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RECEIVED APRIL 29, 1957

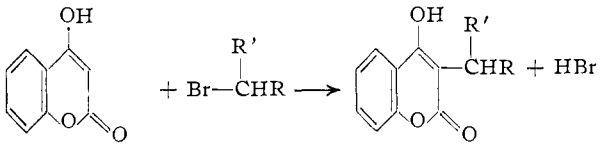
A NEW SYNTHETIC APPROACH TO SOME 3-ARALKYL-4-HYDROXYCOUMARINS[1]

Sir:

Since the introduction of the anticoagulant Dicumarol®, 3,3′-methylenbis-(4-hydroxycoumarin) for clinical purposes,[2] interest in the synthesis of new 3-substituted-4-hydroxycoumarins and in new methods of synthesizing them has been maintained. While the reactivity of the 3-position of 4-hydroxycoumarin (I) is well known,[3,4,5] the direct alkylation of the 3-position of 4-hydroxycoumarin with reactive halides under acidic conditions has not been reported. Grüssner[6] had reported the alkylation of 4-hydroxycoumarins with reactive allyl and substituted allyl bromides under alkaline conditions. This method leaves much to be desired with respect to the yields obtained (usually 10–15%) and the scope of the procedure.

Recently Grüssner and Hegedüs[7] reported a novel, mutiple-step procedure for the preparation of 3-aralkyl-4-hydroxycoumarins, in which organometal compounds are condensed with 3-acyl-4-hydroxycoumarins to form tertiary carbinols which are in turn dehydrated to the corresponding unsaturated compounds and which upon catalytic hydrogenation give the desired 3-aralkyl-4-hydroxycoumarins.

In a recent paper Ziegler and Roszmann[8] reported the synthesis of 3-substituted benzyl-4-hydroxycoumarins by condensing 4-hydroxycoumarin and substituted benzyl alcohols directly using phosphorus oxychloride as the catalyst and solvent.



I II III–XII

We have found that 4-hydroxycoumarin (I) can be alkylated readily in the 3-position by heating it in the molten state with certain reactive aralkyl halides (II) at temperatures of 130–180°. The 3-aralkyl-4-hydroxycoumarins (III–XII) are readily isolated in the pure state and usually in very good yields.

Alkylation of 4-hydroxycoumarin with certain aralkyl bromides (II) (or chlorides) in the molten state (length of heating period and temperature vary depending on the bromide used) gave 3-aralkyl-4-hydroxycoumarins (III–XII) in good yields. The physical and analytical data for the compounds reported herein are in the table.

TABLE I

3-SUBSTITUTED-4-HYDROXYCOUMARINS

	R	R′	M.p.,[a] °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
III	Phenyl[b]	H	197–200	53	$C_{16}H_{12}O_3$				
IV	*o*-Methylphenyl	H	202–206	95	$C_{17}H_{14}O_3$	76.7	76.8	5.3	5.4
V	*o*-Chlorophenyl	H	229–232	28	$C_{16}H_{11}ClO_3$	67.0	66.6	3.8	4.1
VI	Benzyl[c]	H	195–198	82	$C_{17}H_{14}O_3$				
VII	Phenyl[d]	CH_3	201–202	97[d]	$C_{17}H_{14}O_3$				
VIII	Phenyl[d,e,f]	C_2H_5	175–177	98	$C_{18}H_{16}O_3$				
IX	Phenyl[f]	*n*-C_3H_7	191–194	95	$C_{19}H_{18}O_3$				
X	Phenyl[f]	*n*-C_4H_9	179–180	97	$C_{20}H_{20}O_3$				
XI	Phenyl	*n*-C_5H_{11}	148–149	96	$C_{21}H_{22}O_3$	78.4	78.1	6.8	6.8
XII	Phenyl	Phenyl	177–178	99	$C_{22}H_{17}O_3$	80.5	80.3	4.9	5.0

[a] Melting points are uncorrected. [b] I. M. Heilbron and D. W. Hill, *J. Chem. Soc.*, 1705 (1927), report a m.p. of 205°. [c] H. Pauli and K. Lockemann, *Ber.*, **48**, 28 (1915), report a m.p. 205–206°. [d] H. Junek and E. Ziegler, *Monatsh.*, **87**, 218 (1955), report a m.p. 202° and a yield of *ca.* 10% for VII and a m.p. 175–176° for VIII. [e] F. Litvan and W. Stoll, U. S. Patent 2,647,681, Aug. 11, 1953, report a m.p. 179°. [f] A. Grüssner and B. Hegedüs (see ref. 7) report a m.p. 179–180° for VIII, a m.p. of 201–202° for IX, a m.p. 178–180° for X, no yields were reported.

The synthesis of some of the 3-aralkyl-4-hydroxycoumarins listed here by the older procedures would be very tedious if indeed it could be realized.[10,11] The recent method of Grüssner and

Benzylation of the 3-position of 4-hydroxycoumarin by heating with benzyl *p*-toluenesulfonate[9] in the molten state at 100–120° gave 3-benzyl-4-hydroxycoumarin (III) in 15% yield.

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) K. P. Link, *The Harvey Lecture Series*, **39**, 162 (1943–1944).

(3) M. Ikawa, M. A. Stahmann and K. P. Link, THIS JOURNAL, **66**, 902 (1944).

(4) C. F. Huebner and K. P. Link, *ibid.*, **67**, 99 (1945).

(5) H. R. Eisenhauer and K. P. Link, *ibid.*, **75**, 2044 (1953).

(6) A. Grüssner, "Jubilee Volume," F. Hoffman–La Roche and Co., Ltd., Basle, 1946, p. 238.

(7) A. Grüssner and B. Hegedüs, U. S. Patent 2,723,276, Nov. 8, 1955.

(8) E. Ziegler and U. Roszmann, *Monatsh.*, **88**, 25 (1957).

(9) J. K. Kochi and G. S. Hammond, THIS JOURNAL, **75**, 3443 (1953), report the preparation of benzyl *p*-toluenesulfonate.

(10) R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 174–194.

(11) H. Simonis, "Die Cumarine," Ferdinand Enke, Stuttgart, 1916, pp. 200–205.

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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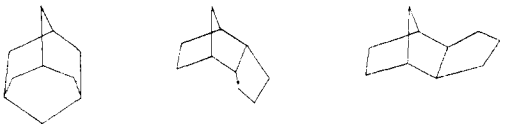
A SIMPLE PREPARATION OF ADAMANTANE

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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RECEIVED MAY 17, 1957

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.