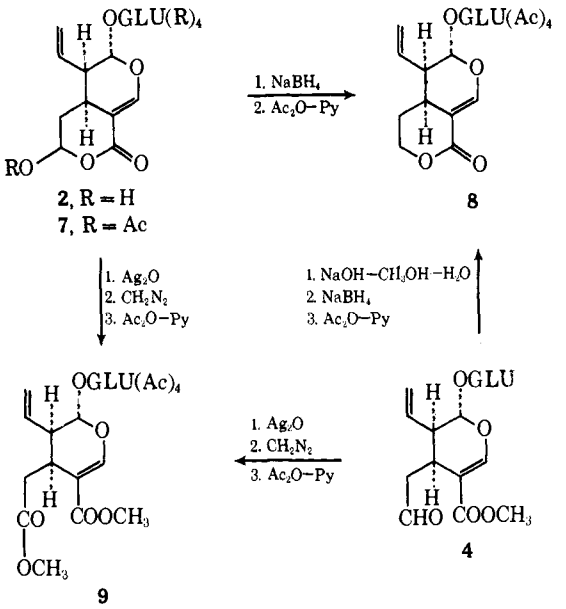
Scheme II



showed no depression and identical chromatographic mobilities were observed. Sweroside tetraacetate (**8**) was also prepared from **4** isolated from this plant.

Upon methylation and acetylation of the second new acidic constituent of *V. rosea*, secologanoside, a methyl ester tetraacetate **9** was obtained: mp 140.5°; optical rotation $[\alpha]_D$ −99° (*c* 1, $CHCl_3$); uv λ_{max}^{EtOH} 230 nm (log ε 4.08); nmr δ 7.4 (d, *J* = 2 Hz, H-3), 5.0–5.5 (m, 8 H's), 4.2 (dd, $-CH_2$ of glucose), 3.73 (s, OCH_3), 3.77 (s, OCH_3), 2.13, 2.06, 2.03, and 1.95 (each s, $4CH_3CO$).[10] Compound **9** was also synthesized from **4** and **2** (Scheme II).

V. rosea plants were fed [2-^{14}C-2-^{3}H]mevalonate and labeled loganic acid (**1**), loganin (**3**), secologanic acid (**2**), and secologanin (**4**) were isolated by adding carrier glucosides (Table I). After purification, derivatives were prepared and recrystallized to constant specific activity. Selective oxidation of the cyclopentano glucosides and the secoiridoids indicated 0.8–1 atom of tritium at C-7 in agreement with previous experiments[13,14] and consistent with incorporation of mevalonate *via* the isoprenoid pathway. The remaining tritium would be expected to be at C-3[13,14] and higher ratios may be attributed to an isotope effect in the earlier occurring hydroxylation of a tritiated C-3 methyl group.[15,16]

Table I. *In Vivo* Tracer Experiments in *V. rosea*

Precursor	Labeled monoterpene	% incorp of ^{14}C	^{3}H/^{14}C atomic ratio Obsd	Calcd
[2-^{3}H-2-^{14}C]MVA				2:1
	Loganic acid	0.25	1.3:2	1.33:2[a]
	7-Oxologanin from loganic acid		0.48:2	0.33:2[a]
	Loganin	0.02	1.3:2	1.33:2
	7-Oxologanin from loganin		0.54:2	0.33:2
	Secologanic acid	0.17	1.6:2[b]	1.33:2
	Secologanoside from secologanic acid		0.68:2[b]	0.33:2
	Secologanin	0.2	1.2:2	1.33:2
	Secologanoside from secologanin		0.49:2	0.33:2

[a] Calculated on the basis of equilibration of the terminal dimethyl groups.[6] [b] The difference in ^{3}H/^{14}C ratios between secologanic acid and other isolated monoterpenes may not be significant. The dilution of secologanic acid led to lower specific activities and less accurate ratios.

Having established the existence of a methyl transferase which converts loganic acid (**1**) to loganin (**3**) *in vitro*[1] we wished to demonstrate this methylation *in vivo*. From experiments with [2-^{14}C]mevalonate in *V. rosea*, labeled loganic acid was obtained and its specific activity (6.75 × 10^5 dpm/mmol) determined by methylation to **3** and recrystallization to constant activity as the free glucoside and its pentaacetate.[6,14] Pure loganic acid-^{14}*C* (**1**) (20 mg), regenerated by saponification followed by ion exchange chromatography,[13] was fed to *V. rosea* plants which afforded loganin (**3**) (1.1% incorporation), secologanic acid (**2**) (6.7% incorporation), and secologanin (**4**) (8.8% incorporation). A sample of labeled loganin (**3**) (31 mg, 8.05 × 10^5 dpm/mmol), similarly obtained and administered to *V. rosea*, was converted to secologanic acid (**2**) (2.0% incorporation).

Purification of a methyl transferase from *V. rosea*, capable of methylating loganic acid (**1**) and secologanic acid (**2**) at comparable rates,[17] coupled with the above results implicates both acids in indole alkaloid biosynthesis. A dual pathway (Scheme I) is thus envisaged in which the acids are either converted to sweroside (**5**) or methylated and utilized in indole alkaloid biosynthesis. *In vivo* conversion of loganin (**3**) to secologanic acid (**2**) indicates the existence of esterase activity in the plant. Previous double labeling studies with loganin (**3**) in *Cephaelis ipecacuanha* also suggest this.[18]

Acknowledgment. Financial support from the NSF and NIH is appreciated.

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(14) C. J. Coscia, L. Botta, and R. Guarnaccia, *Arch. Biochem. Biophys.*, 136, 498 (1970).
(15) J. W. Cornforth, J. W. Redmond, H. Eggerer, W. Buckel, and C. Gutschow, *Nature (London)*, 221, 1212 (1969).
(16) J. Luthy, J. Retéy, and D. Arigoni, *ibid.*, 221, 1213 (1969).
(17) C. J. Coscia, K. M. Madyastha, and R. Guarnaccia, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 30, 1472 (1971).
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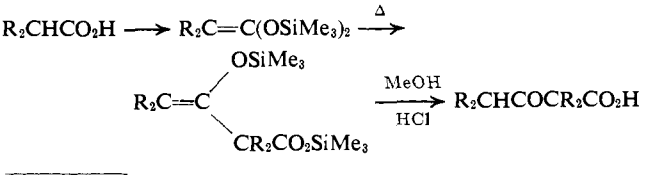
Reactions of Dianions of Carboxylic Acids with Esters and α,β-Unsaturated Esters, Nitriles, and Aldehydes

Sir:

We have recently discovered a new synthesis of β-keto acids *via* the following reaction scheme.[1] We



(1) Y. N. Kuo and C. Ainsworth, to be published elsewhere.

here report an alternative synthesis which is simpler and affords more flexibility of product. It involves reaction of the dianions of carboxylic acids with esters[2] as is illustrated below. The intermediates were trapped with

$$R_2C^-CO_2^- + R'CO_2Me \longrightarrow R'COCR_2CO_2^- \xrightarrow{TMCS} R'COCR_2CO_2SiMe_3 \xrightarrow{MeOH} R'COCR_2CO_2H \xrightarrow{\Delta} R'COCHR_2$$

I

trimethylchlorosilane (TMCS) and isolated as the trimethylsilyl esters (I) (Table I). Compounds I underwent solvolysis under neutral conditions to yield β-keto acids in good yield.[3] The procedure also furnished a practical synthesis of highly substituted ketones,[4] since the latter are so easily formed from β-keto acids.

Table I. Trimethylsilyl β-Keto Carboxylates, $RCOCR'R''CO_2SiMe_3$ (I)

R	R′	R″	Yield, %	Bp, °C (mm)
Et	H	Me	50	65 (1.0)
Et	Me	Me	40[a]	85 (15)
Me_2CH	Me	Me	80	67 (0.7)
tert-Bu	Me	Me	70	52 (0.05)
b	Me	Me	75	80 (0.05)
Ph	Me	Me	75	78 (0.01)
b	$-(CH_2)_5-$		70	130 (0.05)

[a] Contains 20% trimethylsilyl 2,2-dimethyl-3-trimethylsilyloxy-3-pentenoate (see Table II). [b] Cyclohexyl.

As an example, the dianion of isobutyric acid was formed in THF at 0° using 2 equiv of lithium diisopropylamide.[5] One equivalent of methyl pivalate was added and the solution was stirred for 30 min. An excess of TMCS was added and the mixture was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was concentrated and distilled under reduced pressure, bp 50° (0.05 mm), yield 70%. Solvolysis of the trimethylsilyl β-keto ester with methanol at room temperature for 30 min formed the corresponding β-keto acid, quantitatively. Thermolysis of the latter gave *tert*-butyl isopropyl ketone in quantitative yield.

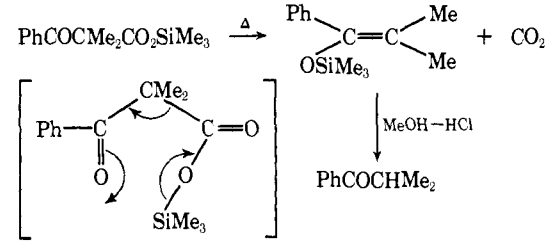
A variation occurred in the reaction sequence when methyl phenyl- or diphenylacetates were employed. A disilyl product II was formed according to the scheme given below[6] (Table II). Compounds II were partially solvolyzed in methanol at room temperature for 20–30 min. The resulting β-trimethylsilyloxy carboxylic acids on standing with methanol containing a catalytic amount of hydrochloric acid gave β-keto acids.

$$R_2C^-CO_2^- + PhCHR'CO_2Me \longrightarrow PhCHR'COCR_2CO_2^- \longrightarrow PhR'C{=}C(O^-)(CR_2CO_2^-) \xrightarrow{TMCS} PhR'C{=}C(OSiMe_3)(CR_2CO_2SiMe_3) \xrightarrow{MeOH} PhR'C{=}C(OSiMe_3)(CR_2CO_2H) \xrightarrow[HCl]{MeOH} PhR'CHCOCR_2CO_2H$$

II

The dianions of isobutyric, propionic, cyclohexanecarboxylic, and phenylacetic acids were employed. They were prepared using 2 equiv of lithium diisopropylamide in THF at 0°, except propionic acid which was prepared at −78°.

All of the silyl esters distilled normally except trimethylsilyl α-benzoyl-α-methylpropionate which decomposed near 100° according to the following scheme.



A six-center transition state as indicated seems likely for this reaction. Solvolysis of the silyl product using methanol containing a catalytic amount of hydrochloric acid gave isopropyl phenyl ketone in high yield.

We next turned to a study of the addition of dianions of carboxylic acids to α,β-unsaturated esters. The dianion of isobutyric acid in such a reaction formed the Michael addition products[7] shown in Table III. The method is an efficient route to monoesters of substituted glutaric acids.[8] Most of the reactions were carried out in THF at room temperature or above. Under these conditions methyl acrylate was polymerized but it underwent addition at −78°.

Table II. Trimethylsilyl 3-Trimethylsilyloxy-3-butenoates, $RR'C{=}C(OSiMe_3)CR''R'''CO_2SiMe_3$ (II)

R	R′	R″	R‴	Yield, %	Bp, °C (mm)
H	Me	Me	Me	20[a]	52 (0.03)
H	Ph	Me	Me	85	135 (1.0)
Ph	Ph	Me	Me	80	175 (1.0)
H	Ph	H	Ph	40	130 (0.05)

[a] Formed with the second compound listed in Table I.

Table III. Michael Adducts, $RC(CMe_2CO_2H)HCHR'CO_2R''$ (III)

R	R′	R″	Yield, %	Bp, °C (mm)
H	H	Me	52	100 (0.15)
H	Me	Me	40	98 (0.1)
H	Me	*n*-Bu	57	118 (0.03)
Me	H	Me	64	107 (0.2)
Ph	H	Me	55	81–82[a]
Ph	H	Et	52	167 (0.05)

[a] Melting point.

(2) P. E. Pfeffer and L. S. Silbert (*Tetrahedron Lett.*, 699 (1970)), used ethyl formate only and obtained aldehydes.

(3) Most of the β-keto acids described in ref 1 were also prepared by this method.

(4) A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *J. Amer. Chem. Soc.*, **93**, 2314 (1971).

(5) P. L. Creger, *ibid.*, **89**, 2500 (1967); **92**, 1396, 1397 (1970).

(6) Methyl propionate and the dianion of isobutyric acid reacted according to both schemes.

(7) No 1,2 addition was observed. Methyl *p*-nitrocinnamate did not react.

(8) The reverse monoesters of substituted glutaric acids are prepared by hydrolysis of the corresponding diesters: W. H. Harwood, R. M. Hurd, and E. S. Snavely, Jr., *Ind. Eng. Chem. Prod. Res. Dev.*, 3(2), 105 (1964).

$$RCH{=}CR'CO_2Me + Me_2C^-CO_2^- \longrightarrow \xrightarrow{H^+} RCHCHR'CO_2Me$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CMe_2CO_2H$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad III$$

The dianion of isobutyric acid caused the polymerization of acrylonitrile and crotononitrile even at −78°. However, cinnamonitrile formed the Michael adduct at

$$PhCH{=}CHCN + Me_2C^-CO_2^- \longrightarrow \xrightarrow{H^+} PhCHCH_2CN$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CMe_2CO_2H$$

room temperature. The dianion of isobutyric acid and crotonaldehyde or cinnamaldehyde underwent 1,2 addition.[9,10]

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health (Grant No. GM 16594). Dean P. Stull checked several of the dianion reactions.

(9) G. M. Moersch and A. R. Burkett, *J. Org. Chem.*, **36**, 1149 (1971).
(10) Satisfactory microanalytical data and/or nmr and mass spectral data were obtained for all new compounds.

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Long-Range Interactions in 6-Nitro- and 6,7-Dinitrobenzonorbornene Anion Radical and Related Radicals

Sir:

Many esr studies of the norbornene system having spin-labeled groups, such as semidiones,[1] semiquinones,[2] and semifuraquinones,[3] have been reported hitherto and the long-range hyperfine splittings of these compounds discussed in relation to their stereochemistry.[4] All of these anion radicals have structures in which the spin-labeled groups are bounded by two equivalent carbon atoms of the bridged bicyclene.

One of the most interesting current problems in bridged bicyclic systems is that of long-range coupling to the anti and exo hydrogens, and it is toward an understanding of this that we have investigated the esr of unsymmetrical nitrobenzonorbornene and symmetrical dinitrobenzonorbornene. Mono- and dinitrobenzonorbornene anion radicals and related radicals were prepared *in situ* from the parent compounds by reduction with propiophenone in DMSO containing potassium *tert*-butoxide.[5]

The esr spectrum of 6-nitrobenzonorbornene anion radical (**1**) is shown in Figure 1. The assignment of the hyperfine splitting constants (hfsc's) of the hydrogen atoms in **1** was established by the experimental data[6] for 6-nitrobenzonorbornen-2-one (**2**) and -9-one (**3**) anion radicals, and is based on the results of Russell,[1] Stock,[2] Nelsen,[3] Geske,[7] and Tori,[8] and coworkers.

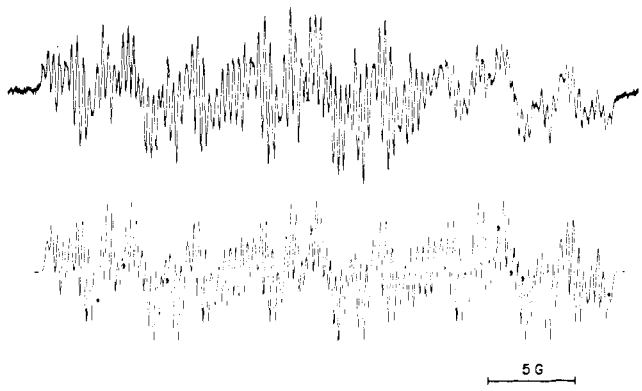
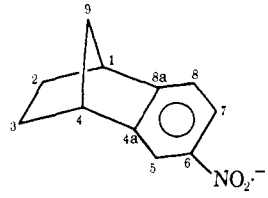


Figure 1. Top: first-derivative esr spectrum observed in the reduction of 6-nitrobenzonorbornene with propiophenone in the presence of potassium *tert*-butoxide in DMSO solution at 25° by a Varian V4502-15 spectrometer. Bottom: calculated spectrum with Gaussian line width of 0.23 G and hfsc's given in the text.



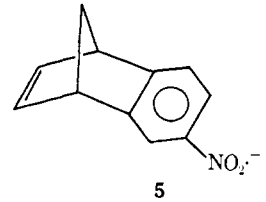
a^N = 10.63 (1 N) a^{H_8} = 1.09 (1 H)
a^{H_6} = 3.66 (1 H) a^{H_1} = 0.63 (1 H)
a^{H_5} = 3.14 (1 H) a^H = 0.37 (1 H)
$a^{H_{exo\text{-}2}}$ = 1.46 (1 H) a^H = 0.24 (2 H)

1

The interesting point is that the hfsc of the exo-C-2 (homo-para-exo) hydrogen is very large, but that of the exo-C-3 (homo-meta-exo) hydrogen atom is rather small. This result gives evidence that the hfsc's of hydrogens in this system are mainly affected by the spin density at the para and meta positions of the nitrobenzene anion radical. The magnitudes of these long-range interactions are not, however, exactly proportional to the spin density of the benzene ring. This may be the result of an additional interaction mechanism being involved.

The magnitude of the splitting of anti-C-9 hydrogen will be either 0.37 or 0.24 G,[9] and although we could not determine which is the correct value, it is in either case small. We believe that the long-range interaction at this position is attributed to a W-plan arrangement from the p_z orbitals of both the 4a and 8a carbon atoms, but that cancelation by the opposite signs of the spin density at these positions results in this value becoming small.

The spectrum of 6-nitrobenzonorbornadiene anion radical (**5**) was analyzed as follows.



a^N = 10.35 (1 N) a^H = 0.44 (2 H)
a^{H_6} = 4.08 (1 H) a^H = 0.26 (1 H)
a^{H_5} = 2.83 (1 H) a^H = 0.19 (2 H)
a^{H_8} = 1.15 (1 H)

5

(1) (a) G. A. Russell and K.-Y. Chang, *J. Amer. Chem. Soc.*, **87**, 4381 (1965); (b) G. A. Russell, G. W. Holland, K.-Y. Chang, and L. H. Zolkow, *Tetrahedron Lett.*, 1955 (1967); (c) G. A. Russell and P. R. Whittle, *J. Amer. Chem. Soc.*, **89**, 6781 (1967).
(2) (a) D. Kosman and L. M. Stock, *ibid.*, **88**, 843 (1966); (b) *Chem. Commun.*, 551 (1968); (c) *J. Amer. Chem. Soc.*, **91**, 2011 (1969).
(3) S. F. Nelsen and E. D. Seppanen, *ibid.*, **89**, 5740 (1967).
(4) G. R. Underwood and V. L. Vogel, *ibid.*, **93**, 1058 (1971).
(5) G. A. Russell, E. G. Janzen, and E. T. Strom, *ibid.*, **86**, 1807 (1964).
(6) a^H = 1.46 G disappeared in **2**, while a^H = 0.63 G was observed in **3**. The assignment of the hfsc's of the ortho hydrogens using 7-deuterio-6-nitrobenzonorbornene is in progress. The coupling of homo-para-exo hydrogens of 6-nitrobenzobicyclo[2.2.2]octene anion radical was determined to be the same as that of the meta hydrogen: R. Konaka and S. Terabe, unpublished results.
(7) D. H. Geske, *Progr. Phys. Org. Chem.*, **4**, 125 (1967).
(8) For the observation of the contact shift of the 6-aminobenzonorbornene complex with bis(acetylacetonato)nickel(II), see K. Tori, Y. Yoshimura, and R. Muneyuki, *J. Amer. Chem. Soc.*, **93**, 6324 (1971).
(9) These couplings are not those of the endo-C-2 or endo-C-3 hydrogens, since the spectrum of *endo,endo*-2,3-dideuterio-6-nitrobenzonorbornene anion radical (**4**) was the same as that of **1**.