Hegedüs[7] has made it possible to synthesize various 3-aralkyl-4-hydroxycoumarins not realizable heretofore by the conventional methods.[10,11] The primary advantage of the method reported herein resides in the fact that the aralkyl halides are either commercially available or can be made readily in the laboratory by conventional methods. The alkylation of 4-hydroxycoumarin is direct without passing through intermediates, the yields are generally very good and purification of the products obtained offers no difficulties.

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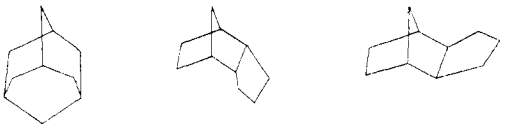
A SIMPLE PREPARATION OF ADAMANTANE

Sir:

Because of the analogy with the structure of the diamond, the highly symmetrical molecule, adamantane (tricyclo[3.3.1.1^{3,7}]decane) (I), has occasioned interest for many years.[1] The total synthesis of this hydrocarbon, first isolated from petroleum naphtha[2] in minute yields,[3] has been accomplished several times, utilizing a number of modifications of the same general approach.[1,4] The over-all yields of even the best of these methods, involving a moderately large number of steps, did not exceed a few per cent.; therefore, investigations of the chemistry of this compound have been hindered to a large extent by its unavailability. We wish to report a facile two-step preparation of adamantane from the very readily available compound, dicyclopentadiene (II).

endo-Trimethylenenorbornane[5] (tetrahydrodicyclopentadiene, III), which can be prepared from II in essentially quantitative yield by hydrogenation,[6] was refluxed with 10 per cent. of its weight of $AlBr_3$ or $AlCl_3$ overnight.[7] At the end of this time the products were distilled directly from the reaction pot, with no attempt at fractionation. The precipitation of adamantane was completed by cooling the distillate to Dry-Ice temperature; a yield of about 10 per cent. of crude I could be obtained by filtration through a coarse filter. Additional I could be obtained by subjecting the filtrate to fractional distillation through an efficient column. The forecuts, b.p. to 185°, contained a large number of components. The main fraction, b.p. 185.0°, $n^{20}D$ 1.4871, consisted of *exo*-trimethylenenorbornane (IV).[8] the expected product of the reaction.[9] The yield of this material, about 50 per cent., could be improved considerably by conducting the isomerization at lower temperatures. From the higher boiling cuts, b.p. to 195°, approximately 5 per cent. additional crude I was recovered. After washing with ethanol, fractional sublimation of the combined samples of I gave a 12–13 per cent. yield of pure adamantane, m.p. 269.6–270.8° (sealed tube). Reported m.p. 268.5–270°.[1] *Anal.* Calcd. for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.31; H, 11.99. The infrared spectrum[10] and mass spectral pattern[11] of the rearrangement product further established its identity as adamantane.



Since, as would be anticipated, IV, under the same conditions, gave a similar yield of I, it may be possible to improve the yield of I considerably The driving force for the rearrangement is undoubtedly the result of the fact that I, in contrast to III and IV, possesses an arrangement of atoms uniquely free from angular and conformational strain. Conceptually, it is possible to visualize several routes for the conversion of III or IV into I. The simplest of these necessitates only three steps involving carbon-to-carbon rearrangements. The possible mechanisms of these unusual transformations will be commented on in greater detail later.

(1) *Cf.* an excellent review, H. Stetter, *Angew. Chem.*, **66**, 217 (1954). More recent references will be found below.[3,4,10]

(2) S. Landa and V. Macháček, *Coll. Czech. Chem. Comm.*, **5**, 1 (1933).

(3) S. Landa, Š. Kriebel and E. Knobloch, *Chem. Listy*, **48**, 61 (1954) (*C. A.*, **49**, 1598 (1955)).

(4) V. Prelog and R. Seiwerth, *Ber.*, **74**, 1644, 1769 (1941); H. Stetter, O.-E. Bänder and W. Neumann, *ibid.*, **89**, 1922 (1956).

(5) The nomenclature used here will be that suggested previously (P. R. Schleyer and M. M. Donaldson, THIS JOURNAL, **78**, 5702 (1956)).

(6) For references, *cf.* E. Josephy and F. Radt, Eds., "Elsevier's Encyclopaedia of Organic Chemistry," Vol. 13, Elsevier Publishing Co., Inc., New York, N. Y., 1946, p. 1022.

(7) For a recent review of the action of Lewis acids upon alkanes, *cf.* H. Pines and J. Mavity in B. T. Brooks, *et al.*, Eds., "The Chemistry of Petroleum Hydrocarbons," Vol. III, Reinhold Publishing Corp., New York, N. Y., 1955, Chap. 39, pp. 9–58.

(8) H. Bruson and T. W. Riener, THIS JOURNAL, **67**, 723 (1945); *cf.* P. D. Bartlett and A. Schneider, *ibid.*, **68**, 6 (1946).

(9) M. M. Donaldson, unpublished results from this laboratory. *Cf.* J. F. Eykman, *Chem. Weekblad*, **1**, 7 (1903); **3**, 687 (1906).

(10) R. Mecke and H. Spiesecke, *Ber.*, **88**, 1997 (1955). The author is indebted to Dr. R. A. Dean, The British Petroleum Co., Ltd., for a copy of the spectrum of synthetic adamantane.

(11) Catalog of Mass Spectral Data, A.P.I. Research Project 44 Carnegie Institute of Technology, Pittsburgh, Pennsylvania, No. 939

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SELENIUM AS AN INTEGRAL PART OF FACTOR 3 AGAINST DIETARY NECROTIC LIVER DEGENERATION

Sir:

Factor 3 is a dietary agent which prevents liver necrosis in the rat.[1] Concentrates of Factor 3 also protect against multiple necrotic degeneration (heart, liver, kidney and muscle necrosis) in the mouse,[2] as well as against exudative diathesis in the chick.[3] These fatal diseases result from a multiple deficiency. They are produced by diets which are low in cystine and simultaneously defi-

(1) K. Schwarz, *Proc. Soc. Exp. Biol. and Med.*, **78**, 852 (1951).

(2) W. B. DeWitt and K. Schwarz, *Experientia*, in press.

(3) M. L. Scott, J. G. Bieri, G. M. Briggs and K. Schwarz, to be published.

cient in vitamin E and Factor 3. Each of these substances protects by itself. Details of the rat assay for Factor 3, using a ration based on Torula yeast as the sole source of protein, have been described.[4]

During the fractionation of Factor 3 from acid hydrolysates of natural source materials we detected that at least two chemically closely related substances with Factor 3 activity were present. These have been designated α- and β-Factor 3.[5] α-Factor 3 was found to be water soluble, strongly anionic, stable against oxidation, but sensitive to reducing agents. Dry ashing eliminated Factor 3 activity entirely.

The fractionation of α-Factor 3 has led to highly concentrated, semi-crystalline preparations. Some of these were found to develop a characteristic, garlic-like odor upon addition of alkali. This observation led to the discovery that selenium is an integral part of Factor 3. The element is present in bound form. Qualitative tests for selenium were observed only upon decomposition of active preparations. Various α-Factor 3 fractions were analyzed for selenium; for this purpose the reaction with codeine[6] was adapted to the Beckman spectrophotometer.[7] It is seen that Factor 3 activity is correlated with the selenium content (Table I).

TABLE I

SELENIUM DETERMINATIONS IN FACTOR 3 PREPARATIONS

Prepn. no.[a]	Units of F3[b] in aliquot analyzed	μg. Se[c] found
4737	Inactive	<1
4759	Inactive	<1
4760	72	7
4197B	330	3.5
4757	410	9
4741	430	12

[a] Fractions of greatly varying degrees of purity, prepared from dried, defatted kidney powder hydrolysate. [b] Dietary rat assay against liver necrosis; ref. 4. [c] Standardized against the selenium analog of cystathionine (M. J. Horn and D. B. Jones, *J. Biol. Chem.*, **139**, 649 (1941)). The authors wish to thank Dr. M. J. Horn for a generous sample of this material.

The conclusion that selenium is an essential part of the active organic material is borne out by the finding that inorganic selenium salts are remarkably effective in protecting against necrotic liver degeneration (Table II). As little as 13.33 μg. of sodium selenite, *i.e.*, 4 μg. of the element, in 100 g. of diet suffice to afford complete protection. This amounts to a daily intake of about 0.250 μg. of selenium per rat. Protection was also obtained by the daily subcutaneous injection of 0.167 μg. of selenium as sodium selenite. Preliminary indications are that potassium selenate is less potent. Potassium tellurite and sodium arsenate were without effect. The latter substance is known to antagonize selenium poisoning successfully in various species.[8]

(4) K. Schwarz, *Proc. Soc. Exp. Biol. and Med.*, **80**, 319 (1952).
(5) K. Schwarz, L. H. Mason and C. M. Foltz, to be published.
(6) M. J. Horn, *Ind. Eng. Chem.*, **6**, 34 (1934).
(7) M. A. Malm and K. Schwarz, to be published. The authors are indebted to Dr. M. A. Malm for the selenium analyses.
(8) A. L. Moxon and M. Rhian, *Physiol. Revs.*, **23**, 305 (1953).

TABLE II

EFFECT AGAINST DIETARY NECROTIC LIVER DEGENERATION

Supplement[a]	Salt mg. per 100 g. of diet	Element μg. per 100 g. of diet	No. of animals Total	No. of animals Dead on 30th day
None (Controls)	...	...	18	17[b]
Sodium selenite	0.0199	6	10	0
($Na_2SeO_3 \cdot 5H_2O$)	.0133	4	10	0
	.0067	2	10	3
	.0033	1	5	4
Potassium selenate	.280	100	5	0
(K_2SeO_4)	.028	10	5	4
	.003	1	5	4
Potassium tellurite	.199	100	5	5
(K_2TeO_3)	.020	10	5	5
Sodium arsenate	.470	100	5	5
($Na_2HAsO_4 \cdot 7H_2O$)	.047	10	5	5

[a] Composition of the basal diet: *Torula* feed yeast 30, sucrose 59, vitamin-E free lard 5, salts 5, vitamins (in lactose) 1; K. Schwarz, *Proc. Soc. Exp. Biol. Med.*, **77**, 818 (1951). [b] Inbred animals of the Fisher strain were used. The average survival time on the basal diet is 21 days. The incidence of necrotic liver degeneration is 100%. The tests were terminated after 30 days.

Our results show that, at least for the rat, Factor 3 is not an essential *organic* dietary constituent, since it can be replaced by selenite. The specific potencies of various inorganic and organic selenium compounds remain to be established. Most of the selenium in normal diets appears to be organically bound. The dose needed for the prevention of dietary necrotic liver degeneration amounts to less than 1% of the chronic toxic dose, which has been placed at 300–400 μg./100 g. of ration.[9]

In comparison with previously reported values for vitamin E and cystine,[10] selenium is exceedingly effective in the prevention of necrotic liver degeneration. When applied in form of sodium selenite it is approximately 500 times as active as vitamin E and 250,00 times as active as L-cystine. The element has been shown to be constantly present in tissues of higher animals.[11] It can be inferred from our results that *selenium is an essential trace element.* A characteristic defect, respiratory decline, is present in oxidative metabolism of liver slices from animals on necrogenic diets several weeks before necrosis occurs[12]; this suggests that selenium may act in intermediary metabolism by participating in oxidation reduction reactions.[13,14]

(9) H. E. Munsell, G. M. Devaney and M. H. Kennedy, U. S. Dept. Agr. Tech. Bull. No. 534 (1936).
(10) K. Schwarz, *Ann. N. Y. Acad. Sci.*, **57**, 878 (1954).
(11) E. J. Underwood, "Trace Elements," Academic Press, Inc., New York, N. Y., 1956, p. 2.
(12) S. S. Chernick, J. G. Moe, G. P. Rodnan and K. Schwarz, *J. Biol. Chem.*, **217**, 829 (1955).
(13) The authors are indebted to Dr. DeWitt Stetten, Jr., for helpful suggestions, stimulating discussions and for his sustained interest.
(14) The efficient technical assistance of Edward E. Roginski, Clifford E. Lee and H. Haskell Parker is gratefully acknowledged.

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