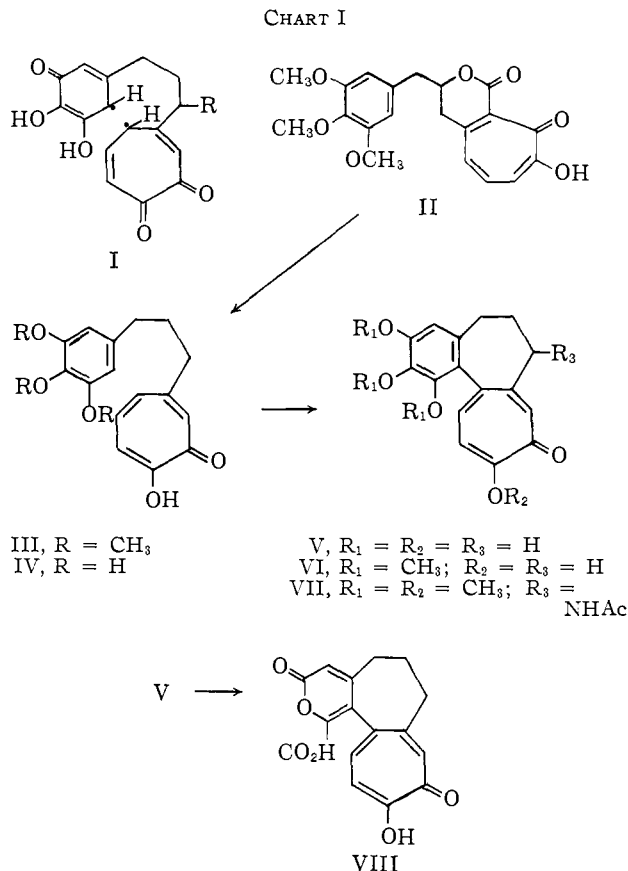
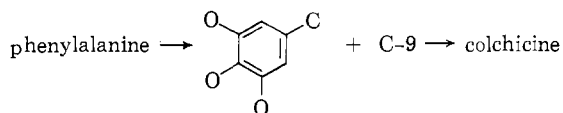


now illustrate our earlier hypothesis,⁵ in which participation of the tropolone radical (as I) is invoked, by a convenient four-step total synthesis of the colchicine framework as shown in Chart I.



Condensation of 3,4,5-trimethoxyphenylacetaldehyde⁶ with the anhydride of 3-carboxy-4-carboxymethyltropolone⁷ at 95° afforded the lactone II, m.p. 172°; ν_{CHCl_3} 1720, 1615 cm.⁻¹; $\lambda_{\text{max}}^{\text{EtOH}}$ 255 (ϵ 20,000), 332 (ϵ 5000), and 377 m μ (ϵ 7000) in 78% yield.⁸ Decarboxylation of II with copper bronze at 260° (10⁻² mm.) now gave β -(3,4,5-trimethoxyphenyl)prop-2-enyltropolone¹⁰ (70%), m.p. 115°; $\lambda_{\text{max}}^{\text{EtOH}}$ 270 (ϵ 23,000), 330 (ϵ 5000), 380 m μ (ϵ 7000). Controlled reduction (10% Pd-C; EtOAc) of the olefinic linkage led quantitatively to III, m.p. 113–115°; $\lambda_{\text{max}}^{\text{EtOH}}$ 245 (ϵ 15,000), 320 (ϵ 10,000), 350 m μ (ϵ 5000). Demethylation of III (HBr, 48%; 30-min. reflux) yielded the pyrogallol IV (50%), m.p. 128–132°. Control of oxidation of IV

(2) For a comprehensive summary see K. Mothes, *Angew. Chem.*, **57**, 357 (1963). The results of administering labeled C-1-C-9 units may be portrayed² as



The "missing" C-9 unit appears to be derived from tyrosine.⁴

- (3) A. R. Battersby, *Quart. Rev.* (London), **17**, 259 (1961).
 (4) E. Leete, IUPAC Meeting, London, 1963, Abstracts A, p. 284.
 (5) A. I. Scott, *Nature*, **186**, 556 (1960).
 (6) Prepared most conveniently by Rosenmund reduction of the corresponding acid chloride in 90% yield.
 (7) R. D. Haworth and J. D. Hobson, *J. Chem. Soc.*, 561 (1951).
 (8) Cf. T. Nozoe, *Proc. Japan Acad.*, **29**, 203 (1953), for a preparation of the phenyl analog. For the reported failure of this condensation in the case of substituted phenylacetaldehydes see ref. 9.
 (9) T. Nozoe, "Nonbenzenoid Aromatic Compounds," D. Ginsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 339.
 (10) This and all subsequent new compounds showed requisite mass, infrared, and n.m.r. spectra, which will be detailed in our full publication.

was maintained by ascending paper chromatography [Whatman No. 1 paper; HOAc-HCl-H₂O (20:10:1)]. In this system IV had R_f 0.81 (carmine fluorescence). After 2 hr. at 10° a solution of IV in sodium iodate (5 M; pH 6) showed a single identifiable spot (R_f 0.75) corresponding in color (yellow-green nonfluorescent) and R_f (0.75) to V, m.p. 238°, λ_{max} 242 (ϵ 17,000) and 361 m μ (ϵ 12,000), prepared by demethylation (HBr, 48%) of desacetylaminocolchicine¹¹ (VI).

For isolation, advantage was taken of the facile conversion (0.1 M; NaHCO₃-K₃Fe(CN)₆; 90 sec.; 50%) of V to the pyrone VIII, m.p. 288°, $\lambda_{\text{max}}^{\text{EtOH}}$ 233 (ϵ 12,000) and 365 m μ (ϵ 9000). Oxidation of IV with the latter reagent (1 hr.) now gave VIII (10%), identical in every respect (m.m.p., mass, infrared, n.m.r. spectra) with the material from V. Methylation of V (MeI-K₂CO₃-acetone; 3 hr.) gave back VI which has been converted to colchicine (VII).^{11,12} Since prolonged treatment (1 hr.) of VIII with alkaline ferricyanide leads to considerable degradation, the radical pairing reaction (I; R = H) must proceed in at least 20% yield.¹³

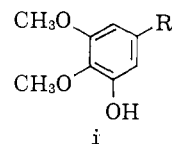
The availability of the various substrates described in this synthesis sets the stage for transfer of laboratory analogy to biological experiment.

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(11) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961).

(12) E. E. van Tamelen, T. A. Spenser, D. S. Allen, and R. L. Orvis, *Tetrahedron*, **14**, 8 (1961).

(13) Other pathways involving protected (but both less reactive and biologically relevant) pyrogallols (as i) have been investigated and will be reported elsewhere.



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Cycloheptatrienide (Tropenide) Anion

Sir:

The unsuccessful attempts¹ to prepare cycloheptatrienide (tropenide) anion, C₇H₇⁻, usually have been ascribed² to unfavorable properties predicted for it by the Hückel molecular orbital method (8 π -electrons, two of which are unpaired and occupy a pair of doubly-degenerate, antibonding molecular orbitals; relatively low DE (C₇H₇⁺, 2.99 > C₇H₇[·], 2.54 > C₇H₇⁻, 2.10 β)).^{2a,c}

(1) (a) J. Thiele, *Ann.*, **319**, 226 (1900); (b) G. Wittig and E. Hahn, *Angew. Chem.*, **72**, 918 (1960); Cf. K. Hafner and W. Rellensman, *ibid.*, **72**, 781 (1960).

(2) (a) E. Hückel, *Z. Physik*, **70**, 204 (1931); **76**, 628 (1932); *Z. Elektrochem.*, **41**, 752 (1937); (b) G. W. Wheland, *J. Chem. Phys.*, **2**, 474 (1960); (c) J. D. Roberts, A. Streitwieser, Jr., and Clare M. Regan, *J. Am. Chem. Soc.*, **74**, 4579 (1952); (d) A. Streitwieser, Jr., *Tetrahedron Letters*, 23 (1960).

Calculations by the Pariser-Parr ASMO method for species with D_{3h} symmetry predict³ a triplet ground state for the anion but greater delocalization energy for the anion than the known⁴ radical. However, recent studies have indicated, as predicted by the Jahn-Teller theorem, that symmetrical cyclic π -electron systems with orbitally degenerate ground states in the Hückel approximation will lose their degeneracy by bond length displacements,^{5a} as presumably in heptalene,^{5b} or by other perturbations that alter symmetry, such as carbanion-solvent interactions.^{5c} Snyder⁶ has estimated that static Jahn-Teller effect in tropenide anion by Hückel molecular orbital calculations in which the resonance integral depends on bond length and finds for the lowest singlet state that bond length distortions which remove the orbital degeneracy stabilize the two configurations of C_{2v} symmetry by about 6 kcal./mole, an amount which would be reduced on introduction of electron repulsion.^{5a} We wish to report the preparation of this interesting, elusive anion as solutions or suspensions of its salt, potassium cycloheptatrienide (tropenide), $K^+ C_7H_7^-$, and some of its properties.⁷

(i) Slow addition (12 hr.) of 7-methoxy-1,3,5-cycloheptatriene (I) in tetrahydrofuran to a stirred suspension of excess 1:5 Na-K alloy in tetrahydrofuran at -20° gradually produced a deep blue color which after further stirring (4 hr.) was discharged on carbonation (1 hr., CO_2 gas); work-up yielded 74-78% bis(7-cycloheptatrienyl) (II) [m.p. and m.m.p. 59-60°; $\lambda_{max}^{pentane}$ 252 $m\mu$ (ϵ 6700)], a trace of neutral polymer, and 8.5-9.8% of 1,3,5-cycloheptatriene-7-carboxylic acid (III) [m.p. 28°; $\lambda_{max}^{95\% EtOH}$ 257 $m\mu$ (ϵ 3100); n.m.r. $\begin{smallmatrix} Me_4Si \\ CCl_4 \end{smallmatrix}$, 3.34(t), 3.66(q), 4.60(q), and 7.46(t); completely free from traces of isomeric acids]. Since separate experiments have shown that II was produced by facile displacement of tropenide anion on ionogenic I under these conditions, cleavage of I by Na-K alloy to potassium tropenide (IV) must have been 75-80% effective when allowance is made for I consumed in formation of by-product II. Attempted modification of these reaction conditions by conducting the reaction at 0° or higher, by faster addition at -20° , or in more concentrated solutions all led to diminished yields of III and extensive or complete formation of a neutral, 1,6-addition polymer ($\lambda_{max}^{Et_2O}$ 250 $m\mu$). Generation of IV by the aforesaid method at -10 to -20° in the presence of 2-3 equivalents of (a) triphenylmethane, (b) diphenylmethane, or (c) toluene and work-up by the usual carbonation procedure showed by the products obtained [(a) 17.5% Ph_3CCOOH (V), 23% $Ph_3C-C_7H_7$, 17% (II); (b) 8.3% $Ph_2CH-C_7H_7$, 36% (II); (c) 6.7% (III), trace $PhCH_2COOH$ (VI), 37% (II)], along with appreciable amounts of polymers, that the relative acidity (pK_a)^{2a} of cycloheptatriene (VII) is: Ph_3C-H (33) > Ph_2CH-H (35) > C_7H_7-H (36) > $PhCH_2-H$ (37). The low yields of products isolated containing triphenylmethyl or diphenylmethyl moieties are due largely to competitive initiation of polymerization of I or VII by the corresponding anions.

(ii) Addition (4 hr.) of 7-triphenylmethyl-1,3,5-cycloheptatriene (VIII) (m.p. 260° (uncor.)) in tetrahydrofuran to a stirred suspension of excess 1:5 Na-K

alloy in tetrahydrofuran at -20° and additional stirring (12 hr.) produced a dark red solution within 3 hr. that became dark purple after 8 hr.; carbonation at -20° and work-up gave 39% of III, ca. 20% of V, some acidic polymer, and appreciable neutral polymer different from that obtained in i. Alternative work-up by fast quenching with excess Et_2COD ⁷ yielded 7-deuterio-1,3,5-cycloheptatriene as the only deuterated cycloheptatriene product. The higher yield of tropenide anion, as shown by the amount of III isolated, is attributable very likely to its less favored displacement on VIII than I for both steric and electronic reasons, as no II could be detected. Analogous cleavage in benzene-hexane solvent mixture failed.

(iii) Preparation of tropenide anion by proton abstraction from cycloheptatriene is complicated by competing anionoid polymerization as the triene is converted completely by sodium phenyl (pK_a benzene, 39), and almost completely by sodium benzyl⁸ in toluene at 25° into the 1,6-addition polymer ($\lambda_{max}^{Et_2O}$ 250 $m\mu$), only 0.2% of III being isolated from the latter reaction on carbonation. However, slow addition (7 hr.) of cycloheptatriene at 25° to a toluene suspension of dark red potassium benzyl⁸ prepared by heating potassium phenyl with toluene under reflux (2.5 hr.) and freed of excess potassium by stirring with mercury (3 hr.), produced a black suspension which on carbonation and work-up gave 30% of III, ca. 30% of VI, and ca. 40% of neutral polymer. Alternatively, when a suspension of potassium benzyl in hexane, prepared by isomerizing potassium *p*-tolyl at 80° (20 hr.),⁸ was treated with VII at 25° (20 hr.) and stirred (8 hr.), carbonation of the black suspension and work-up as before gave only 6.5% of III and much neutral polymer.

Limited studies have provided evidence of the formation of very low yields of lithium tropenide by i and of sodium tropenide by iii. Potassium tropenide is not formed in diethyl ether or dimethoxyethane; it is soluble in tetrahydrofuran, in which it is unstable at $\geq 0^\circ$ and undergoes proton exchange at $\geq -20^\circ$; it is insoluble in toluene or hexane but its suspensions in these solvents appear stable at 25° . Solutions of potassium tropenide in tetrahydrofuran or suspensions of it in inert hydrocarbons are deep blue colored (λ_{max}^{THF} ca. 750 $m\mu$ (broad)).⁹ Complete ultraviolet, visible, n.m.r., and e.s.r. spectral studies, as well as preparation of metal sandwich complexes, are currently being investigated.

From the relation between experimental pK_a values of the conjugate acids of weak hydrocarbon bases and the gains in delocalization energy on their formation by Streitwieser,^{2d} who estimated a pK_a value for cycloheptatriene of 31,^{2d,10} it may be approximated that the empirical resonance energy of the tropenide anion is about 0.8-1.1 β greater than for cycloheptatriene, or about 22-27 kcal./mole, if β has the same value for cyclic carbanions as for benzenoid aromatic hydrocarbons.

(8) H. Gülman, H. A. Pacevitz, and O. Baine, *J. Am. Chem. Soc.*, **62**, 1514 (1940).

(9) It has been our experience that pure tetrahydrofuran does not form blue solutions with Na-K alloy at -20° , 0° , or 25° ; cf. similar results of E. Grovenstein, Jr., and R. W. Stevenson, *J. Am. Chem. Soc.*, **81**, 4850 (1959) (ref. 3), but different findings by J. L. Down, J. Lewis, B. Moore, and G. Wilkinson, *Proc. Chem. Soc.*, 209 (1957).

(10) A. Streitwieser, Jr., W. C. Langworthy, and J. I. Braumann, *J. Am. Chem. Soc.*, **85**, 1761 (1963), propose a revised scale of acidities based on HMO predictions with the following tentative values: triphenylmethane, 21; diphenylmethane, 38.5; cycloheptatriene, 45; and toluene, 59.

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(6) L. C. Snyder, Bell Telephone Laboratories, private communication.

(7) Cf. deuterium exchange evidence of tropenide anion in adjacent communication, W. von E. Doering and P. P. Gaspar, *J. Am. Chem. Soc.*, **85**, 3043 (1963).