TABLE I

COMPARISON OF THE SPECTRA OF 4-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO)-QUINOLINE WITH 7-SUBSTITUTED CONGENERS, IN 0.1 *N* HYDROCHLORIC ACID

Compound	Maxima, mμ and (ε × 10⁴)			
4-(4-Diethylamino-1-methylbutylamino)-quinoline	232 (18.9)		330 (18.8)	340 (18.5)
4-(4-Diethylamino-1-methylbutylamino)-7-phenoxyquinoline	228 (33.6)	250[a] (19.0)	330 (18.8)	336 (18.6)
4-(4-Diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline	233 (28.7)	259[b] (17.8)	330 (14.5)	

[a] Inflection point. [b] Small secondary maximum.

quinoline[2,3] (SN 10,663)[4] and the parent compound, 4-(4-diethylamino-1-methylbutylamino)-quinoline (SN 6732)[4,5] both in 0.01 *N* hydrochloric acid, shows that there is a slight but definite hypsochromic shift of 4 mμ throughout the whole spectrum. This is doubtless due to the combined influences of an ether link and the unconjugated aryl group attached in position 7. As we have earlier noted,[6] the views of Irvin and Irvin[7] concerning the effect of a 7-substituent upon the tautomerism of the 4-aminoquinoline type are well substantiated. In this instance, the weighting due to the phenoxy group is greater than the halogens and is also more pronounced. The unconjugated phenyl radical behaves very much as the simpler alkoxy substituents in the case of the 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline,[8] inasmuch as benzene shows no pronounced absorption in this general region.[9] Since the ethoxy compound also bears a methyl substitution, it also exhibits the slight batho- and hypochromic shift inherent to 3-methyl substitution, as we have shown (*cf.* Fig. 2, ref. 6).

(2) Drake, *et al.*, THIS JOURNAL, **68**, 1208 (1946); Riegel, *et al.*, *ibid.*, **68**, 1264 (1946); Clinton and Suter, *ibid.*, **69**, 704 (1947).

(3) The authors are indebted to Dr. R. O. Clinton for the sample employed.

(4) All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey office have been tabulated, with antimalarial activities, in the work by Wiselogle, editor, "Antimalarial Drugs, 1941-1945," Edwards Bros., Ann Arbor, Mich., 1946.

(5) Steck, Hallock and Suter, THIS JOURNAL, **70**, unpublished (1948).

(6) Steck, Ewing and Nachod, *ibid.*, **70**, 3410 (1948).

(7) Irvin and Irvin, *ibid.*, **69**, 1091 (1947).

(8) Steck, Ewing and Nachod, *ibid.*, forthcoming paper.

(9) Dimroth, *Angew. Chem.*, **52**, 548 (1939).

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Preparation of Methanesulfonyl Chloride

BY C. R. NOLLER AND P. J. HEARST

Three methods commonly have been used for the preparation of methanesulfonyl chloride, a valuable reagent, namely, by the action of phosphorus pentachloride on sodium methanesulfonate,[1] and by the action of chlorine and water on *s*-methylisothiourea[2] or on methyl thiocyanate.[3]

Yields are not very satisfactory by the first method, and it is difficult to remove phosphorus compounds from the product.[4] The second method is potentially dangerous since violent explosions of products apparently formed by excessive chlorination have been reported.[5] The third method works well but is disagreeable because cyanogen chloride is one of the products of the reaction.

So far as the writers are aware, there is no reference in chemical literature to the preparation of sulfonyl chlorides directly from sulfonic acids by the action of thionyl chloride, although this reagent commonly is used to prepare carboxylic acid chlorides from carboxylic acids. With the availability of methanesulfonic acid commercially, the preparation of methanesulfonyl chloride by this reaction was tried. It was obtained in good yield and the procedure developed far excels those previously reported.

ADDED TO PROOF:—A recent publication[6] indicates that alkanesulfonyl chlorides may be prepared by the action of either thionyl chloride or phosphorus trichloride on the sulfonic acids. Directions are given for the preparation of methanesulfonyl chloride in 57% yield from methanesulfonic acid and phosphorus trichloride.

Experimental

In a 200-cc., three-necked flask, fitted with a mechanical stirrer, a reflux condenser, a thermometer and a separatory funnel, and set up in a hood, is placed 152 g. (105 cc., 1.5 moles) of 95% methanesulfonic acid (Standard Oil Co. of Indiana). The acid is heated to 95° on a steam-bath, and 146 cc. (238 g., 2.0 moles) of thionyl chloride (Eastman Kodak Co. grade) is added over a period of four hours. The temperature is kept at 95° throughout the addition, and heating is continued for three and one-half hours after the addition has been completed.

The product is transferred to a modified Claisen flask and distilled at reduced pressure, using an oil-bath to supply heat. Most of the thionyl chloride distills at room temperature. A free flame should be avoided, since local superheating causes charring and decomposition. The fumes from the decomposition cause the normally clear product to darken. The bath temperature should not exceed 115° at the end of the distillation. The yield of product distilling at 67–73° (20 mm.) is 122 g. (71% of the theoretical amount).

(1) Marvel, Helfrick and Beasley, THIS JOURNAL, **51**, 1272 (1929).

(2) Johnson and Sprague, *ibid.*, **58**, 1348 (1936).

(3) Johnson and Douglass, *ibid.*, **61**, 2548 (1939).

(4) Helferich and Gnüchtel, *Ber.*, **71**, 712 (1938).

(5) Folkers, Russell and Bost, THIS JOURNAL, **63**, 3530 (1941).

(6) Proell, Adams and Shoemaker, *Ind. Eng. Chem.*, **40**, 1129 (1948).

DEPARTMENT OF CHEMISTRY
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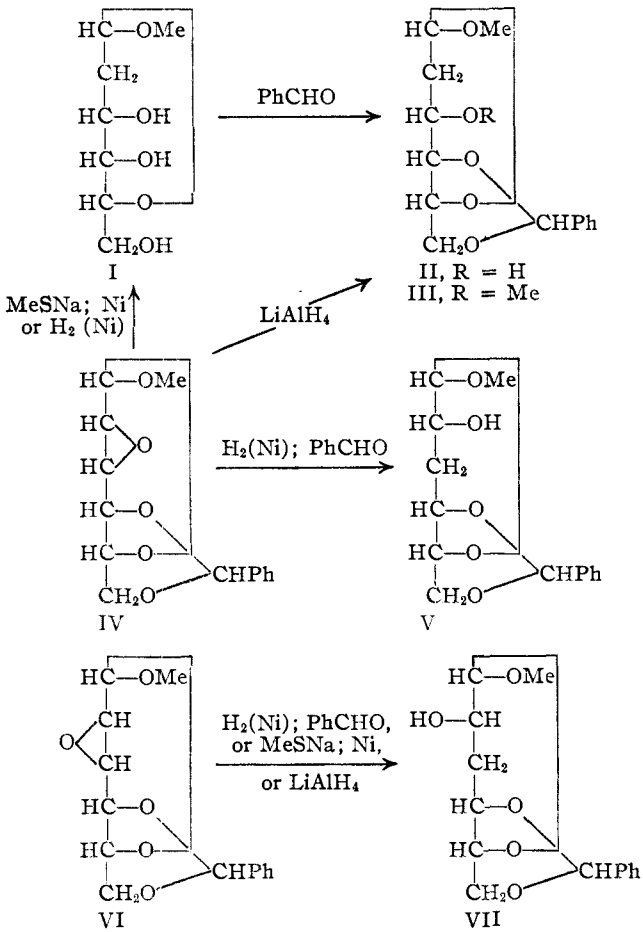
Reduction of Sugar Epoxides to Desoxysugars

BY D. A. PRINS

Derivatives of 2-desoxy-D-allose have been prepared from the convenient and readily available

intermediate, methyl 2,3-anhydro-4,6-benzylidene-α-D-allopyranoside (IV).[1]

It has now been found that derivatives of 2-desoxy-D-allose (*syn*-D-*ribo*-2-desoxyhexose[2]) (*cf.* I) may be obtained by a single step procedure. Thus, if the 2,3-anhydroallopyranoside derivative IV reacts with excess lithium aluminum hydride in anhydrous ether as in the general procedure of Nystrom and Brown,[3] methyl 4,6-benzylidene-2-desoxy-α-D-allopyranoside (II) is obtained in satisfactory yield.



Similarly, methyl 4,6-benzylidene-3-desoxy-α-D-mannopyranoside (*syn*-methyl-4,6-benzylidene-3-desoxy-α-D-altropyranoside) (VII)[4] was obtained from methyl 2,3-anhydro-4,6-benzylidene-α-D-mannopyranoside (VI) in good yield.

Direct hydrogenation of IV afforded derivatives of 3-desoxy-D-glucose (*syn*-3-desoxy-D-allose) (*cf.* V) as the principal products.[5] The formation of derivatives of 2-desoxy-D-allose from IV was not demonstrated at that time. However, by using larger quantities of IV it was possible, by careful processing of the products obtained on hydrogenation, to isolate a small amount of II, indicating that direct transformation of IV to I by hydrogenation indeed takes place. The derivative II has hitherto not been described. Its identity was confirmed by methylation, which gave the known derivative, methyl 3-methyl-4,6-benzylidene-2-desoxy-α-D-allopyranoside (III).[1]

It is felt that the lithium aluminum hydride reduction of carbohydrate epoxides of the type discussed possesses definite advantages over the method[1] previously reported.

Experimental

All melting points were determined on the Kofler micro hot-stage and are corrected.

Hydrogenation of IV and Isolation of II.—Seven and five-tenths grams of the 2,3-anhydroallopyranoside derivative IV (m. p. 201°)[6] was hydrogenated and worked up according to the procedure previously described.[5] The dried sirup obtained from the aqueous extract weighed 4.09 g. (81 %). It was rebenzalated following the procedure of Bolliger and Prins.[4] The residue from the aqueous extract obtained from this operation weighed 320 mg. and was not further investigated. The residue from the chloroform extract afforded 3.3 g. (54%) of methyl 4,6-benzylidene-3-desoxy-α-D-glucopyranoside (V), prisms from aqueous methanol, m. p. 190–191°, without depression on admixture with an authentic sample. The mother liquors weighed 1.45 g. and were carefully chromatographed on a column of 30 g. of alumina; 150-ml. portions of solvent were used for elution. Benzene–ligroin mixtures (3:1 and 2:1) eluted crystalline material, which on recrystallization from ether–pentane gave 145 mg. of methyl 4,6-benzylidene-2-desoxy-α-D-allopyranoside (II), double m. p. 117–119° and 126–128°; $[\alpha]^{21}D$ +151.9 ± 3° (*c* = 0.632 in chloroform). This substance is probably identical with the by-product, m. p. 128°, previously reported.[5]

Anal.[7] Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.99; H, 6.70. The Keller–Kiliani reaction gave a bluish-gray color, diffusion of which into the upper layer proceeded very slowly. On an acid-hydrolyzed sample of II the color reaction developed was identical to that reported for 2-desoxy-D-allose.[8]

Further elution with benzene–ligroin (2:1 and 1:1) benzene, and benzene–ether (9:1) gave crystalline material from which 274 mg. of the 3-desoxyglucopyranoside derivative (V), m. p. and mixed m. p. 188–190°, as well as 124 mg. of the 2-desoxyallopyranoside derivative (II), m. p. 122–126° could be isolated. The total yield of II was 269 mg. or 3.5 %.

Reduction of IV with $LiAlH_4$.—One hundred and fifty mg. IV (m. p. 201°) was treated with 200 mg. of $LiAlH_4$ in 50 ml. of anhydrous ether; the procedure of Nystrom and Brown[3] for difficultly soluble materials was used. After three hours of refluxing another 100 mg. of $LiAlH_4$ was added and the reaction continued for one more hour. The excess reagent was destroyed by the addition of a small amount of water; 2 *N* sulfuric acid and more ether were added, the mixture thoroughly shaken and the clear layers separated. The ether-phase was washed with 2 *N* sodium carbonate and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave

(1) R. W. Jeanloz, D. A. Prins and T. Reichstein, *Experientia*, **1**, 336 (1945); *Helv. Chim. Acta*, **29**, 371 (1946).

(2) J. C. Sowden, THIS JOURNAL, **69**, 1047 (1947).

(3) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

(4) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **29**, 1061 (1946).

(5) D. A. Prins, *Helv. Chim. Acta*, **29**, 1 (1946).

(6) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1730 (1941).

(7) Performed by W. Manser, Zürich, Switzerland.

(8) M. Gut and D. A. Prins, *Helv. Chim. Acta*, **30**, 1223 (1947).

a solid residue which was recrystallized from ether to afford 75 mg. II in the form of thick hexagonal prismatic plates, double, m. p. 118–120° and 127–129°; $[\alpha]^{19}D$ + 155.6° ± 3° (c = 0.649 in chloroform). A mixed m. p. determination with the product described above gave no depression. The mother liquors yielded 10 mg. of prisms, m. p. 122–126°; total yield 85 mg. or 56%. The Keller–Kiliani reaction gave results identical with those recorded above.

Methylation of II.—A sample of II was methylated following Purdie's procedure. The product III crystallized from ether–pentane in thin prisms, m. p. 98–99°, not depressed on admixture of an authentic specimen[1] of the methyl ether.

Reduction of VI with $LiAlH_4$.—150 mg. of VI (m. p. 147°)[9] was dissolved in 40 ml. of anhydrous ether. This solution was added slowly to a well-stirred and mildly refluxing solution of 500 mg. of $LiAlH_4$ in 50 ml. of anhydrous ether. The reaction was run for one hour and then worked up as described above. The product was recrystallized from ether–pentane, giving hexagonal plates, m. p. 111–112°; $[\alpha]^{22}D$ + 107.3 ± 2° (c = 0.941 in chloroform).[10] Admixture of an authentic sample[11] of VII caused no depression of the m. p. The yield was 129 mg. or 86%.

(9) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(10) Value previously[4] recorded: $[\alpha]^{12}D$ +95.0 ± 1° (c = 2.904 in chloroform).

(11) Kindly furnished by Prof. T. Reichstein, Basel.

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Preparation of Ketones from α,α-Disubstituted Acetoacetic Esters

BY W. B. RENFROW AND G. B. WALKER

α,α-Disubstituted acetoacetic esters undergo two competing reactions with alkali.

$$CH_3COCRR'CO_2C_2H_5 \xrightarrow{KOH} \begin{cases} \rightarrow CH_3COCHRR' + C_2H_5OH + K_2CO_3 \\ \rightarrow HCRR'CO_2K + CH_3CO_2K + C_2H_5OH \end{cases}$$

The ketonic cleavage is favored by a low concentration of alkali,[1] but maximum yields of ketones vary widely with the nature of the groups R and R′. Esters in which both R and R′ are methyl, ethyl or *n*-butyl groups give 60–84% yields[2,3] of ketones, but we have found that when R was an *n*-butyl group and R′ was either an *i*-butyl or *s*-butyl group the yields of ketones were very low (10%) and yields of disubstituted acetates were high even when the alkali concentration was kept at a minimum by adding it slowly to refluxing solutions of the esters in aqueous methanol.

After it was found that other hydrolysis procedures[2,4] were also unsatisfactory, the pyrolysis of *t*-butyl esters[5] of these dibutyl-substituted β-keto acids was investigated. By this method corresponding ketones have been obtained in good yield.

We have incidentally prepared several disubstituted ethyl acetates by alcoholysis[6] of α,α-disubstituted acetoacetic esters.

Experimental

Boiling and melting temperatures were determined with partial immersion thermometers. Yields, physical properties and analytical data for new liquids are listed in Table I.

Preparation and Ketonic Cleavage of *t*-Butyl Acetoacetates.—*t*-Butyl acetoacetate has been prepared by self-condensation of *t*-butyl acetate with sodium *t*-butoxide,[7] sodium amide or *i*-propylmagnesium bromide.[8] We have found sodium hydride to be a better condensing agent. Sodium hydride (9.6 g., 0.40 mole) was added to *t*-butyl acetate[9] (62 g., 0.53 mole) and the mixture refluxed from an oil-bath maintained at 90–110° for three and one-half hours. The bath temperature was then raised to 140° and heating continued for two hours longer. The mixture became almost solid. The reaction mixture was cooled to room temperature and treated with ice (70 g.) and concentrated hydrochloric acid (35 ml.). The organic layer was separated, washed with 5% sodium bicarbonate, dried and distilled through 18 cm. of glass helices. The *t*-butyl acetoacetate (27.7 g., 66% yield) boiled 81–82° at 15 mm. The reaction time could be shortened to two and one-half hours by using a ratio of two moles of ester to one mole of hydride, but the resulting yield of *t*-butyl acetoacetate was only 50%. We were unable to make all of the sodium hydride react when a ratio of one mole of ester to one mole of sodium hydride was used.

Alkylation of *t*-butyl acetoacetate with *n*-butyl bromide by the potassium *t*-butoxide method[10] gave *t*-butyl α-*n*-butylacetoacetate. Further alkylation of this product with *i*-butyl or *s*-butyl iodides by the same method gave the α,α-disubstituted acetoacetic esters. The disubstituted esters underwent some decomposition to ketones, carbon dioxide and *i*-butylene when fractionated, so they were purified by distillation from an ordinary Claisen flask.

The *t*-butyl acetoacetates were cleaved to ketones by mixing with 5% of their weight of *p*-toluenesulfonic acid and heating on a boiling water-bath until evolution of gas had ceased (about one hour). The liquids were then extracted with saturated sodium bicarbonate, dried over sodium sulfate and distilled. Semicarbazones of the new ketones were prepared and crystallized from ethanol–water. These semicarbazones have the same empirical formula. Calcd. for $C_{12}H_{25}ON_3$: C, 63.39; H, 11.09. 3-(2-Methylpropyl)-2-heptanone semicarbazone, m. p. 121°; C, 63.37; H, 11.15. 3-(2-Butyl)-2-heptanone semicarbazone, m. p. 127°; C, 63.64; H, 11.10.

Cleavage of Disubstituted Ethyl Acetoacetates to Disubstituted Ethyl Acetates.—Ethyl acetoacetates with the following substituents in the two alpha positions were cleaved: di-*n*-butyl, *n*-butyl-*i*-butyl, *n*-butyl-*s*-butyl, di-*i*-butyl. In a typical experiment, the acetoacetic ester (0.25 mole) was refluxed with a solution of sodium (0.125 g.-atom) in absolute ethanol (125 ml.) for five hours. Some of the alcohol (100 ml.) was removed by distillation and the residue poured into ice-water containing hydrochloric acid (0.12 mole). The layers were separated, the aqueous layer extracted with benzene and the combined organic layers fractionated through 18 cm. of glass helices. For further characterization, these esters were saponified and the acids converted to anilides *via* the acid chlorides. Melting points and analytical data for new anilides are

(1) Wislicenus, *Ann.*, **190**, 257 (1878).

(2) Connor and Adkins, THIS JOURNAL, **54**, 3420 (1932).

(3) Renfrow, *ibid.*, **66**, 144 (1944).

(4) Hudson and Hauser, THIS JOURNAL, **63**, 3163 (1941); Newman, *ibid.*, **63**, 2431 (1941); Heller and Hoffman, *Ber.*, **62**, 871 (1929); James, *Ann.*, **231**, 244 (1885).

(5) This reaction has been used in a similar way by Hauser and co-workers. THIS JOURNAL, **66**, 1286 (1944); **69**, 2326 (1947).

(6) Beckham and Adkins, *ibid.*, **56**, 1119 (1934).

(7) Fisher and McElvain, *ibid.*, **56**, 1766 (1934).

(8) Hudson, Shivers and Hauser, *ibid.*, **65**, 2051 (1943).

(9) "Organic Syntheses," **24**, 18 (1944), Acetic Anhydride Method. Failure to dry this ester thoroughly (either over "Drierite" or by distillation) led to seriously depleted yields of *t*-butyl acetoacetate.

(10) Renfrow and Renfrow, *ibid.*, **68**, 1801 (1946).