Summary

A series of thirty-nine basic esters of a variety of arylacetic acids were prepared and studied *in vitro* for spasmolytic action. Changes in structure, particularly in the acid portion of the molecule, gave a wider variation in the neurotropic potency than in musculotropic potency. The introduction of a carbon–carbon linkage or bridge between the two benzene nuclei in certain esters of diphenylacetic acid, thus forming derivatives of fluorene-9-carboxylic acid, results in an increase in spasmolytic activity with little or no increase in toxicity.

The most promising spasmolytic of the series is β-diethylaminoethyl fluorene-9-carboxylate.

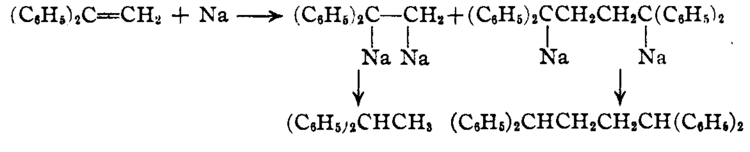
CHICAGO, ILL. RECEIVED SEPTEMBER 14, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Addition of Metals to Some Phenylated Olefins in Liquid Ammonia Solution[1]

BY HENRY GILMAN AND J. CLYDE BAILIE

It has been shown by Ziegler and co-workers[2] that when a solution of 1,1-diphenylethylene in ether was added to a solution of excess sodium in liquid ammonia the sole product of hydrolysis was 1,1-diphenylethane. Subsequently, Wooster and Ryan[3] also isolated a lesser quantity of 1,1,4,4-tetraphenylbutane.



$$(C_6H_5)_2C{=}CH_2 + Na \longrightarrow \underset{Na}{(C_6H_5)_2C}-\underset{Na}{CH_2} + (C_6H_5)_2\underset{Na}{C}CH_2CH_2\underset{Na}{C}(C_6H_5)_2$$

$$\downarrow \qquad\qquad \downarrow$$

$$(C_6H_5)_2CHCH_3 \quad (C_6H_5)_2CHCH_2CH_2CH(C_6H_5)_2$$

Related reactions, as now reported, take place with lithium, calcium, strontium and barium. On the basis of some formulations on the relative reactivities of organometallic compounds, the following hypothesis was proposed: "In general, it may be stated that where there is a 1,4-addition or a dimerizing addition of a metal to 1,1-diphenylethylene to give 1,1,4,4-tetraphenylbutane an RM compound of this metal will add to an olefinic linkage."[4] This generalization now finds adequate support, inasmuch as the RM compounds of each of the five metals mentioned above add to an olefinic linkage. The addition of the newly prepared diethylstrontium to 1,1-diphenylethylene is described in the accompanying paper.[5]

Magnesium, manganese and aluminum, which form RM types of lesser activity, that are known not to add to any measurable extent to the olefinic linkage, showed no evidence of solution in liquid ammonia and were without action on 1,1-diphenylethylene in that solvent.

Liquid ammonia solutions of calcium, strontium, and barium, respectively, reduce 1,1,2-triphenylethylene to 1,1,2-triphenylethane.

An organobarium compound is also formed in liquid ammonia by interaction of triphenylmethane with barium, as shown by carbonation which yielded some triphenylacetic acid.

Experimental

Reactions with 1,1-Diphenylethylene.—To 200 cc. of liquid ammonia in a Dewar flask was added 10 g. (0.44 g. atom) of sodium metal in small portions. Then to the deep blue solution was added 10 g. (0.056 mole) of diphenylethylene in 10 cc. of ether. The solution became red (formation of organoalkali compound), and the color persisted for two hours and until the mixture was ammonolyzed with ammonium chloride. After the ammonia had evaporated, the residue was shaken with water and extracted with ether. The ether was distilled, and the remaining oil distilled under reduced pressure. The products isolated were 6.7 g. (67%) of 1,1-diphenylethane and 1.7 g. (17%) of 1,1,4,4-tetraphenylbutane. These results check essentially those of Wooster and Ryan.[3]

Under corresponding conditions, a reaction between 6 g. of calcium chips and 10 g. of diphenylethylene gave a red organocalcium solution in liquid ammonia. Subsequent to ammonolysis by ammonium chloride there was obtained a 45% yield of 1,1-diphenylethane. From a second experiment in which 8 g. of calcium was used, there was obtained (after hydrolysis of the residue by 10% hydrochloric acid) 7 g. (70%) of 1,1-diphenylethane and 1.4 g. (14%) of 1,1,4-4-tetraphenylbutane.

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[1] Paper XLVI in the series: "Relative Reactivities of Organometallic Compounds." The preceding paper is THIS JOURNAL, **65**, 33 (1943).

[2] Ziegler, Colonius and Schäfer, *Ann.*, **54**, 473 (1929). See, also, Schlenk and Bergmann, *Ann.*, **479**, 78 (1930), for the addition of Li to 1,1-diphenyl-2-benzylethylene in ether.

[3] Wooster and Ryan, THIS JOURNAL, **56**, 1133 (1934). See, particularly, Wooster, *Chem. Rev.*, **11**, 48–52 (1932), for a full discussion of mechanisms proposed for these reactions.

[4] Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1938, p. 459.

[5] Gilman, Meals, O'Donnell and Woods, THIS JOURNAL, **65**, 268 (1943).

Strontium and barium reacted in a manner similar to that of calcium, and the yields of diphenylethane were 20 and 70%, respectively; the yields of 1,1,4,4-tetraphenylbutane were 14 and 35%, respectively.

Reactions with 1,1,2-Triphenylethylene.—The triphenylethylene was prepared in accordance with the directions of Hell and Wiegandt.[6] The same general procedure was used as with 1,1-diphenylethylene, and the organometallic compounds formed in liquid ammonia were red. The yields of 1,1,2-triphenylethane from experiments with calcium, strontium and barium were 40, 61 and 48%, respectively. The authentic specimen used for characterization of the products from the liquid ammonia reactions was prepared by the addition of phenyllithium to 1,1-diphenylethylene in ether.

Reaction with Triphenylmethane.—Six grams of barium in 200 cc. of liquid ammonia was treated with 9.8 g. of triphenylmethane to give a red solution. This was forced into a three-necked flask and 50 cc. of ether was added. After the ammonia had evaporated, powdered carbon dioxide was added. From the mixture was isolated triphenylacetic acid (mixed melting point). From a second experiment in which the red ammonia solution was poured upon solid carbon dioxide there was again isolated a very small quantity of triphenylacetic acid, and the yield of recovered triphenylmethane was 83%.

Summary

Lithium, calcium, strontium and barium add, in liquid ammonia, to the olefinic linkage of 1,1-diphenylethylene to give the corresponding red colored organometallic compounds. These when ammonolyzed yield 1,1-diphenylethane and 1,1,4,4-tetraphenylbutane. Calcium, strontium and barium add, under corresponding conditions, to 1,1,2-triphenylethylene to give 1,1,2-triphenylethane. The significance of these experiments on the addition of the corresponding RM compounds to an olefinic linkage is pointed out.

Barium reacts with triphenylmethane in liquid ammonia to give traces of triphenylmethylbarium.

Ames, Iowa Received October 30, 1942

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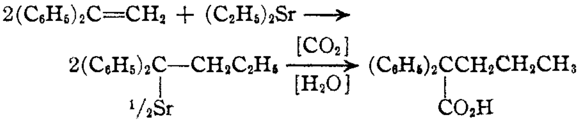
(6) Hell and Wiegandt, *Ber.*, **37**, 1431 (1904).

[Contribution from the Chemical Laboratory of Iowa State College]

Organostrontium Compounds[1]

By H. Gilman, R. N. Meals, G. O'Donnell and L. Woods

This report describes some reactions of a new class of organometallic compounds, the organostrontium compounds. Perhaps the most interesting reaction is the addition to an olefinic linkage. Diethylstrontium adds to the olefinic linkage of 1,1-diphenylethylene to give another R_2Sr compound, which was identified by carbonation to a known acid.



$$2(C_6H_5)_2C{=}CH_2 + (C_2H_5)_2Sr \longrightarrow 2(C_6H_5)_2\underset{\frac{1}{2}Sr}{\underset{|}{C}}{-}CH_2C_2H_5 \xrightarrow[{[H_2O]}]{[CO_2]} (C_6H_5)_2\underset{CO_2H}{\underset{|}{C}}CH_2CH_2CH_3$$

It has not been established definitely whether the diethylstrontium adds as $[2C_2H_5]$ $[Sr]$ or as $[C_2H_5]$ $[SrC_2H_5]$; however, it appears more likely that the former mode of addition takes place.

The addition of diethylstrontium to an olefinic linkage serves to classify organostrontium compounds with the very highly reactive organoalkali compounds, and supports the prediction (see preceding paper[2]) of such high reactivity.

Metalation.—Nuclear metalation is a reaction which is generally characteristic of the more reactive RM types. Diethylstrontium metalates anisole in the expected *ortho*-position to give di-*o*-anisylstrontium, identified as *o*-anisic acid, subsequent to carbonation. Dibenzofuran was also metalated in the expected 4-position, a position invariably involved irrespective of the kind of metalating agent (metals, inorganic salts like mercuric acetate or organometallic compounds). However, metalation of the related dibenzothiophene was, in a sense, quite anomalous.

It was shown earlier[3a] that although RLi and RK compounds metalated dibenzothiophene in the 4-position, phenylcalcium iodide effected metalation in the 3-position.[3b] It seemed altogether reasonable to expect that organostrontium compounds would, like the presumably very closely related organocalcium compounds, also metalate in the 3-position. This was not the case, however, for the only metalation product

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(1) Paper XLVII in the series, "Relative Reactivities of Organometallic Compounds." The preceding paper is This Journal, **65**, 267 (1943).

(2) Gilman and Bailie, *ibid.*, **65**, 267 (1943).

(3) (a) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); (b) Gilman, Jacoby and Pacevitz, *ibid.*, **3**, 120 (1938); (c) Krause and von Grosse, "Die Chemie der metall-organischen Verbindungen," Gebrüder Borntraeger, Berlin, 1937, p. 123.