that the effect of successive isotopic substitution at *ortho*, *meta*, or *para* positions is cumulative. Least-squares analysis gives a set of individual position isotope effects per deuterium atom, $(K_D/K_H)_{ortho} = 1.0133 \pm 0.0004$, $(K_D/K_H)_{meta} = 1.0133 \pm 0.0007$, and $(K_D/K_H)_{para} = 1.0082 \pm 0.004$, which fit the data within the experimental uncertainty (Table I, columns 3 and 4).

Table I. Isotope Effects on the Equilibrium Formation of Triphenyl Cation from Triphenylcarbinol[a]

Substrate[b]	K_D/K_H Obsd[c]	K_D/K_H Calcd	K_D/K_H Obsd − calcd
Triphenyl-2,2′,2″-d_3-methanol	1.0443 ± 0.0030	1.0403	+0.0040
Triphenyl-3,3′,3″-d_3-methanol	1.0458 ± 0.0027	1.0404	−0.0054
Triphenyl-4,4′,4″-d_3-methanol	1.0222 ± 0.0030	1.0250	−0.0028
Triphenyl-2,2′,2″,-6,6′,6″-d_6-methanol	1.0784 ± 0.0027	1.0822	−0.0038
Triphenyl-3,3′,3″,-5,5′,5″-d_6-methanol	1.0800 ± 0.0019	1.0824	−0.0024
Triphenyl-2,2′,2″,-4,4′,4″-6,6′,6″-d_9-methanol	1.1094 ± 0.0014	1.1093	+0.0001
Triphenyl-d_{15}-methanol	1.2014 ± 0.0016	1.2007	+0.0007

[a] At 25° in a solvent consisting of four parts by volume of 50% aqueous H_2SO_4 and one part of glacial acetic acid. [b] Deuterium content at labeled position, 97–99%. [c] Error estimates are standard deviations of mean values; measurements were performed at least in triplicate.

These isotope effects are all inverse: ring deuteration at any position increases the extent of ionization of triphenylcarbinol. This is the same as the direction of isotope effects found in other cases where positive charge is generated next to a benzene ring[4] and is opposite to the direction of isotope effects found in situations where negative charge is produced at a similar position.[4b,5] It seems likely, therefore, that charge (inductive effect) plays an important role in the origin of these isotope effects. A steric explanation, on the other hand, is inconsistent with the direction and relative magnitude of these isotope effects. Since the present reaction is a process in which a tetrahedral substrate is converted to a trigonal carbonium ion, it should proceed with relief of steric strain[6] provided principally by nonbonded interactions between *ortho* ring hydrogens. This relief of steric repulsion should lower the *ortho* C–H force constant, loosening this bond and producing an isotope effect in the normal direction ($K_H/K_D > 1$). There should, of course, be no isotope effect at the *meta* and *para* positions. The observed isotope effect at the *ortho* position, however, is inverse, and the *meta* and *para* effects are not unity.

Thus, steric effects cannot be the major cause of the presently observed isotope effects; the explanation must lie in an inductive tightening of *ortho*, *meta*, and *para* C–H bonds. Nevertheless, a case can be made for a *minor* steric contribution to the isotope effect at the *ortho* position. In the solvolysis of benzhydryl chlorides,[4b,c] a system closely analogous to the present reaction, isotope effects of 1.9 ± 0.1, 1.5 ± 0.1, and 1.0 ± 0.1% per deuterium atom were found for isotopic substitution at *ortho*, *meta*, and *para* positions, respectively. When account is taken of the fact that the electron demand of this reaction ($\rho = -4.0$)[7a] is slightly greater than that of triphenylcarbinol ionization ($\rho = -3.5$),[7b] these *meta* and *para* isotope effects agree remarkedly well with those measured here: *meta*, $(1.33 \pm 0.07)\% \times {}^{4.0}/_{3.5} = 1.52 \pm 0.08\%$; *para*, $(0.82 \pm 0.04)\% \times {}^{4.0}/_{3.5} = 0.94 \pm 0.05\%$. On this basis, however, the present *ortho* isotope effect is too small: $(1.33 \pm 0.04)\% \times {}^{4.0}/_{3.5} = 1.52 \pm 0.05\%$. This suggests that an additional effect is operative in the present reaction which is absent from the solvolysis case, and, since triphenylcarbinol is a much more crowded molecule than benzhydryl chloride, it is reasonable that this added effect be steric. This possible steric lowering of the *ortho* isotope effect, however, amounts only to one-fifth of the expected *ortho* inductive isotope effect, and this shows that steric isotope effects in this system are decidedly of secondary importance.

(4) (a) A. J. Kresge, K. N. Rao, and N. N. Lichtin, *Chem. Ind.* (London), 53 (1961); (b) A. Streitwieser, Jr., and H. S. Klein, *ibid.*, 180 (1961); (c) *J. Am. Chem. Soc.*, **86**, 5170 (1964); (d) C. Bernasconi, W. Koch, and H. Zollinger, *Helv. Chim. Acta*, **46**, 1184 (1963).

(5) A. Streitwieser, Jr., and H. S. Klein, *J. Am. Chem. Soc.*, **85**, 2759 (1963); A. Streitwieser, Jr., and J. S. Humphrey, Jr., *ibid.*, **89**, 3767 (1967).

(6) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

(7) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962: (a) p 164; (b) p 102.

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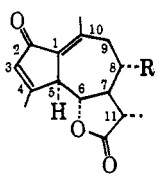
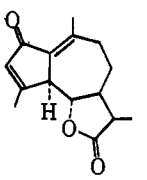
The Synthesis and Stereochemistry of Desacetoxymatricarin and Achillin

Sir:

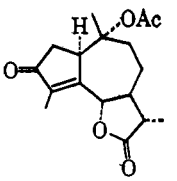
We wish to report syntheses of desacetoxymatricarin[1–4] (Ia) and achillin[1,5] (II) that establish the absolute stereochemistry of the compounds and provide ready access to the 2-ketoguianolides. The stereochemistry of matricarin[1,6] (Ic),[7] jacquenilin,[8] and ar-



Ia, R = H
b, R = OH
c, R = CH_3CO_2



II



III

(1) E. H. White and R. E. K. Winter, *Tetrahedron Letters*, 137 (1962).

(2) M. Holob and V. Herout, *Collection Czech. Chem. Commun.*, **27**, 2980 (1962).

(3) K. S. Rybalko, *Zh. Obshch. Khim.*, **33**, 2734 (1963); called leucomycine in this paper.

(4) T. A. Geissman, T. Stewart, and M. A. Irwin, *Phytochemistry*, **6**, 901 (1967).

(5) S. J. Smolenski, C. L. Bell, and L. Bauer, *Lloydia*, **30**, 144 (1967).

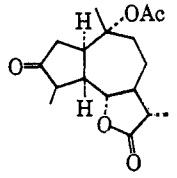
(6) Z. Čekan, V. Prochazká, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 1554 (1959); W. Herz and K. Ueda, *J. Am. Chem. Soc.*, **83**, 1139 (1961).

(7) The 3-nitrobenzenesulfonate of desacetylmatricarin (Ib) proved stable under solvolytic conditions, and also on exposure to bases. This stability suggests that the oxygen function at C-8 is *cis* to the tertiary hydrogen at C-7 (see text for a similar experience involving C-3).

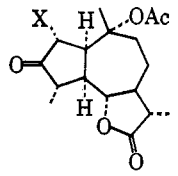
(8) J. Bermejo Barrera, J. L. Breton Funes, and A. Gonzales Gonzales, *J. Chem. Soc., Sect. C*, 1298 (1966).

biglovin (except at C-1 and C-10)[9] follow since each has been correlated with compound Ia.

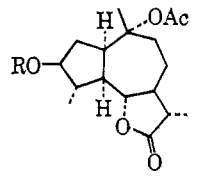
O-Acetylisophotosantonic lactone[10] III was hydrogenated over Pd–C to give the dihydro derivative IV, mp 169–170°, $[\alpha]^{24}D$ −61.7° (*c* 1.2, $CHCl_3$). Isomerization of IV on alumina yielded the C-4 epimer Va[11] (mp 165–166°, $[\alpha]^{24}D$ −26.6° (*c* 1, $CHCl_3$)), the stereochemistry of which has been determined *via* X-ray analysis of the bromo derivative Vb;[12] the absolute configuration as shown follows from earlier work.[13]



IV



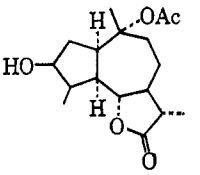
Va, X = H
b, X = Br
c, X = O_2CCH_3



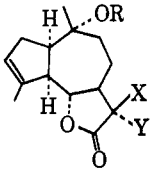
VIa, R = H
b, R = $CH_3C_6H_4SO_2$

Reduction of ketone Va with sodium borohydride yielded an alcohol VIa (mp 101–103°, $\lambda_{max}^{CHCl_3}$ 5.63 and 5.78 μ), the *p*-toluenesulfonate of which (VIb, mp 146–147°) proved stable to bases and to solvolysis in hot acetic acid; the mesylate was also unreactive.[14] A similar reduction of ketone IV yielded largely two alcohols, one of which (VII) on treatment with methanesulfonyl chloride and pyridine at room temperature led to the unsaturated lactone VIIIa (45%, mp 66–67°, $[\alpha]^{24}D$ +8° (*c* 1.7, $CHCl_3$), $\lambda_{max}^{CCl_4}$ 5.58 and 5.75 μ; nmr τ 4.62 (C-3 H, half-width 7 Hz), 5.98 (C-6 H, triplet, J = 9.5 Hz), 8.04 (OAc), 8.13 (C-4 Me, half-width 5 Hz), 8.57 (C-10 Me), and 8.85 (C-11 Me, doublet, J = 6 Hz)). The marked difference between compounds VIa and VII in the ease of elimination and the fact that no Δ^2 olefin is produced indicate that in this rigid 5,7,5 system only *trans* elimination to the tertiary hydrogen at C-4 is occurring.

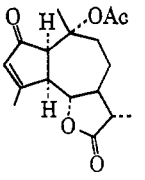
The oxidation of compound VIIIa with *t*-butyl chromate[15] yielded acetoxy ketone IX (15%, mp 146–148°, $[\alpha]^{24}D$ +45° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.62, 5.78, 5.90, and 6.14 μ; nmr, τ 5.95 (C-3 H, half-width 5 Hz) and 7.72 (C-4 Me, half-width 5 Hz)), plus small amounts of III and the 3,4-α epoxide of VIIIa. Treatment of IX with sodium acetate in refluxing acetic acid then yielded desacetoxymatricarin (Ia), mp 205–205.5°, $[\alpha]^{21}D$ +52.5° (*c* 1.0 $CHCl_3$), identical in every respect (spectra, R_f, no depression of mixture melting point) with material synthesized from matricarin[1] and with samples isolated from natural sources.[2,3] The last three steps in the synthesis were repeated using deuterated reagents throughout; compounds VIIIa, IX, and Ia were obtained free of deuterium (nmr analysis), indicating that epimerization at C-5 and C-11 had not occurred during the synthesis.



VII



VIIIa, R = CH_3CO; X = H; Y = CH_3
b, R = H; X = H; Y = CH_3
c, R = H; X = CH_3; Y = H



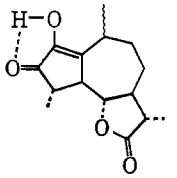
IX

Achillin. Treatment of VIIIa with potassium *t*-butoxide[11,16] gave an equimolar mixture of two hydroxy olefins which were epimeric only at C-11, as shown by the incorporation of deuterium only at this center (nmr analysis) when the reaction was carried out in *t*-butyl alcohol-O-*d*. The hydroxy olefin melting at 151–153°, $[\alpha]^{24}D$ +102° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.65 μ, which was assigned structure VIIIc, upon oxidation with *t*-butyl chromate gave rise to II, mp 142–143°, identical in every respect (spectra, R_f, no depression of melting point) to achillin isolated from *Achillea lanulosa*.[1] The other hydroxy olefin, $[\alpha]^{24}D$ +24° (*c* 1.0, $CHCl_3$), assigned structure VIIIb, gave rise to desacetoxymatricarin on oxidation.[17]

The magnitude of the coupling constant (10 Hz) for the C-6 and C-7 protons in the nmr spectrum of achillin (II) has led to the suggestion that the lactone fusion in achillin is *cis*.[5] Assignments of this type are unreliable for five-membered rings, as illustrated by the similarity in coupling constants for *cis* and *trans* protons on model ketals and carbonates.[18] Molecular models corresponding to structure II indicate that conformations exist for a *trans* lactone in which the dihedral angle[19] for the protons at C-6 and C-7 is close to 180°; similarly, the corresponding angle for a *cis* lactone is near 0°. Thus, the observation of a 10-Hz coupling constant for the *trans* lactone in achillin and its precursors and a 9-Hz coupling constant for the *cis* lactone in confertiflorin[20] is reasonable.

Acknowledgment. Financial support of this work by the National Institutes of Health (Grant No. 2RO1 CA 05234) is gratefully acknowledged. We also thank Dr. F. Bachelor for the synthesis of compound Vc, Dr.

(9) W. Herz and P. S. Santhanam, *J. Org. Chem.*, **30**, 4340 (1965).
(10) D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 929 (1957).
(11) D. H. R. Barton, J. E. B. Levisalles, and J. T. Pinhey, *ibid.*, 3472 (1962).
(12) J. D. Archer and G. A. Sim, *Proc. Chem. Soc.*, 111 (1962).
(13) D. H. R. Barton, *Helv. Chim. Acta*, **42**, 2604 (1959).
(14) The *p*-nitrobenzenesulfonate of the alcohol obtained by reduction of Vc (from Va + $Pb(OAc)_4$) was similarly unreactive. Ketone Vc on reaction with base underwent the expected rearrangement and elimination, but further changes leading to i rendered this path useless.



i

(15) K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 284 (1952); W. Herz, A. K. Pinder, and R. N. Mirrington, *J. Org. Chem.*, **31**, 2257 (1966); S. B. Nerali, P. S. Kalsi, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron Letters*, 4053 (1965).
(16) D. H. R. Barton, J. T. Pinhey, and R. J. Wells, *J. Chem. Soc.*, 2518 (1964).
(17) Satisfactory elemental analyses were obtained for all characterized compounds.
(18) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 747 (1962).
(19) M. Karplus, *ibid.*, **85**, 2870 (1963).
(20) N. H. Fischer and T. J. Mabry, *Tetrahedron*, **23**, 2529 (1967).

S. Eguchi for the synthesis of compounds VIb and i, Dr. K. S. Rybalko (Vilar, Moscow) for a sample of desacetoxymatricarin isolated from *Artemesia leucodes*, and Dr. R. E. K. Winter for helpful discussions.

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Ring Selectivity in the Reduction of Certain Indoles and Quinolines by Lithium and Methanol in Liquid Ammonia

Sir:

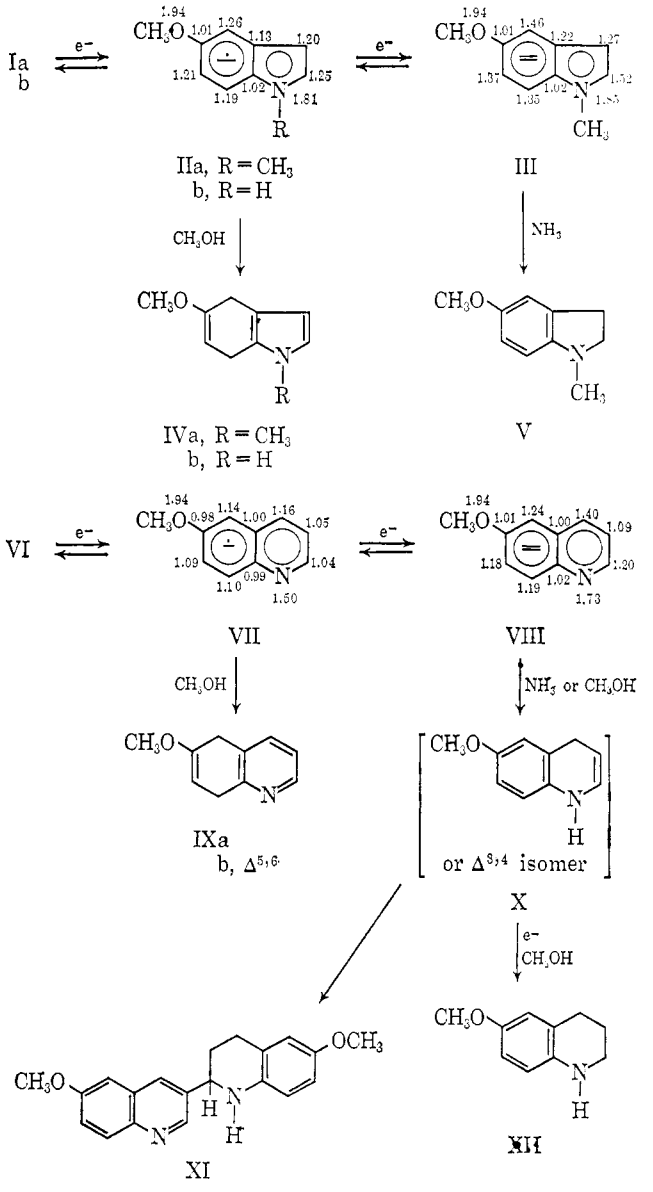
We wish to report that in the reduction of certain indole and quinoline derivatives by lithium and methanol in liquid ammonia the nature of the product is determined by the stage at which the methanol is added. When such compounds are treated with lithium, and methanol is added later or omitted, reduction occurs preferentially in the heterocyclic ring, probably *via* dianion intermediates; however, when excess methanol is present from the beginning of the reaction, reduction occurs in the benzene ring, apparently by interception of radical anion intermediates.

Thus treatment of 10 mmoles of 5-methoxy-1-methylindole (Ia)[1] with 80 mg-atoms of lithium in 200 ml of ammonia (no methanol) for 4 hr, followed by discharge of the excess lithium with ferric ion, afforded indoline V[1] as the sole product (70%). In contrast, if 20 ml of methanol was present prior to the addition of lithium, the reduction was very rapid and the product mixture contained 60% of 4,7-dihydro derivative IVa (n^{25}D 1.5465; nmr: pyrrole protons at δ 6.55 and 5.91, vinyl proton at 4.75, four aliphatic protons at 3.23 ppm), 4% of V, and 8% of Ia.[2,3]

When methanol is added to an ongoing reduction of Ia to V, the formation of IVa supersedes so that the ratio of V to IVa is determined by the time elapsed (10 min to 4 hr) before methanol addition (see Scheme I).

The equilibrium between Ia and its radical anion IIa apparently lies well to the left since Ia decolorizes lithium in ammonia quite slowly. However, methanol (a relatively strong acid) rapidly converts the small concentration of IIa to 4,7-dihydroindole IVa.[4] When methanol is absent, IIa is apparently insufficiently basic to deprotonate ammonia and reduction to IVa does not occur. Instead, the equilibrium between IIa and dianion III is established. This strongly basic dianion

Scheme I



is protonated by ammonia in the pyrrole ring to give indoline V. One reasonable explanation for the difference in the site of protonation between radical anion IIa and dianion III is that these intermediates have different patterns of electron distribution. Indeed, the depicted total π-electron densities, calculated by the LCAO–MO method,[5] reveal this difference and in the case of the dianion give an unequivocal indication of the site of protonation (C-2).

Treatment of 5-methoxyindole (Ib) in ammonia with 4 equiv of lithium results in vigorous reaction until 1 equiv is consumed, and thereafter blue color appears. Addition of methanol to this mixture affords 82% of 4,7-dihydro-5-methoxyindole [IVb, mp 65–68°, nmr: pyrrole protons at δ 6.68 and 6.00 (triplets), vinyl proton at 4.79 ppm]. If excess methanol is present from the beginning, IVb is still the sole product isolated (80%). The difference in behavior of Ib from Ia upon reduction is undoubtedly due to the acidic hydrogen of Ib. Apparently Ib is converted into a salt which is not reduced

(1) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951).

(2) In all experiments the ammonia was evaporated and the residue was treated with water and ether. The concentrate from the ether phase was compared with purified standards by glpc on a 6-ft Carbowax 20M column at 250°. With indoles the ether extract was totally volatile; however, only the monomeric quinoline products were volatile. Quinoline mixtures were partially resolved by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol system, although some 30–60% of the crude consisted of inseparable polymers. All compounds gave acceptable microanalyses (L. Brancone). Ultraviolet spectra were determined in methanol and nmr spectra were determined in $CDCl_3$ (W. Fulmor).

(3) Both IVa and V are unchanged by lithium amide in ammonia. Although IVa is stable toward excess lithium and methanol, V is reduced further. However, V is stable in the absence of methanol.

(4) For discussion of mechanisms of the Birch reduction see A. P. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3658 (1959); W. Hückel, *Fortshr. Chem. Forsh.*, **6**, 197 (1966).

(5) The parameters used were suggested in A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1962, p 135.