824. Fatiadi, A. J.; Sager, W. F. *Ibid.* Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. V, p 1011.
(6) Yang-Lan, S.; Mueller-Johnson, M.; Oehldrich, J.; Wichman, D.; Cook, J. M.; Weiss, U. *J. Org. Chem.* **1976**, *41*, 4053. Bertz, S. H; Adams, W. O.; Silverton, J. V. *Ibid.* **1981**, *46*, 2828.
(7) Whipple, E. B. *J. Am. Chem. Soc.* **1970**, *92*, 7183.
(8) Fischer, E.; Landsteiner, K. *Ber.* **1892**, *25*, 2549.
(9) Khomenko, T. I.; Lezina, V. P.; Stepanyants, A. U.; Sakharov, M. M.; Golovina, O. A.; Krylov, O. V. *Kinet. Katal.* **1976**, *17*, 911; *Kinet. Catal. (Engl. Transl.)* **1976**, *17*, 795.
(10) Bertz, S. H.; Rihs, G.; Woodward, R. B. *Tetrahedron*, in press. Bertz, S. H.; Cook, J. M.; Gawish, A.; Weiss, U. "Organic Syntheses", in press.

When the precipitate, which was a mixture of "White Salt" [the bis enolate of 2,4,6,8-tetrakis(methoxycarbonyl)bicyclo[3.3.0]octane-3,7-dione[10]] and sodium sulfite, was acidified with dilute acid, the product did not precipitate and had to be extracted with large volumes of ether. A better procedure was found to be grinding the precipitate with 1 equiv of concentrated hydrochloric acid followed by filtration. With all of these precautions, a 71% yield of product was obtained. This good yield of highly deuterated material is attributable to the use of preformed dimethyl sodio-3-oxoglutarate, which condenses with glyoxal-d_2 much faster than it induces the 1,2 hydride shift of glyoxal[11] or the H–D exchange of glyoxal bisulfite.

Experimental Section

Melting points were measured with a Thomas-Hoover apparatus and are uncorrected. Mass spectra were obtained with an AEI MS9 instrument.

Glyoxal-d_2 Bis(sodium bisulfite)-*O*-d_2. A 26.5-g (99.7 mmol) quantity of glyoxal bis(sodium bisulfite) dissolved in 120 mL of D_2O (99.8%) was held at 100 ± 0.5 °C in a 200-mL three-necked flask fitted with a reflux condenser and two rubber septa. Two temperature-controlling thermometers[12] inserted through the septa were connected to relays wired in series with the oil bath maintaining the temperature. A gas-inlet tube on the condenser admitted a static nitrogen atmosphere. Samples (0.50 mL) of the magnetically stirred solution were withdrawn periodically and added to 5.0 mL of a stock solution prepared by dissolving 10 g of phenylhydrazine hydrochloride and 12 g of sodium acetate in 200 mL of water. The yellow solids were filtered off after being allowed to stand overnight in sealed 25-mL Erlenmeyer flasks, washed with 5 mL of water, and then dissolved in 15 mL of boiling ethanol in the same flasks. After the mixture cooled, the solvent was evaporated in a vacuum desiccator to give the osazones, which were weighed to obtain the yields shown in Figure 1 and analyzed by mass spectroscopy (15 eV, 140–150 °C). After 39 h the bright yellow reaction mixture was allowed to cool, its mass was reduced to 40 g on a high-vacuum rotary evaporator, and it was refrigerated to give 12.5 g (46%) of white crystals, which were isolated by filtration under nitrogen, washed with two 5-mL portions of D_2O, and dried under vacuum. After correction for the 10 mL of solution removed as samples, the yield was 50%. The yield of phenyl osazone from a sample of this material was 99%.

2,4,6,8-Tetrakis(methoxycarbonyl)bicyclo[3.3.0]octane-3,7-dione-*1,5*-d_2. Dimethyl 3-oxoglutarate (31.0 g, 178 mmol) in 200 mL of methanol was treated with 35.0 mL of 5.00 M NaOH (175 mmol) and, after 15 min, with 12.1 g (44.8 mmol) of glyoxal bis(sodium bisulfite)-d_4 (95% deuterated). The temperature was raised from 35 to 65 °C, and the reaction mixture was stirred *mechanically* for 24 h. Filtration gave 24 g of white solid which was ground to paste with 15 mL of water, using a *silver* spatula. (A purple color developed when an ordinary metal one was used.) Acidification with 15 mL of concentrated HCl and further grinding gave a white gum that was dried by pressing it on a sintered glass frit with the aid of suction. Further drying under vacuum over phosphorus pentoxide yielded 9.29 g of white solid, mp 98–100 °C. An additional 2.56 g (71% total) was harvested by continuous extraction of the aqueous filtrate with ether. Hydrolysis and decarboxylation according to the literature procedure[13] produced bicyclo[3.3.0]octane-3,7-dione-*1,5*-d_2, which mass spectroscopic analysis showed to be 93% deuterated. The deuterium contents were calculated by using the formula % $d = 100(d_1 + 2d_2)/2(d_0 + d_1 + d_2)$ where d_1 and d_2 are the intensities of the molecular ions of the monodeuterated and dideuterated compounds, corrected for natural isotopic abundance (M + 1 and M + 2).

(11) Arcus, C. L.; Jackson, B. A. *Chem. Ind. (London)* **1964**, 2022.
(12) This arrangement ensured that if one relay became stuck in the closed position, the oil bath temperature would not rise above the desired value; since the other relay would still control it. If one stuck in the open position, the oil bath would cool off; thus no product would be lost due to overheating. If the bath temperature is increased so that vigorous boiling sets in, the yield is decreased.
(13) Vossen, G. Dissertation, University of Bonn, 1910. Yates, P.; Hand, E. S.; French, G. B. *J. Am. Chem. Soc.* **1960**, *82*, 6347.

Registry No. Glyoxal-d_2 bis(sodium bisulfite)-*O*-d_2, 78529-84-7; dimethyl 3-oxoglutarate, 1830-54-2; 2,4,6,8-tetrakis(methoxycarbonyl)bicyclo[3.3.0]octane-3,7-dione-*1,5*-d_2, 78529-85-8; bicyclo[3.3.0]octane-3,7-dione-*1,5*-d_2, 78515-15-8.

Bicyclo[1.1.0]butanes. Reactions with Cyclic Azo Compounds†

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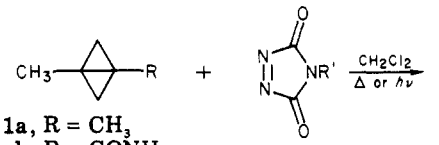
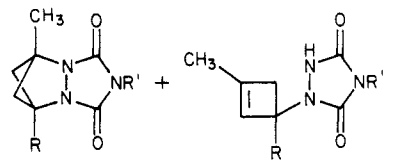
Although bicyclo[1.1.0]butanes (1) undergo addition reactions with olefins,[1a–d] dienes,[1b] alkynes,[2] and ketones,[1b] they have not been observed to react with azo compounds. We report here the addition of cyclic azo species to bicyclobutanes 1. Thermal and, in certain cases, photochemical reactions of 1 with 1,2,4-triazoline-3,5-diones (2) give [2 + 2] cycloadducts 3 and ene products 4 (Table I). Compounds 3 are the first examples of 2,3-diazabicyclo[2.1.1]hexanes. Only the related etheno-bridged species **5a**,[3a] **5b**,[3b] and the monoaza analogue 6[3c–e] have been reported.

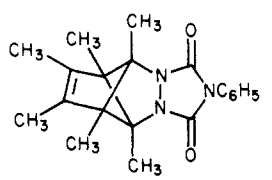


1a, R = CH_3
b, R = $CONH_2$
c, R = CO_2CH_3
d, R = CN

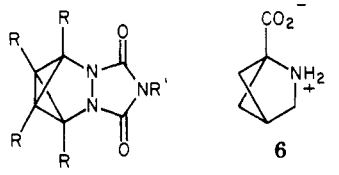
2a, R′ = C_6H_5
b, R′ = CH_3



3 **4**



5a



5b, R = CF_3
R′ = CH_3, C_6H_5

6

Total yields of products are moderate to good, and the ratios of the products (3/4) are highly dependent on the bicyclobutane substituent R. Thus, **1a** (R = CH_3) yields exclusively ene product; **1d** (R = CN) yields only cycloadduct. Between these limits, varying mixtures of 3 and 4 are obtained.

The reaction of bicyclobutane with benzyne,[2d] the reaction of **1a** with ethylene at elevated temperatures,[1b] and the reaction of 1-cyanobicyclobutane with tricyanoethylene[1d] are the only other known cases in which bicyclobutanes give both ene and cycloaddition products.

We also observed a dramatic effect of the substituent R on the relative reactivity of the bicyclobutanes. The following qualitative (thermal) order of reactivity is found: **1a > 1b > 1c ≫ 1d**. The range of reactivity, from seconds

† Contribution No. 2889.

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