The Reaction of Diazomethane with Phenols in the Presence of Propanol

BY SAMUEL M. GERBER AND DAVID Y. CURTIN

Schönberg and Mustafa[1] have reported that the reaction of stilbesterol with diazomethane and *n*-propanol in ether at 0° gave stilbesterol di-*n*-propyl ether as the only product isolated. The compound was obtained in unspecified yield and was identified by its satisfactory analysis, melting point and mixed melting point with an authentic sample of the dipropyl ether prepared by the method of Reid and Wilson.[2] Schönberg and Mustafa have used their results as evidence for a mechanism in which either I or II is the propylating agent. It has been widely accepted that related reactions of diazo compounds with the general formula III involve the initial addition of a proton to give IV which then undergoes a displacement or solvolysis reaction with a base.[3] It was of interest, therefore, to attempt to confirm and extend their work.

$$\begin{array}{cccc} CH_2{=}NNHOC_3H_7 & CH_3N{=}NOC_3H_7 & RCHN_2 & RCH_2N_2^+ \\ \mathrm{I} & \mathrm{II} & \mathrm{III} & \mathrm{IV} \end{array}$$

We have repeated the reaction of stilbesterol with diazomethane in the presence of propanol under the conditions used by Schönberg and Mustafa and have obtained only the dimethyl ether (45% yield), monomethyl ether (33% yield of slightly impure product) and recovered stilbesterol (12%). Methylation at room temperature gave comparable results. In no case was there any evidence for the presence of the dipropyl ether.

The reactions of *p*-nitrophenol and 2,4,6-tribromophenol with diazomethane in the presence of propanol were also carried out and yielded in each case only the methyl ether and recovered starting material.

We are unable to explain the discrepancy between our results and those of Schönberg and Mustafa.

Experimental[4]

Reaction of Stilbesterol with Diazomethane.—A solution of 1.00 g. of stilbesterol[5] in propanol and ether was treated with diazomethane[6] under the conditions used by Schönberg and Mustafa. Their method of isolation of the product (recrystallization from petroleum ether) was found to be unsatisfactory, however, and therefore that of Reid and Wilson[2] was used. Stilbesterol (11%) was recovered and nearly pure stilbesterol dimethyl ether (0.50 g., 45% yield) was obtained. It was identified by its melting point (122–124°) and mixed melting point with an authentic sample prepared from stilbesterol and methyl iodide.[2] Crude stilbesterol monomethyl ether (0.24 g., 22% yield, m. p. 110–112°) was also obtained. The reported melting point is 117°.[2] Its identity was confirmed by methylation by methyl iodide in a yield of 87% to stilbesterol dimethyl ether, m. p. 123.5–124.5°.

Methylation of 2,4,6-Tribromophenol.—Three grams of tribromophenol was treated with excess diazomethane in a propanol–ether mixture for thirty-six hours at room temperature. Tribromophenol (1.5 g., m. p. 92–93.5°) was recovered and a 42% yield of tribromoanisole, m. p. 86.5–87°, was obtained. The recorded melting point is 87°.[7]

Methylation of *p*-Nitrophenol.—*p*-Nitrophenol (3.4 g.) was methylated similarly (in propanol–ether for twenty-four hours at room temperature) to give *p*-nitroanisole, m. p. 53–54°, in a yield of 89%. The reported melting point is 54°.[8]

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK 27, N. Y.

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(1) Schönberg and Mustafa, *J. Chem. Soc.*, 746 (1946).

(2) Reid and Wilson, THIS JOURNAL, **64**, 1625 (1942).

(3) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, p. 288.

(4) All melting points are corrected.

(5) We are indebted to S. B. Penick and Company for a sample of stilbesterol.

(6) The diazomethane used was prepared and standardized by the method of Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(7) Kohn and Fink, *Monatsh.*, **44**, 192 (1923).

(8) Willgerodt and Ferko, *J. prakt. Chem.*, [2] **33**, 152 (1886).

The Preparation of *n*-Butyllithium

BY H. GILMAN, J. A. BEEL, C. G. BRANNEN, M. W. BULLOCK, G. E. DUNN AND L. S. MILLER

The method of preparation of *n*-butyllithium used until recently in these Laboratories gave from 50–65% yields in ninety minutes in diethyl ether as determined by the double-titration method.[1] A study of the reaction at lower temperatures has revealed that yields of 75–90% can be consistently obtained at about −10° using *n*-butyl bromide with diethyl ether as the solvent. Only conventional apparatus is needed and the reaction is substantially complete in ninety minutes. Table I gives data on several preparations made under varying conditions. *n*-Propyl, *n*-amyl and *n*-hexyl bromides gave by this procedure 78, 81 and 77% yields, respectively, of the corresponding lithium compounds.

Experimental

***n*-Butyllithium.**—The following is a description of a typical preparation. Into a 500-ml. three-necked flask equipped with a stirrer, low temperature thermometer, and a dropping funnel, was placed 200 ml. of anhydrous ether (dried over sodium). After sweeping the apparatus with dry, oxygen-free nitrogen, 8.6 g. (1.23 g. atoms) of lithium wire[2] (weighing 4.2 to 4.3 g. per meter) was wound in a loose coil, rinsed with ether, and the flattened coil was cut into pieces about 7 mm. in length which fell directly into the reaction flask in a stream of nitrogen. With the stirrer started, about 30 drops of a solution of 68.5 g. (0.5 mole) of *n*-butyl bromide[3] in 100 ml. of ether was added from a dropping funnel and the reaction mixture was then cooled to −10° with a Dry Ice–acetone bath kept at approximately −30° to −40°. (The solution becomes slightly cloudy and bright spots appear on the lithium when the reaction has started.) The remainder of the *n*-butyl bromide was then added at an even rate over a thirty-minute period while maintaining the internal temperature at −10°. After addition was complete, the reaction mixture was allowed to warm up to 0 to 10° while stirring for one to two hours. The reaction mixture was then filtered by decantation through a narrow tube plugged with glass wool into a graduated dropping funnel previously flushed with nitrogen. The yield, as deter-

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(1) Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944).

(2) Supplied by The Metalloy Corp., Minneapolis, Minn.

(3) The alkyl bromides used were all Eastman grade from The Eastman Kodak Co.

TABLE I

PREPARATION OF n-BUTYLLITHIUM

Run	Time of addition, min.	Temp. during addition, °C.	Type of lithium	G. atoms lithium	Moles n-butyl bromide	Final concn., molar	Yield[a] %	Stirring after addition Hr.	Temp., °C.
1	30	−20	Cut[b]	2.2	1.0	0.835	77.7	1.25	0–20
2	25	− 5	Cut	1.0	0.5	1.20	82.9	1	0
3	35	0	Sand[c]	1.0	0.5	1.47	77.3	2	0
4	35	−10	Cut	1.14	0.5	1.25	85.4[d]	2	0
5	35	−10	Wire	1.23	0.5	1.14	83.7[e]	2	0
6	15	−10	Cut	3.3	1.5	0.89	80.0	3	4

[a] Yield after filtration as determined by double-titration. [b] Prepared as described in THIS JOURNAL, 63, 2327 (1940). [c] Supplied by the Metalloy Corp., Minneapolis, Minn. [d] In this run helium was used in place of nitrogen and double-titrations were made five minutes, one hour, and two hours after addition; yields were 78.5, 83.9, and 85.4%, respectively. [e] Yield determined by double-titration before filtration was 90%; the above yield was determined after storing sixteen hours at 10° following filtration.

mined by double-titration[1] was 90% before filtration and 83.7% after filtering and storing sixteen hours at 10°. After four days at 10°, the yield was 82.5%.

CHEMICAL LABORATORY
IOWA STATE COLLEGE
AMES, IOWA

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Fluorene Analog of Amidone

BY DAVID GINSBURG[1] AND MANUEL M. BAIZER

Present interest in amidone analogs and derivatives[2,3] prompts us to report on the synthesis of a fluorene analog of amidone. This work was completed about a year ago but we have had no opportunity to establish the structure[4] of the isomer which was characterized.

Blicke and Zambito[5] state that the related "1,1-biphenylene-1-(β-dimethylaminoethyl)-butanone-2" is in the process of preparation. No details have appeared to date.

Experimental[6]

9-Formylfluorene.—This compound was prepared in 74% yield by the procedure of Von and Wagner.[7]

9-Formylfluorene Oxime.—A 78% yield was obtained by the procedure of Vorländer.[8]

9-Cyanofluorene.—A 90% yield was obtained in the dehydration of 9-formylfluorene oxime by thionyl chloride in absolute ether.[8]

Condensation of 9-Cyanofluorene with 1-Dimethylamino-2-chloropropane.—The procedure followed was similar to the one used in the condensation of diphenylacetonitrile with the chloroamine to yield the precursors of the amidones.[9]

In a 250-ml., three-necked flask, equipped with thermometer, mercury-sealed stirrer and reflux condenser, 19.1 g. (0.1 mole) of 9-cyanofluorene and 12.2 g. (0.1 mole) of 1-dimethylamino-2-chloropropane were dissolved in 100 ml. of dry benzene at 25°. Sodium amide (4.3 g., 0.11 mole) was added, portionwise, with continuous stirring in the course of thirty minutes. The temperature rose spontaneously to 40° in one hour; ammonia was evolved. The mixture was refluxed for thirty minutes, cooled and 50 ml. of water added. The benzene layer was separated and shaken with 50 ml. of 20% hydrochloric acid. The benzene layer on evaporation left 2.5 g. of unchanged 9-cyanofluorene. The acid extract was made alkaline by the addition of 33% sodium hydroxide, and the oil which separated was extracted with 200 ml. of ether. The ethereal solution was dried and the solvent removed by distillation. The residual oil, presumed by analogy to be mixture (I) of 9-cyano-9-(β-dimethylaminopropyl)-fluorene and 9-cyano-9-(α-methyl-β-dimethylaminoethyl)-fluorene, weighed 25.5 g. Upon distillation a yellow oil was obtained; b. p. 195–199° (8 mm.).

Reaction of I with Ethylmagnesium Bromide.—A Grignard reagent was prepared from 9.7 g. (0.40 mole) of magnesium turnings and 44 g. (0.38 mole) of ethyl bromide in 100 ml. of dry ether. To the ethereal solution was added, in one portion, a solution of 29 g. (0.11 mole) of I in 35 ml. of dry xylene. A greenish precipitate formed after a few minutes of heating under reflux in an oil-bath at 95–100°. The heating was continued for three and one-half hours; the mixture was then decomposed, while still hot, by the careful addition of 40 ml. of concentrated hydrochloric acid dissolved in 100 ml. of water. After the addition of benzene three layers were formed. The two upper layers were removed together and heated on a steam-bath until the solvents had been vaporized. The residual oily hydrobromide was moistened with alcohol and chilled briefly in an acetone–solid carbon dioxide-bath, whereupon crystallization occurred. The solid was filtered and recrystallized from ethanol. The yield of II,[10] m. p. 232–234°, was about 75% based upon one-half the input of I.

Anal. Calcd. for $C_{21}H_{26}BrNO$: C, 64.94; H, 6.75; N, 3.61. Found: C, 64.43; H, 7.02; N, 3.77.[11]

The melting point of the base, liberated from II, is 57–60° and of the hydrochloride 262–263°.

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[1] Present address: Daniel Sieff Research Institute, Rehovoth, Israel.

[2] Gardner, *et al.*, THIS JOURNAL, **70**, 2906 (1948).

[3] May and Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

[4] Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947), outline a structure proof for the isomeric nitriles which are the precursors of the amidones.

[5] Abstracts of American Chemical Society meeting April, 1947, p. 3K.

[6] Melting points and boiling points are not corrected.

[7] Von and Wagner, *J. Org. Chem.*, **9**, 162 (1944).

[8] Vorländer, *Ber.*, **44**, 2468 (1911).

[9] O. P. B. Report PB 981, p. 97.

[10] By analogy with the findings in the amidone synthesis,[9] we consider it probable that II is 9-propionyl-9-(β-dimethylaminopropyl)-fluorene hydrobromide and that the by-products remain in the mother liquors.

[11] Microanalyses by Schwarzkopf Laboratories, Elmhurst, L. I., N. Y.

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The Configuration at the 20-Position in Certain Steroids

BY W. KLYNE AND D. H. R. BARTON

Isomeric C_{21} steroids bearing a secondary hydroxyl group at C_{20} are commonly distinguished