3. Absorption spectra of some arylsulfurchlorides and their anilides have been presented and discussed.

4. New arylsulfurchlorides and anilides have been prepared.

PRINCETON, NEW JERSEY

[CONTRIBUTION NO. 40 FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY]

ACTION OF THE GRIGNARD REAGENT ON ALKYLBARBITURIC ACIDS

By ARTHUR W. DOX

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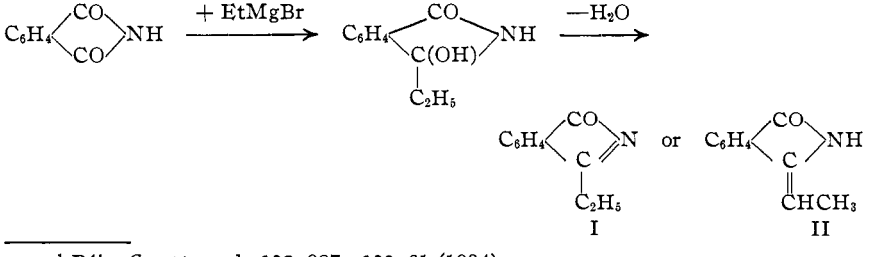
The 5,5-dialkylbarbituric acids, a number of which have come into extensive use as sleep-producing drugs, all contain three carbonyl groups, one or more of which should be expected to react with the Grignard reagent. Although commonly termed "acids," because the unsubstituted parent substance has certain very pronounced acid properties, these derivatives possess more the character of imides. For example, their solubility in alkali is due to a replacement of imide hydrogen by metal. Although two such imide groups are present only one is thus replaceable.

According to Béis[1] the more familiar types of imides, such as phthalimide, react with the Grignard reagent, but here only one of the two carbonyls is affected. With Grignard reagent prepared from normal alkyl halides, Béis noted a dehydration of the initial reaction product. This is attributed to a splitting out of water between the hydroxyl on the nucleus and a hydrogen of the side chain. The product obtained from phthalimide and ethyl magnesium bromide would be, therefore, not an ethyl-*iso*-indolone (Formula I) but rather an ethylidene phthalimidine (Formula II). The phenyl group, on the other hand, cannot give up a hydrogen in this manner and dehydration does not occur, the product with phenyl magnesium bromide being a phenylhydroxy-*iso*-indolinone. However, Sachs and Ludwig[2] obtained from N-ethylphthalimide and ethyl magnesium bromide a product analogous to Béis' phenyl Grignard product. In other words, with imide hydrogen already replaced by alkyl the dehydration



[1] Béis, *Compt. rend.*, **138**, 987; **139**, 61 (1904).

[2] Sachs and Ludwig, *Ber.*, **37**, 388 (1904).

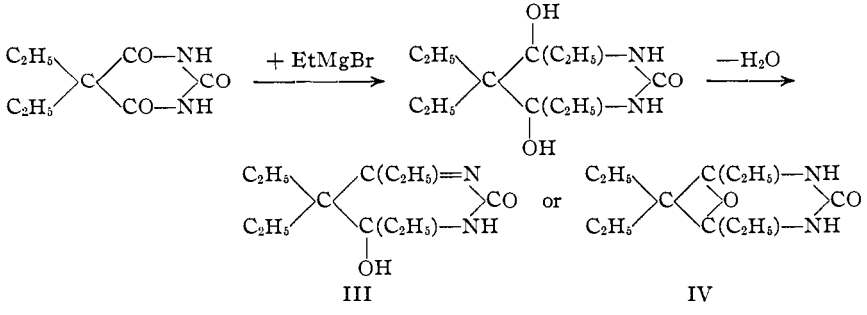
did not occur. The location of the double bond resulting from dehydration is still in question, leaving a choice between Formulas I and II.

With dialkylbarbituric acids and the Grignard reagent two carbonyls react, but in the dehydration which also occurs only one molecule of water is removed. Moreover, phenyl magnesium bromide gives the same type of product as do the alkyl magnesium bromides; and, further, a tetra-alkylbarbituric acid with no replaceable hydrogens gave a reaction between all three carbonyls and the Grignard reagent, but only one molecule of water was split out. The dehydration in the case of alkylbarbituric acid reaction products must, therefore, occur in a manner different from that represented in either Formula I or II.

Experimental

In all of the preparations described herein an excess of the Grignard reagent was used. To this was slowly added, with continuous stirring, an ethereal solution of the alkylbarbituric acid. Each drop gave momentarily a white precipitate, possibly a magnesium salt of the barbituric acid, which immediately dissolved again. After all had been added the mixture was refluxed for one and a half to two hours, and then treated in the usual way with dilute sulfuric acid. Products containing smaller alkyl groups had a tendency to crystallize out of the ether layer; those of higher molecular weight usually remained in solution and were obtained crystalline by evaporation of the solvent. Recrystallization from alcohol gave fine, slender needles. None of the products melted at 250°, and those with lower molecular weight sublimed without melting and apparently without decomposition.

Analysis of the product obtained from diethylbarbituric acid and ethyl magnesium bromide showed that two carbonyls had reacted and that one molecule of water had been split out. The calculated empirical formula is $C_{12}H_{22}O_2N_2$, which may be represented by either of two structures, III or IV.



For reasons to be discussed presently, Formula IV appears the more probable of the two. The substance will, therefore, be designated, pro-

visionally, endo ether of 4,6-dihydroxy-4,5,5,6-tetra-ethyl-2-ketohexahydropyrimidine. It is insoluble in water and benzene, moderately soluble in alcohol, but unlike diethylbarbituric acid it is insoluble in sodium hydroxide. Removal of any traces of unreacted dialkylbarbituric acid is easily effected by extraction with dilute alkali. The substance dissolves readily in concentrated sulfuric, hydrochloric and acetic acids, and is precipitated unchanged from these solutions by dilution with water.

Anal. Subs. 0.1446, 0.1577: CO_2, 0.3394; H_2O, 0.1304; N_2, 18.2 cc. (738 mm., 28°). Calcd. for $C_{12}H_{22}O_2N_2$: C, 63.72; H, 9.73; N, 12.39. Found: 64.01, 10.02, 12.29.

The substance is surprisingly resistant to hydrolysis. When the solution in concentrated hydrochloric acid is gently refluxed, the original substance separates out again as soon as the loss by evaporation diminishes the concentration of acid to the constant-boiling solution. After two hours' refluxing 94% of the original material was recovered unchanged. Six hours' heating in a sealed tube at 160–180° with ten parts of 25% sulfuric acid was insufficient to effect hydrolysis; 89% of the substance was recovered unchanged. Three hours' refluxing of 1 g. with 1 g. of potassium hydroxide in 50 cc. of alcohol likewise failed to effect hydrolysis, the recovery in this case being 89%. Hydrolysis was accomplished, however, by heating for seven hours at 150–160° in a sealed tube with ten parts of concentrated hydrochloric acid, and also by seven hours' heating in an oil-bath at 130–135° with 50% by volume sulfuric acid. The products obtained were ammonium chloride and sulfate, respectively, and a volatile oil with characteristic ketone odor. The oil, after purification by steam distillation, was soluble in water and reacted with hydroxylamine and with phenylhydrazine, forming liquid products which failed to crystallize in a freezing mixture. The initial products of hydrolysis should be a diketone of the formula $(C_2H_5)_2C(COC_2H_5)_2$ and urea. These probably undergo further hydrolysis to form diethylketone and ammonia.

In a similar manner other dialkylbarbituric acids reacted with various alkyl magnesium halides, giving products of much the same properties. In all cases the nitrogen content agreed with that calculated for products of the same type, that is, alkylation of two carbonyls and loss of one molecule of water.

DIALKYLBARBITURIC ACIDS + RMgBr

Barbituric acid	Grignard	Product	N Calcd.	N Found
Diethyl	Ethyl	$C_{12}H_{22}O_2N_2$	12.39	12.29
Ethylphenyl	Ethyl	$C_{16}H_{22}O_2N_2$	10.22	9.98
Ethyl-*iso*-amyl	Ethyl	$C_{15}H_{28}O_2N_2$	10.11	10.16
Diethyl	Phenyl	$C_{20}H_{22}O_2N_2$	8.70	8.62
Diethyl	Propyl	$C_{14}H_{26}O_2N_2$	11.02	11.05
Diethyl	*n*-Butyl	$C_{16}H_{30}O_2N_2$	9.93	10.18
Diallyl	Ethyl	$C_{14}H_{22}O_2N_2$	11.20	10.88
Diallyl	*iso*-Amyl	$C_{20}H_{34}O_2N_2$	8.38	8.37

The choice between Formulas III and IV could not be determined satisfactorily by hydrolysis whereby a ketone, probably diethylketone, was obtained. If the dehydration occurs between the tertiary alcohol grouping and the adjacent NH, it seems unlikely that only one molecule of water should be split out rather than two. On the other hand, the internal ether structure represented by Formula IV, which contains no double linkage, gives a symmetrical structure for which the observed stability and resistance to hydrolysis might be predicted.

If a similar dehydration takes place when a tetra-alkylbarbituric acid reacts with the Grignard reagent, the only manner in which it could occur would be by formation of an inner ether, since both nitrogens are substituted and no replaceable hydrogen is present. As will be shown directly, this is apparently what takes place.

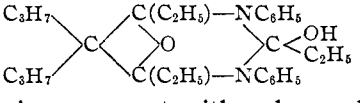
5,5-Dipropyl-1,3-diphenylbarbituric acid was prepared by dissolving molecular proportions of dipropylmalonic acid and carbanilide in anhydrous chloroform, adding two molecules of freshly distilled phosphorus oxychloride and heating the mixture in an oil-bath for four hours at 65–70°. The chloroform was then evaporated and the residue dissolved in water. Extraction with ether took up the condensation product, along with some dipropylmalonyl chloride, and precipitated out the unreacted carbanilide. Evaporation of the ether left a sirup which could not be crystallized. It was then purified by vacuum distillation. The portion distilling between 150 and 190° at 4 mm. solidified in the receiver, and after washing with petroleum ether and recrystallizing from benzene, it was obtained in white prisms melting at 104–105°. Unlike the di- and trialkylbarbituric acids, which contain replaceable hydrogen, this substance is insoluble in alkali. The yield was small (30%), owing probably to insufficient time of reaction.

Anal. Subs. 0.2254: N_2, 14.9 cc. (749 mm., 23°). Calcd. for $C_{22}H_{24}O_3N_2$: N, 7.69. Found: 7.35.

The above product was treated in the usual manner with ethyl magnesium bromide. No transient precipitate of a magnesium salt was formed during the reaction. The product after recrystallization from benzene consisted of white needles melting at 102° A mixed melting point with the tetra-alkylbarbituric acid gave a depression of 8°.

Anal. Subs., 0.1979, 0.1992: CO_2, 0.5607; H_2O, 0.1664; N_2, 11.4 cc. (745 mm., 26°). Calcd. for $C_{28}H_{40}O_2N_2$: C, 77.06; H, 9.17; N, 6.42. Found: 77.27, 9.34, 6.35.

The empirical formula represents an endo ether of 1,3-diphenyl-2,4,6-triethyl-5,5-dipropyl-2,4,6-trihydroxyhexahydropyrimidine:



The analysis is not in agreement with values calculated for products that would result from the reaction of two carbonyl groups, with or without dehydration. Substitution of both NH groups in the barbituric acid evidently modifies the properties of the third carbonyl in such a way as to render it capable of reacting with the Grignard reagent.

Summary

The reaction between 5,5-dialkylbarbituric acids and the Grignard

reagent consists in the alkylation of two carbonyls and the loss of one molecule of water, probably with formation of an internal ether. With a tetra-alkylbarbituric acid the same reaction occurs, also an additional reaction of the third carbonyl.

DETROIT, MICHIGAN

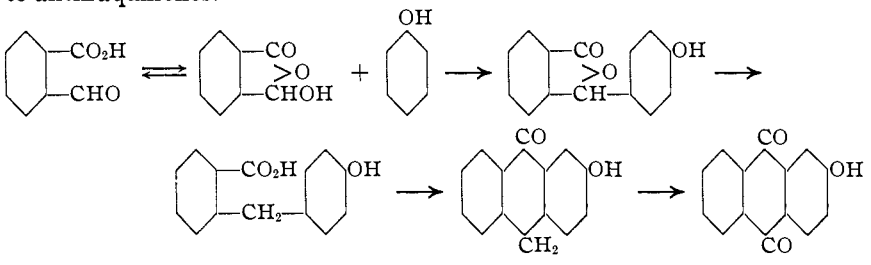
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

THE STRUCTURE OF THE CONDENSATION PRODUCTS OF ORTHO-PHTHALALDEHYDIC ACIDS WITH PHENOLS AND PHENOL ETHERS. VIII.[1]

BY M. M. BRUBAKER[2] WITH ROGER ADAMS

RECEIVED MAY 23, 1927 PUBLISHED SEPTEMBER 2, 1927

The preparation of substituted phthalides from *ortho*-phthalaldehydic acid by condensation with phenols was discovered by Bistrzycki.[3] He found that the phthalides formed could be reduced to benzyl-benzoic acids and these in turn could be dehydrated and the anthrones oxidized to anthraquinones.



This procedure for preparing certain types of anthraquinones appeared, at first, not to be entirely general, since he was unable to reduce phthalides from opianic acid (2-carboxy-3,4-dimethoxybenzaldehyde) and phenols to the corresponding benzyl-benzoic acids. Jacobson and Adams,[1d] however, found that under the proper conditions these latter phthalides could be reduced, and, although the benzyl-benzoic acids could not in all cases be obtained crystalline and pure, the products served well for the preparation of anthraquinones. In this Laboratory the method has already been applied to the synthesis of morindone,[1e] rufiopin[1g] and

[1] For previous articles in this field see (a) Graves with Adams, THIS JOURNAL, **45,** 2439 (1923); (b) Gardner with Adams, *ibid.*, **45,** 2455 (1923); (c) Jacobson with Adams, *ibid.*, **46,** 1312 (1924); (d) **46,** 2788 (1924); (e) **47,** 283 (1925); (f) **47,** 2011 (1925); (g) Puntambeker with Adams, *ibid.*, **49,** 486 (1927).

[2] This communication is an abstract of a thesis submitted by M. M. Brubaker, Carr Fellow for 1926–1927, in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[3] (a) Bistrzycki and Oehlert, *Ber.*, **27,** 2632 (1894); (b) Bistrzycki and Yssel de Schepper, *Ber.*, **31,** 2790 (1898); (c) Bistrzycki and Zen-Ruffinen, *Helv. Chim. Acta.*, **3,** 369 (1920); (d) Bistrzycki and Krauer, *ibid.*, **6,** 750 (1923).