Benzylsodium reacted smoothly with bis-(β-chloroethyl) and bis-(chloromethyl) ethers to give the corresponding bis-(γ-phenylpropyl) and bis-(β-phenylethyl) ethers, respectively.

Phenyl- and amylsodium reacted with the dichloromethyl ether to give the corresponding benzyl and heptyl ethers, respectively. Both reagents reacted vigorously with the dichloro ethyl ether, forming, however, products of a more extensive action on the ether molecule. Succinic acid was isolated from the carbonation products.

No reaction occurred between the dichloro ethyl ether and sodium metal.

Amylsodium reacted with mercuric chloride to form amylmercuric chloride.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 233]

Condensations by Sodium. XX. Preparation and Properties of Organosodium Compounds Derived from Butyl and Propyl Chlorides[1]

BY AVERY A. MORTON, GRAHAM M. RICHARDSON AND A. THOMAS HALLOWELL

When *n*-butyl and *n*-propyl are used instead of *n*-amyl chloride in preparation of organosodium compounds, the change to alkyl radicals of lower molecular weight is progressively accompanied by (1) more difficulty in effecting reaction between alkyl chloride and sodium metal, (2) poorer yields, (3) greater tendency toward disproportionation as judged by the proportion of malonic acid formed when the organosodium compounds are carbonated under comparable conditions (0.35 to 0.8 to 1.3 for amyl, butyl and propyl, respectively), and (4) greater stability of the alkylsodium toward benzene and toluene. So much does the reactivity with these hydrocarbons decrease that they can be used to advantage as solvents for the reaction. In a mixture of benzene and petroleum ether, for example, the yield of organosodium reagent from butyl chloride was nearly as high as any from amyl chloride and the best conditions for propylsodium were in fact realized in toluene as a solvent.

By raising the temperature of toluene to 72° the propylsodium first formed in the reaction exchanges with the toluene rapidly enough to be effective for preparation of butylbenzene in 42% yield according to the sequence of changes previously discovered[1a] for syntheses of *n*-alkylbenzenes.

$$\mathrm{RX} \xrightarrow[\text{Toluene}]{\text{Na in}} \mathrm{RNa} \xrightarrow{\text{Toluene}} \mathrm{C_6H_5CH_2Na} \xrightarrow{\text{RX}} \mathrm{C_2H_5CH_2R}$$

Accompanying this product was a high boiling fraction which appeared to be chiefly *m*-butylpropylbenzene together with some of the *p*-isomer. Metalation of butylbenzene therefore occurs in the nucleus rather than in the side chain with meta orientation predominating.

Other by-products from the reaction at 72° were unsaturated hydrocarbons boiling in the hexene and nonene range. Ozonolysis of one fraction showed that 3-methylpentene-2 was one component. Its presence might be explained by breaking of a carbon–carbon linkage during polymerization of an active propylene fragment. A somewhat similar break during dehydration and subsequent polymerization of methylisopropylcarbinol under influence of sulfuric acid has been noted already by Drake, Kline and Rose.[2]

Experiments

Butyl Chloride and Sodium. (By G. M. R.).—The apparatus was an ordinary three-necked flask with triple addition tube, stirrer, etc., as described in earlier[3] work. Conditions and results in a number of experiments are given in Table I.

Special attention is called to (a) the proportion of di- to mono- acid which is much higher than observed[3] with the products from reaction between amyl chloride and sodium, (b) the gradual loss in experiments 1, 2, and 3 of butylsodium (valeric acid) with no proportionate gain in propylmalonic acid when the mixture was heated at 42°, (c) the peculiar increase in yields of octane without parallel decrease in yields of valeric acid when the mixture was heated at 42° and (d) the relatively low yields of acids as compared with those from amyl chloride since an experiment[3] exactly comparable to the fourth using amyl chloride instead of butyl chloride gave 68% of mono- and 21% of dicarboxylic acids or a total of 89%.

Efforts to increase the yield by use of fine carborundum as an abrasive on the theory that a coating on the sodium surface inhibited the reaction improved the result by a few per cent. only.

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[1] Original manuscript received March 27, 1940.

[1a] Morton and Fallwell, Jr., THIS JOURNAL, **60**, 1429 (1938).

[2] Drake, Kline and Rose, THIS JOURNAL, **56**, 2076 (1934).

[3] Morton and Richardson, *ibid.*, **62**, 123 (1940).

Table I

Effect of Stirring at 42° on the Products of Reaction between Butyl Chloride and Sodium in Petroleum Ether

Constant factors, in first three experiments, butyl chloride 65 ml. in an equal volume of petroleum ether, sodium sand 70 g., activated by 10 ml. of *n*-amyl alcohol, solvent 250 ml., addition during two hours at 18–22°, stirring for one hour at room temperature, carbonation at 42°. In fourth experiment: butyl chloride 17.5 ml. in 40 ml. of petroleum ether; sodium sand, 30 g., activated by 2 ml. of amyl alcohol; solvent 150 ml.; addition during one hour at 0 to −4°; carbonation at 0 to −4°. In all cases the mixture was stirred at 42° before carbonation for the period indicated in column 2.

	Time of stirring at 42°,	Yields of acids							
		Valeric		Propyl-malonic		Total	Ratio di/mono	Yield of octane	
No.	hr.	G.	%	G.	%	%	acid	Ml.	%
1	0	12.0	19	15.3	34	53	1.8	1.5	1.4
2	2	8.5	13	15.5	34	47	2.6	11.0	11.0
3	8	7.0	11	13.2	29	40	2.6	13.1	13.0
4	2	4.4	26	2.6	22	48	0.8		

Exchange Reaction between Butylsodium and Benzene. (By G. M. R.).—Exchange with benzene was tested (a) by warming with butylsodium prepared in petroleum ether and finding that more benzene was required for a complete exchange than was needed in a parallel study already reported[4] of amylsodium with benzene, (b) by carrying out the reaction in benzene as a solvent and finding that the organosodium compounds from butyl chloride did not exchange as readily as those from amyl chloride at the temperature of the experiment, and (c) by comparing the amount of conversion of butylsodium in a mixed solvent with that for amylsodium. In the first set of experiments, butylsodium was made by adding 65 ml. of butyl chloride, dissolved in an equal volume of solvent, to 35 g. of sodium sand, activated by 5 ml. of amyl alcohol while suspended in 250 ml. of petroleum ether, over a two hour period at 18–22°, followed by stirring for one hour at 25–30°. In five successive experiments this mixture was in each case refluxed for two hours at 42° with 0, 20, 40, 60, and 150 ml. of benzene, and then carbonated at 27°. The corresponding acid products in each case were: 8.5, 7.0, 7.5, 6.9, and 0 g. (13, 11, 12, 11, and 0%) of valeric acid; 0, 2.8, 4.4, 4.5, and 11.5 g. (0, 4, 4, 6, and 15%) of benzoic acid; 15.5, 14.6, 8.8, 13.1, and 9.2 g. (34, 32, 19, 29, and 20%) of propylmalonic acid, and 0, 0.3, 1.1, 1.1, and 2.8 g. (0, 0.6, 2, 2, and 6%) of phthalic acids. The total acids were, respectively, 47, 48, 39, 48, and 41%. Percentage yields are plotted in Fig. 1 which illustrates, by comparison with a similarly constructed graph for amylsodium published earlier,[4] the greater resistance to exchange of organosodium compounds derived from butyl chloride.

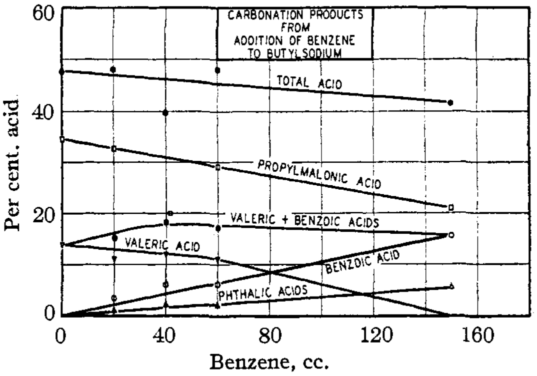

Fig. 1.—Carbonation products from addition of benzene to butylsodium.

In the second set of experiments, 65 ml. of butyl chloride in an equal volume of benzene was dropped over a two-hour period at 18–22° on 70 g. of sodium, activated by 10 ml. of amyl alcohol, while suspended in benzene. The time of stirring after addition had been completed was in one case one hour at room temperature and in another instance an additional two hours at 50°. Yields of benzoic acid were, respectively, 9.6 and 20.9 g. (13 and 27%), of propylmalonic acid 6.2 and 2.9 g. (14 and 9%), of phthalic acid 3.3 and 2.9 g. (6 and 6%). Total acids were 32 and 39%, respectively. Under generally similar conditions the organosodium compounds from amyl chloride[5] were completely converted to aromatic sodium compounds. It is interesting to note that the phthalic acid content in these two experiments was not increased by heating.

The third test was made with 17.5 ml. of butyl chloride mixed with 40 ml. of benzene dropped on 30 g. of sodium activated by 2 ml. of amyl alcohol while suspended in a mixture of 80 ml. of benzene and 25 ml. of petroleum ether. The addition time was one hour at 0 to −4°; stirring time was two hours at room temperature; carbonation temperature was 0 to −4°. The yield was comparatively large, being 3.9 g. (20%) of valeric, 4.5 g. (22%) of benzoic, 3.4 g. (29%) of propylmalonic acid or a total acid content of 71%. Under exactly similar conditions the yield from an equivalent quantity of amyl chloride was 8% caproic, 54% benzoic, and 13% butylmalonic acid or a total of 76%. Besides revealing the greater resistance of butylsodium toward reaction with benzene, this experiment also shows the larger yield obtained in a mixture of benzene and petroleum ether as a solvent compared with other results for butyl chloride in petroleum ether alone.

Propyl Chloride and Sodium. (By A. T. H.).—As a result of some twenty experiments under varying conditions the following procedure can be given as the best so far obtained. Propyl chloride, 55 ml. (0.6 mole) in an equal volume of sulfur-free toluene, was added in the usual manner over a one hour period at −3 to 7° to 70 g. (4.9 gram atoms of sodium to 1 mol of alkyl chloride) of fine sodium sand which had been previously activated by 4 ml. of *n*-amyl alcohol while suspended in 250 ml. of toluene and stirred in a 1-liter creased flask. Stirring was continued for one hour longer at 8 to 19°. Some propyl chloride had not reacted with sodium until well toward the end of the stirring period judged by the evolution of gas and the temperature rise. The carbonation temperature was −3 to −13°. After decomposing excess sodium with water, the aqueous layer was separated and the mono- and dicarboxylic acids recovered by extraction with petroleum ether and then with ether in the usual

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(4) Morton and Richardson, This Journal, **62**, 129 (1940).

(5) Morton and Fallwell, Jr., This Journal, **60**, 1429 (1938); Morton and Richardson, *ibid.*, **62**, 129 (1940).

manner. From this experiment 5.6 g. (10%) of butyric acid, 6.7 g. (16%) of propylmalonic acid, and 0.5% of unsaturated acid which showed unsaturation to permanganate were obtained. Butyric acid was identified by the boiling point, 162–163° (recorded value 164°), refractive index (1.4024 at 20°) (recorded value[6] 1.3978 at 20°), melting point of the amide 112–113.5° (recorded value 115°)[7] and melting point of the *p*-phenylphenacyl ester 78–78.5°. An authentic sample of the last melted 80.7–81.2° (uncor.) and a mixture with this prepared sample melted at 80°. Ethylmalonic acid was identified by neutralization equivalent 66.2 (calcd. is 66.0), melting point 108–110° (recorded value[8] is 111°) and the fact that it loses carbon dioxide at about 170°.

Similar experiments were made in benzene as a solvent yielding 14 and 8% of mono- and dicarboxylic acids, respectively, when the addition temperature was 0 to −7°; in benzene and petroleum ether mixture giving 10% of each of the acids; and in petroleum ether where the yields varied from 2 to 7%. An experiment in a mixture of toluene and petroleum ether gave 4 and 6%, respectively, of the two acids. In ethyl ether no organosodium compounds could be detected.

Attempts to increase yields by adding ordinary sand as an abrasive met with no success. Neither did the use of sodium sand prepared in the toluene to be used as a solvent just prior to the reaction influence the result. The rate of addition of propyl chloride in nearly all of the above experiments was about twice as fast as that used in previous work with other halides. This fact added to the comparative sluggishness of the reaction of propyl chloride with sodium caused much of the reaction to be delayed until the stirring period was well nigh completed. Control at this stage was usually not difficult but in a final experiment where very rapid stirring was employed the reaction got out of control, the temperature increased, and the pressure blew out one of the stoppers. It is believed that air then got into the apparatus and formed an explosive mixture with the organosodium compounds. In any event, the contents exploded violently. The advantages gained from rapid addition of alkyl chloride are negligible. It is recommended that a slower rate (two hours) be maintained, particularly in the case of propyl chloride which reacts with sodium metal less readily than does the amyl homolog.

Presence of 0.5 to 1.6% of acids, unsaturated to permanganate and to bromine, was noted in several experiments with benzene and toluene as solvents. The quantity was too small for identification, although crude anilide and dibromide mixtures were obtained.

Exchange of Propylsodium with Benzene (By A. T. H.).—Relative stability of propylsodium to benzene and toluene has been shown by the fact that (a) both benzene and toluene are suitable solvents in preparation of this organometallic compound and (b) conversion was incomplete even in hot benzene as a solvent. When 49 g. of propyl chloride was added to 70 g. of sodium in benzene during one hour at 0–7° with stirring afterward at 10–16°, the yield of butyric acid was 7.7 g. (14%) and of ethylmalonic acid 3.5 g. (8%) or a total of 23% with no exchange taking place. When propyl chloride was added at 20–25° with stirring at 50–60°, the yield of butyric acid was 0.7 g. (1%); of ethylmalonic acid 1.3 g. (3%); of benzoic acid 8.8 g. (12%); of a mixture of phthalic acids 3.2 g. (6%) and of some unsaturated acid was 2% or a total of 24% of acids. The total yields of acids in the two experiments were nearly the same but conversion of propylsodium even in hot benzene was not complete.

Butylbenzene (By A. T. H.).—Propyl chloride, 89 g. (1.13 mole) was dropped onto 100 g. (4.4 atoms) of sodium sand suspended with stirring at 69–75° in 250 ml. of toluene contained in a 1-liter creased flask. After the one-hour addition period the mixture was stirred for one hour longer at the same temperature. Upon cooling to room temperature, carbonating, decomposing with water, and fractionating the organic layer, 32.3 g. (43%) of butylbenzene (boiling range 179–181°) was recovered. Acidifying the aqueous layer and extracting as usual yielded a quantity of acid equivalent to 0.4%. Lowering the temperature at which addition was made to 60–70° decreased the yield of butylbenzene to 21%. When addition of propyl chloride was made at 48–54° with subsequent stirring at 51–56°, no butylbenzene was obtained, and the mono- and dicarboxylic acids recovered were, respectively, 5.0 and 9.8%. At temperatures of 85–94° the yield of butylbenzene fell to 37% and the recoverable acids amounted to 0.8 and 2.2%, respectively. The crude butylbenzene had a refractive index of 1.4893 at 20° (recorded value[9] 1.4899) but showed the presence of a small amount of material unsaturated to permanganate. On oxidation with permanganate benzoic acid only was obtained.

The higher boiling portions from all of the experiments were collected and fractionated at reduced pressure. At 42–43° (9 mm.) some additional butylbenzene was recovered. Between 74 and 81° at 6 mm., three cuts containing a total of 16 g. were collected. These fractions showed the presence of a small amount of unsaturated material. A sample was accordingly treated with a seventh of its volume of concentrated sulfuric acid. After diluting with water, washing to remove all acid, drying over calcium chloride, and redistilling at 20 mm. (b. p. 120–125°), the product was found to be stable to permanganate except on long shaking. From the boiling point (237–238° cor.) the refractive index (1.4837 at 20°), and carbon and hydrogen analyses (87.8 and 11.5, respectively) the material was suspected of containing either heptyl- or butylpropylbenzene. Oxidation by vigorous stirring with hot permanganate solution yielded acids which after crystallization from 25% alcohol partly sublimed at 295–315° leaving a solid which melted at 343–344°, both facts suggesting a mixture of tere- and isophthalic acids. A small amount (0.06 g.) of the acid was converted to the *p*-bromophenacyl ester, and the crude crystals treated with chloroform. The larger portion was thereupon dissolved, indicating[10] the presence of a large amount of the iso derivative. On adding petroleum ether to the chloroform solution crystals were obtained which melted at 174–175°. The value for the isophthalic ester[11] is 179°. The portion insoluble in

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[6] Falk, THIS JOURNAL, **31**, 96 (1909).

[7] Mitchell and Reid, *ibid.*, **53**, 1881 (1931).

[8] Markownikow, *Ann.*, **182**, 332 (1876).

[9] Schmidt, Hopp and Schoeller, *Ber.*, **72**, 1895 (1939).

[10] Morton and Fallwell, Jr., THIS JOURNAL, **60**, 1924 (1938).

[11] Kelly and Kleff, *ibid.*, **54**, 4444 (1932).

chloroform melted at 214–216°. The pure ester of the terephthalic acid is recorded[11] as melting at 225°. Neutralization equivalent of the mixture of acids was 84.3; calculated for phthalic acid 83.3. No trace of benzoic acid could be detected among the oxidation products. Apparently the mixture is largely isophthalic acid. The yield calculated on the basis of four propyl chloride molecules to one of the butylpropylbenzene mixture varied from 14 to 38%, an estimation based upon the quantity of high boiling residue left after distilling the butylbenzene from each experiment.

About 6 to 12 g. of a mixture of saturated and unsaturated compounds, boiling in the hexane and nonane range, was obtained from each of these preparations, the quantity being larger the higher the temperature of reaction. Careful fractionation in an eighteen-plate column failed to show any single product. All fractions also showed presence of unsaturated material. Upon ozonolysis of a 63 to 66° cut, decomposition of the ozonides with zinc and water, and careful fractionation of the resulting aldehydes and ketones, definite evidence in the form of the dinitrophenylhydrazone derivative was obtained for the presence of acetaldehyde. The melting point observed was 146–150°; that of an authentic sample was 147.5–148°; and that of the mixture was 148–150°. A mixed melting point with the like derivative of propionaldehyde (m. p. 190°) was 141°. Owing to the small amount of material left after attempts at purification, a satisfactory melting point for 2-butanone-2,4-dinitrophenylhydrazone could not be secured but the crystals obtained were shown to be identical with an authentic sample in having parallel extinction, pleochroism, centered acute bisectrix, and elongated obtuse bisectrix, and were not in whole agreement with observations on known samples of the like derivatives of acetone and butyraldehyde. A trace of propionaldehyde may also be present, for a few crystals prepared from one of the fractions appeared to have similar optical properties.[12]

Summary

Organosodium compounds from *n*-butyl and *n*-propyl chlorides have been prepared, the ease of reaction being progressively less, the yields lower, and the ratio of di- to monocarboxylic acid greater than observed with the amyl homolog.

n-Butyl- and *n*-propylsodium are progressively less reactive with benzene and toluene than is *n*-amylsodium.

n-Butylbenzene can be prepared conveniently by adding propyl chloride to sodium in toluene at 72°.

Metalation of butylbenzene takes place largely in the *meta* position.

[12] We are greatly indebted to Mr. Gibb for assistance on the optical studies.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

The Geometrical Attack on Protein Structure

BY DOROTHY M. WRINCH

It is unnecessary at the present time to state the case for the cyclol hypothesis, since authoritative accounts have already been given by Langmuir of the way in which the theory accounts satisfactorily for many of the well-known properties of the globular proteins.[1,2] In a recent summary,[3] however, Pauling and Niemann repeat a number of statements purporting to disprove the theory already made by other writers. Attention must therefore be directed to a number of publications in which these criticisms have already been discussed, at least so far as their scientific importance appeared to warrant.[2,4–9] We then proceed to discuss, necessarily in a preliminary manner, two issues (first raised in my publications[10,11]) to which Pauling and Niemann refer, namely (a) certain short interatomic distances in the original cage structures and (b) the energy of formation of these structures. In particular it is shown that the claim by Pauling and Niemann that the cyclol hypothesis can be disposed of by means of Anson and Mirsky's heat of denaturation of trypsin must be rejected.

(a) In my first studies of possible protein structures, very exacting metrical conditions were adopted, mainly in order to demonstrate in a simple manner the possibility of handling problems of protein structure by strictly mathematical methods. These, it appears from crystallographical data, are unnecessarily onerous. Evidently a discussion of certain short interatomic distances in the original cyclol structures can only

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(1) Langmuir, *Cold Spring Harbor Symposia Quant. Biol.*, **6**, 135 (1938).

(2) Langmuir, *Proc. Phys. Soc.* (London), **51**, 542 (1939).

(3) Pauling and Niemann, THIS JOURNAL, **61**, 1860 (1939).

(4) Wrinch, *Cold Spring Harbor Symposia Quant. Biol.*, **6**, 122 (1938).

(5) Langmuir, *Nature*, **143**, 280 (1939).

(6) Langmuir and Wrinch, *ibid.*, **143**, 49 (1939).

(7) Wrinch, *ibid.*, **143**, 482 (1939).

(8) Wrinch, *ibid.*, **143**, 763 (1939); **145**, 660, 1018 (1940).

(9) Langmuir and Wrinch, *Proc. Phys. Soc.* (London), **51**, 613 (1939).

(10) Wrinch, *Proc. Roy. Soc.* (London), **A160**, 59 (1937); **A161**, 505 (1937).

(11) Wrinch, *Nature*, **138**, 241 (1936).