

β -Piperidinoethyl Diphenylchloroacetate Hydrochloride (16).—(a) Five and six-tenths grams of β -piperidinoethyl benzilate hydrochloride³ was mixed with 3 cc. of thionyl chloride and after twelve hours the product was precipitated with petroleum ether. The material was dissolved in ethyl acetate, precipitated with ether and finally recrystallized from dioxane; yield 4.0 g. (69%).

(b) To 6.7 g. of β -piperidinoethyl benzilate, dissolved in 20 cc. of benzene, there was added 3.9 g. of acetyl chloride. After the mixture had been refluxed for one and one-half hours the product was precipitated with petroleum

ether and recrystallized from amyl acetate; yield 6.1 g. (85%).

Summary

Twenty esters of β -piperidinoethyl alcohol were prepared and tested for mydriatic activity.

Two esters were found to be strong mydriatics, namely, the β -piperidinoethyl esters of tropic and dicyclohexylglycolic acid.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Chemistry of Vitamin E. XXXI. 3,5-Dinitrobenzazide as a Reagent for Preparation of Derivatives of Tocopherols¹

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Although *p*-nitrophenyl isocyanate has been used for preparation of solid derivatives of tocopherols,² the most common reagent is cyanic acid, which gives sparingly soluble allophanates with these substances.^{2a,3} It usually requires several days for the allophanates to crystallize, and the preparation and handling of the large amounts of cyanic acid required is tedious and unpleasant.

In 1934 Sah and Ma⁴ found that phenols, when heated in dry toluene with 3,5-dinitrobenzazide, were smoothly converted into the corresponding phenylurethans. Since the reagent is readily converted into 3,5-dinitrophenyl isocyanate when its solution in toluene is heated, the isocyanate is obviously an intermediate. But the azide is a stable solid, easy to prepare quickly and in quantity either by action of nitrous acid upon the hydrazide⁵ or by action of sodium azide upon a solution of the acid chloride in acetic acid.⁶

It appeared worth while to try 3,5-dinitrobenzazide as a reagent for preparation of solid derivatives of tocopherols. The results have shown that the reagent is an excellent one for this purpose. The reaction requires but an hour, and the derivatives crystallize well and in yields of 70–90%. Recrystallization from alcohol is sufficient to give a pure product. All of the pure 3,5-dini-

trophenylurethans crystallized as waxy yellow needles, although they gave perfectly colorless solutions in alcohols. This behavior is apparently characteristic of the 6-hydroxychroman structure, for it was exhibited by the simple pentamethyl-6-hydroxychroman as well as by those chromans having a long, aliphatic side chain (tocopherols).

The melting points of the 3,5-dinitrophenylurethans of α -, β - and γ -tocopherol are, respectively, 145–147°, 153–155° and 143–145°. A mixture of the urethans of α - and γ -tocopherols melted at 140–145°. This is a very small depression of the melting point, but this phenomenon appears to be characteristic of derivatives of the tocopherols, especially α - and γ -, for the allophanates of these substances also give very small melting point depressions when mixed.

In order to test the suitability of the 3,5-dinitrophenylurethans as derivatives for isolation purposes, a gram of α -tocopherol was converted into the urethan. After one crystallization from alcohol, the derivative weighed 1.13 g. (76%) and melted at 142–144°. Hydrolysis of this material gave back 0.64 g. of α -tocopherol. The dinitrophenyl residue was recovered as 3,5-dinitrophenol, m. p. 126–127°, instead of 3,5-dinitroaniline.⁷

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Experimental⁸

3,5-Dinitrobenzazide.—The method of Blanksma and Verberg was used. The dinitro acid (50 g.) and phosphorus

(1) Paper XXX, THIS JOURNAL, 63, 1887 (1941).

(2) (a) Evans, Emerson and Emerson, *J. Biol. Chem.*, 113, 319 (1936); (b) Karrer and Fritzsche, *Helv. Chim. Acta*, 22, 260 (1939).

(3) (a) Drummond and Hoover, *Biochem. J.*, 31, 1852 (1937); (b) Todd, Bergel and Work, *ibid.*, 31, 2257 (1937); (c) Emerson, Emerson, Mohammad and Evans, *J. Biol. Chem.*, 122, 99 (1937); (d) Karrer, Fritzsche and Escher, *Helv. Chim. Acta*, 22, 661 (1939); (e) Karrer, Koenig, Ringier and Salomon, *ibid.*, 22, 1139 (1939).

(4) Sah and Ma, *J. Chinese Chem. Soc.*, 2, 229 (1934).

(5) Sah and Ma, *ibid.*, 2, 41, 162 (1934).

(6) Blanksma and Verberg, *Rec. Trav. Chim.*, [4] 53, 989 (1934).

(7) Sidgwick and Taylor, *J. Chem. Soc.*, 121, 1854 (1922).

(8) Microanalyses by E. E. Reafrew and C. H. Stratton.

TABLE I
 MELTING POINTS AND ANALYTICAL DATA

6-Hydroxychroman	3,5-Dinitrophenylurethan	M. p., °C.	Carbon, %		Hydrogen, %	
			Found	Calcd.	Found	Calcd.
2,2,5,7,8-Pentamethyl-	C ₂₁ H ₂₉ O ₇ N ₂	207-208	58.98	58.74	5.43	5.35
5,7,8-Trimethyltolcol ^a (α-tocopherol) ^b	C ₃₆ H ₅₈ O ₇ N ₂	145-147	67.70	67.56	8.41	8.35
5,8-Dimethyltolcol (β-tocopherol)	C ₃₅ H ₅₁ O ₇ N ₂	153-155	67.32	67.15	8.10	8.22
7,8-Dimethyltolcol (γ-tocopherol)	C ₃₅ H ₅₁ O ₇ N ₂	143-145	67.34	67.15	8.16	8.22
7,8-Dimethyl-5-ethyltolcol ^c	C ₃₇ H ₅₉ O ₇ N ₂	46-48	67.82	67.95	8.27	8.47
5,8-Dimethyl-7-ethyltolcol	C ₃₇ H ₅₉ O ₇ N ₂	67-69	68.02	67.95	8.55	8.47
5,7-Dimethyl-8-ethyltolcol	C ₃₇ H ₅₉ O ₇ N ₂	58-60	67.78	67.95	8.53	8.47

^a For the meaning of the term tocol, see Karrer and Fritzsche, *Helv. Chim. Acta*, 21, 1234 (1938). ^b The authors are greatly indebted to Dr. R. T. Major and to Merck and Co., Inc., for the specimens of synthetic tocopherols used in this investigation. ^c The dimethylethyltolcols were prepared by Dr. W. B. Renfrow, Jr., and will form the subject of a later communication.

pentachloride (49.5 g.) were intimately mixed and the mixture was heated on the steam-bath for thirty minutes. Fractional distillation of the solution gave the acid chloride, which boiled at 180° under 8 mm. pressure. The distillate was dissolved in dry benzene and precipitated by addition of petroleum ether. The product (45 g.) then melted at 67-70°. The acid chloride (10 g.) was dissolved in acetic acid (30 cc.) and technical sodium azide (3.0 g.) was added with stirring, not allowing the temperature to rise above 45°. After standing for thirty minutes at room temperature, the solid was removed, washed with cold water and dried in a vacuum desiccator. The dried solid was suspended in low-boiling petroleum ether, digested for a few minutes, then filtered and dried. It weighed 7.5 g. and melted at 105° with decomposition.

3,5-Dinitrophenylurethans.—α-Tocopherol (0.5 g.) was dissolved in dry toluene (5 cc.), an equivalent weight of the azide was added, and the solution was refluxed for one hour. The deep red color gave way to yellow. The toluene was removed under reduced pressure and the residual oil was taken up in 90% alcohol and crystallized. The yields of urethans, after one crystallization, were 70-90%; these usually melted about three degrees below the melting point of the analytical specimens, which were obtained by one or two additional crystallizations from 90% alcohol. The results are shown in Table I.

Recovery of α-Tocopherol.—By the procedure described above, one gram of α-tocopherol was converted into the urethan. After one crystallization from alcohol, the product weighed 1.13 g. (76%) and melted at 142-144°. The urethan (0.47 g.) was added to methanolic potassium hydroxide (10 cc., 4%) and the solution was refluxed in an atmosphere of nitrogen for one hour. The cooled solution was neutralized with a few drops of hydrochloric acid, enough water was added to dissolve the precipitated potassium chloride, and the mixture was extracted twice with

petroleum ether (b. p. 60-68°). The faintly yellow petroleum ether extract was washed once with water, filtered, dried (sodium sulfate) and the solvent was removed under reduced pressure. The residue of α-tocopherol weighed 0.25 g. (79% recovery). In a duplicate experiment, 0.66 g. of the urethan gave 0.39 g. of α-tocopherol (87% recovery).

The aqueous-alcoholic layer from the petroleum ether extractions was diluted with water, and the solid was removed and crystallized from dilute ethanol. It formed nearly colorless flat needles which melted at 126-127°. The substance was soluble in alkali and was probably 3,5-dinitrophenol, reported m. p. 126.1°.⁷

Summary

1. 3,5-Dinitrobenzazide is a relatively stable substance, easily and quickly prepared in quantity, and is an excellent reagent for conversion of 6-hydroxychromans into solid derivatives. The 3,5-dinitrophenylurethans may be prepared in an hour; they crystallize well and have good melting points. The procedure is much superior in convenience and rapidity to the conversion of tocopherols into allophanates.

2. The 3,5-dinitrophenylurethans of six tocopherols and one simple 6-hydroxychroman have been prepared.

3. As is the case with the allophanates, the 3,5-dinitrophenylurethans of α- and γ-tocopherols do not give a pronounced melting point depression.

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