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sodium acetate in acetic anhydride (five times the weight of one of the other reagents) was boiled under reflux for 10 minutes. After cooling, the reaction mixture was poured into water; a yellow solid separated out, which was filtered off, washed with water, and recrystallized from 95% ethanol.

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PREPARATION AND DEHYDRATION OF DI-(1-HYDROXYCYCLOALKYL)-ALKANES¹

A. S. BAILEY,² D. G. M. DIAPER, AND M. V. H. SCHWEMIN

1-Alkylcycloalkanols have been employed (1, 2) as intermediates in the extension of monofunctional aliphatic chains. An obvious extension of this synthetic method would be the use of di-(1-hydroxycycloalkyl) compounds in chain extension of α,ω -dicarboxylic acids of the aliphatic series. Although there is no record (3) of the use of such intermediates for this purpose, diols of the requisite structural type have been made in isolated previous investigations. We have now prepared diols having five-, six-, seven-, and eight-membered rings and with 2 to 10 methylene groups connecting them, using procedures already described. The results are summarized in Table I.

Method A, reaction of a diester with two moles of a Grignard reagent from a dihalide, has been studied previously only in the synthesis of 1,1'-ethylenedicyclopentanol and 1,1'-ethylenedicyclohexanol from ethyl succinate and respectively tetramethylene dibromide and pentamethylene dibromide (4). We attempted to use hexamethylene dibromide and 1,3-dibromo-2,2-dimethylpropane in similar syntheses but in each case obtained no crystalline product but the major outcome was evidently a polymer. Diethyl 2,2-dimethylglutarate was successfully condensed with 2 moles of the derived Grignard reagent from pentamethylene dibromide although one might have expected the gem dimethyl group to hinder or deactivate one of the ester groups sterically.

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ΤA	BL	Æ	1

				÷		Analysis						
	М	Method	lethod			С		Н		Dehydration product		
Compound	°C	or prep.	<i>x</i> ield, *	Lit. m.p.	Ref.	Found	Calc.	Found	Calc.	B.p.	n	H. equiv.¶
1,1'-Ethylenedicyclopentanol	134	A	65 48	131.2-1.4 135	$\frac{12}{4}$					85-9°/	1.4810 (21°)	27,21%
1,1'-Ethylenedicyclohexanol	130–1	Ă C		128-9	9					90–7°/ 0.5 mm	1.4821 (20°)	28,33%
1,1'-Ethylenedicycloheptanol 1,1'-Ethylenedicyclooctanol	123-4 123-4	Č	16 18	Oil	10†	$\begin{array}{c} 75.6\\ 76.4\\ \end{array}$	$\begin{array}{c} 75.6\\ 76.6\\ \end{array}$	$\begin{array}{c} 11.7 \\ 12.0 \end{array}$	$\begin{array}{c} 11.8\\ 12.0\\ \end{array}$		x - <i>y</i>	
1,1'-Trimethylenedicyclopentanol 1,1'-Trimethylenedicyclohexanol	119-21 122-3	A A	58 69	120	25	73.4	73.6	11.4	11.3	1115°/	1.4916	97%
1,1'-Tetramethylenedicyclopentanol	98-9	B	$\frac{49}{68}$	91.8-2.5	14‡					1 T IIIII	(20)	
1,1'-Tetramethylenedicyclohexanol	113.5-5	B D	$53 \\ 71$	103	26					157–9°/ 15 mm	1.5104 (25°)	101%
1,1'-Tetramethylenedicycloheptanol 1,1'-Pentamethylenedicyclopentanol	$\begin{array}{c} 856\\ 63\text{,}54\end{array}$	D B	65 83			$\begin{array}{c} 76.3 \\ 75.1 \end{array}$	$\begin{array}{c} 76.6 \\ 75.0 \end{array}$	$\begin{array}{c} 12.1 \\ 11.7 \end{array}$	$\begin{array}{c} 12.0\\11.7\end{array}$	101–4°/	1.5103	94%
1,1'-Pentamethylenedicyclohexanol 1,1'-Hexamethylenedicyclopentanol	72 - 3 87 - 9	B B	$\frac{76}{86}$			$\begin{array}{c} 76.4 \\ 75.8 \end{array}$	$\begin{array}{c} 76.2 \\ 75.6 \end{array}$	$\begin{array}{c} 11.8\\11.9\end{array}$	$\begin{array}{c} 11.9\\ 11.8 \end{array}$	109–14°/	(20 [°])	96%
1,1'-Hexamethylenedicyclohexanol 1,1'-Octamethylenedicyclopentanol	$83-4 \\ 83-4$	B A	$71 \\ 52$			$\begin{array}{c} 76.3 \\ 76.4 \end{array}$	$\begin{array}{c} 76.6 \\ 76.6 \end{array}$	$\begin{array}{c} 12.1 \\ 11.8 \end{array}$	$\substack{12.0\\12.0}$	141–5°/	1.4811	0.407
1,1'-Octamethylenedicyclohexanol	87.5-8	А	31			77.4	77.5	12.2	12.3	0.8 mm 157–61°/ 0.4 mm	(25°) 1,4911 (25°)	$94\% \\ 96\%$
1,1'-Decamethylenedicyclohexanol HO. C_6H_{10} . CH_2 . CMe_2 . CH_2 . C_6H_{10} . OH	56-7 146-7	B B	$\frac{38}{18}$			$\begin{array}{c} 77.9 \\ 76.1 \end{array}$	$\begin{array}{c} 78.1 \\ 76.2 \end{array}$	$\frac{12.2}{11.9}$	$\frac{12.4}{11.9}$		1 40.00	000
$HO. C_6H_{10}. CMe_2. CH_2. CH_2. C_6H_{10}. OH$	Liq.	А	47							1659°/ 0.3 mm	1,4903 (25°)	96%

*The yield of the coupling reaction is given in methods A, B, and C. The hydrogenation steps of methods C and D and the oxidation step in method D is for the ethynylation step.
†1,1'-Ethynylenedicycloheptanol (1,4-dihydroxy-1,1,4,4-bishexamethylene-2-butyne) had m.p. 81-2° (literature, 10, 78-80°).
‡1,1'-Diacetylenedicycloheptanol (1,6-dihydroxy-1,1,6,6-bistetramethylene-2,4-hexadiyne) had m.p. 136-7° (literature, 14, 133.2-134.2°).
§M.p. (thermometer immersed) 8°.
M.p. (thermometer immersed) 5°.
¶Hydrogenation equivalent, expressed as a percentage of the theoretical uptake for the diolefin.

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Method B (18) was the conversion of a cyclic ketone to the symmetrical diol by reaction with the double Grignard reagent derived from an α,ω -dihalide having from 4 to 10 carbon atoms in the chain. In agreement with Lukes and Blaha (5), good results were obtained in this range, but it is generally recognized that aliphatic dihalides having three carbon atoms or fewer between the halogen atoms are useless in Grignard syntheses (6). We have, however, converted 1,3-dibromo-2,2-dimethylpropane (7) to a Grignard reagent and obtained a condensation product from it with cyclohexanone. The success of this reaction is the more remarkable in the light of the reaction of the dihalide with zinc (8) which gives dimethylcyclopropane in 96% yield. Whatever the reasons for the general failure of trimethylene halides in Grignard reactions, cyclopropane ring closure is evidently not one of them. In this instance it is suggested that the 2,2-dimethyl group functions either to limit polymeric coupling of the dihalide by steric hindrance or to preclude olefin formation as there are no hydrogen atoms α to the halogen.

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Method C was the interaction of ethynylenemagnesium bromide (BrMgC=CMgBr)with 2 moles of the appropriate cyclic ketone. Using cyclopentanone, cyclohexanone, and cycloheptanone, this reaction has been investigated previously (9, 10, 11, 12); we have used cyclooctanone also. The 1,1'-ethynylenedicycloalkanol thus obtained is hydrogenated in good yield to give the 1,1'-ethylenedicycloalkanol. It is possible to arrest the hydrogenation of the acetylenic diol in each case to give the olefinic derivative, but complete hydrogenation may be ensured by using either platinum or palladium catalysts in preference to nickel or by performing the hydrogenation over nickel at high pressures. The use of high temperatures in the hydrogenation must be avoided because the tertiary diols are susceptible to dehydration.

Method D, which also involved acetylenic intermediates, was confined to those diols having four methylene groups between the rings. By oxidation of 1-ethynylcycloalkanols, coupling of two molecules to give a diacetylene derivative results (13, 14, 15). This may be hydrogenated to a 1,1'-tetramethylenecycloalkanol. Both steps are practically quantitative.

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All of the polymethylene diols were obtained as crystalline solids. One of the diols with a branched connecting chain, the symmetrical one, was also solid, but its unsymmetrical isomer was liquid. Many tenaciously retained sticky impurities, which were best removed by chromatography, and from the nature of the preparative methods adopted, one may infer that these impurities were polymeric. Attempts to prepare crystalline derivatives were unsuccessful, for the customary reagents for alcohol characterization are acidic and need heating. Under such conditions, dehydration of the diol results.

A detailed study of dehydration of ethylene and trimethylene diols of this series is still in progress. Members with four or more carbon atoms between the rings were found to give the expected olefinic dehydration products, and it may be assumed that they are of the alkylcycloalkene type rather than the less stable alkylidenecycloalkane type. It has been reported (4) that the product of dehydration of 1,1'-ethylenedicyclopentanol is also of this nature, although in this compound the presence of an α,δ -diol system might be expected to give a product with a butadienoid system, namely dicyclopentylidene-ethane. Previous studies also indicate that the dehydration of such an α,δ -diol might give a cyclic ether rather than a diolefin; for example, Henry (16) obtained 2,2,5,5tetramethyltetrahydrofuran from 2,5-dimethylhexane-2,5-diol and Reppe (17) reported the conversion of 1,1'-ethylenedicyclohexanol to 7-oxaspiro-(5,1,5,2)-pentadecane. The quantitative microhydrogenation data on our dehydration products from both 1,1'-

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ethylenedicyclohexanol and 1,1'-ethylenedicyclopentanol indicate that a mixture of diolefin and epoxide was obtained.

EXPERIMENTAL

All melting points, except where otherwise noted, were determined by the capillarytube method on a thermometer calibrated against an Anschütz set with a National Bureau of Standards certificate. Melting points and other temperatures are recorded as degrees centigrade.

1,1'-Octamethylenedicyclohexanol (Method A, cf. ref. 4) and its Dehydration

Pentamethylenedimagnesium bromide and dimethyl sebacate were condensed by the known procedure (4) but benzene was added to the reaction mixture and it was worked up with ammonium chloride to minimize dehydration loss. The crude product was sticky and melted between 60 and 80°. It was adsorbed from benzene on alumina and eluted successively with benzene and diethyl ether. Crystals were deposited by evaporation of each eluate and these were united and crystallized once from heptane, m.p. 87.5–88°. Further elution of the column with ethyl acetate gave a viscous oil which was not further investigated.

The crystalline diol (7.0 g, 0.025 mole) was heated to 150° for 4 hours in the presence of iodine (10 mg). A further portion of iodine (5 mg) was then added and heating continued for 1 hour at 170°. The product, an oil, was taken up in ether and shaken with sodium thiosulphate solution. After drying, the solvent was removed and the residual oil distilled, yield 4.1 g, 67%, b.p. 157-161°/0.4 mm, n_D^{25} , 1.4911, m.p. (thermometer immersed) 5°. Other diols listed in Table I were dehydrated similarly.

1,1'-Ethylenedicyclooctanol (Method C)

Interaction of cyclooctanone and ethynylenemagnesium bromide (the Iotsitch reagent) (19) was achieved essentially by the method described by Pinkney and Marvel (11) for other ketones. Using ammonium chloride as described above for decomposition of the magnesium complex, 1,1'-ethynylenedicyclooctanol (1,4-dihydroxy-1,1,4,4-bisheptamethyl-ene-2-butyne) was isolated in ether and finally obtained as a solid, m.p. 115°. Found: C, 77.8; H, 10.8, hydrogenation equivalent 132. Calc. for $C_{18}H_{30}O_2$: C, 77.8; H, 10.8%, hydrogenation equivalent 139.

By hydrogenation of the acetylenic diol in ethyl acetate as previously described, 1,1'-ethylenedicyclooctanol was obtained in nearly quantitative yield, m.p. 123–124°.

1,1'-Tetramethylenedicycloheptanol (Method D)

Ethynylation of cycloheptanone was performed in a manner analogous to the recorded ethynylation of cyclohexanone (20, 21). Oxidative coupling of this alcohol to yield the diacetylene derivative was accomplished by copper-catalyzed autoxidation in an experiment similar to that performed by Zal'kind and Aizikovich (13) on its lower homologue. 1-Ethynylcycloheptanol (70 g, 0.5 mole) in ethanol (75 ml) was added during 2 hours to a vigorously stirred solution of ammonium chloride (36 g), cuprous chloride (11.5 g), and hydrochloric acid (10 N, 2.5 ml) in water (100 ml) at 50° while a slow stream of oxygen bubbled through. The solution was stirred with oxygen passed in for 4 hours more, and then 250 ml of a saturated aqueous solution of ammonium chloride was added. Next day the solid product was collected by filtration and washed with ammonium chloride solution. It was then washed with hydrochloric acid (2 N) until the washings

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were no longer colored. The crude product (70 g, an almost quantitative yield) melted at 164-166°. This was raised to 165-166° by one crystallization from ethanol.

This diacetylenic diol (2.5 g, 0.01 mole) was hydrogenated in ethyl acetate suspension (50 ml) over palladized calcium carbonate at ambient temperature and 32.5 p.s.i. Uptake was complete in 3 hours and the filtered solution deposited crystals of 1,1'-tetramethylenedicycloheptanol (2.5 g, quantitative yield, m.p. 80-84°). This product was stable to aqueous potassium permanganate and was purified by one crystallization from a mixture of petroleum ether and benzene, in which it is very soluble (m.p. 85–86°).

Diethyl 2,2-Dimethylglutarate

In our hands, the previously published procedures (e.g. ref. 22) for conversion of 2,2-dimethyl-4-cyanobutyraldehyde to 2,2-dimethylglutaric acid gave 55 to 60% yields of a sticky product melting at 55-60°. Such procedures employ nitric acid alone or mixed with concentrated sulphuric acid as the reagent for simultaneous hydrolysis and oxidation of the starting material and it is possible that side reactions of polymerization or further oxidation can take place. Much loss of material occurred during purification.

The method adopted resembled that employed by Bruson and Riener (23) for conversion of 2,2-diethyl-4-cyanobutyraldehyde to 2,2-diethylglutaric acid. 2,2-Dimethyl-4-cyanobutyraldehyde (24) was used as soon as possible after it was prepared, because it is unexpectedly susceptible to autoxidation and on one occasion an explosion occurred when a sample that had been kept for some months without precautions against peroxide formation was distilled. The cyanoaldehyde (60 g, 0.5 mole) was boiled with sodium hydroxide (25 g, 0.63 mole) in water (250 ml) until a homogeneous solution was obtained $(\frac{1}{2}$ hour). After cooling, a further 25-g portion of sodium hydroxide and a further 250 ml of water were added. Potassium permanganate (114 g, 0.7 mole) was ground to a slurry with water (1 liter) and added to the cooled, stirred solution at such a rate that the temperature was $35-40^\circ$. Following a further $\frac{1}{2}$ hour of stirring, sulphur dioxide was passed until all the manganese dioxide was reduced. The 2,2-dimethylglutaric acid was isolated by ether extraction of the solution (66 g, 86%, m.p. 74-76°). By recrystallizing from a mixture of benzene and petroleum ether the melting point was raised to 83-84°, but the bulk of the product was esterified without purification, yielding diethyl 2,2dimethylglutarate, b.p. 147/46 mm, $n_{D}^{22.5}$, 1.4262. (Found: saponification equivalent, 107. Calc. for $C_{11}H_{20}O_4$: 108).

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ADDUCTS FROM THE REACTION OF N-ETHYLMALEIMIDE WITH L-CYSTEINE AND WITH GLUTATHIONE

C. C. LEE AND E. R. SAMUELS

Since the first report of a quantitative reaction between thiols and N-ethylmaleimide (NEM) (1), a number of workers have described the use of NEM as a reagent for the assay of the sulphydryl group (2-6). However, it was only recently that the product from the reaction of L-cysteine and NEM was isolated and characterized as S-(N-ethylsuccinimido)-L-cysteine (I) (7). This note reports an independent isolation of I as well

> (1)

as the preparation of S-(N-ethylsuccinimido)-glutathione (II), the adduct from the reaction of NEM with glutathione. Adduct II has not been recorded in any earlier publication.



The present work was undertaken as part of a project involving the determination of relative amounts of sulphhydryl and disulphide groups in certain proteins in which S^{35} has been incorporated. A suitable carrier for the reaction product between NEM and thiols was sought so that isotope dilution studies may be carried out. With this aim in mind, the behaviors of I and II on acid hydrolysis were studied. Somewhat surprisingly, it was found that after treatment for 18 hours in refluxing 6 N hydrochloric acid, I was recovered without change. The products from the hydrolysis of II were identified by paper chromatography as glycine, glutamic acid, and adduct I, exactly as expected for hydrolysis of the peptide bonds with I remaining unaffected. It was also noted that paper chromatographic separation of I from II, cysteine, and cystine can be easily accomplished. These observations indicate that it is likely feasible to use I as a

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