The keto acids V could be secured by dissolving the lactones in sodium hydroxide, and acidifying, care being taken to keep the temperature low.

Upon chromic acid oxidation, the lactones gave benzoic and an *o*-benzoylbenzoic acid; the same products resulted if the lactone was first dissolved in sodium hydroxide, and then oxidized with permanganate.

When treated in the Grignard machine, the lactone showed no active hydrogen but two additions as expected. The product, worked up in the usual way, gave the ketone VIII (R = C_6H_5), the carbinol group having been dehydrated. With phenylmagnesium bromide, a carbinol VII (R = C_6H_5) was secured without any difficulty.

The bromohydrin XXII resulted when the epoxide from 2-ethyl-3-phenylindenone was allowed to stand at 10–15° for one-half hour with five times its weight of 30–32% hydrogen bromide in acetic acid. The yield was 80%. It gave an oily carbinol with methylmagnesium iodide that still retained the halogen.

2-Phenyl-2-benzoyl-(*Bz*-4,5-diphenyl)-cyclobutenone-1, XXIII.—Five grams of the epoxide from 2,3,5,6-tetraphenylindenone was added to 40 cc. of 15% hydrogen bromide in acetic acid, the whole mixture boiled for ten minutes, cooled, and crystallization initiated by scratching the side of the flask. The red ketone that separated was filtered and recrystallized from benzene–ligroin. The yield was 4 g. The ketone crystallizes in brick-red prisms, often diamond-shaped, m. p. 219–220°.

Anal. Calcd. for $C_{33}H_{22}O_2$: C, 88.0; H, 4.9. Found: C, 88.4; H, 4.9.

The same substance was formed when a 25% solution of sulfuric acid in acetic acid was used, and even by six hours of refluxing in acetic acid alone.

In the Grignard machine, the red ketone shows no active hydrogen and two additions. With the Grignard reagent, it gave the same product (VIII) as the lactone. Upon chromic acid oxidation, it gave benzoic and 4,5-diphenyl-2-benzoylbenzoic acids.

When 1.5 g. of the red ketone was added to 50 cc. of alcohol containing 2 g. of potassium hydroxide, refluxed for three hours, poured into water, and acidified cold, the acid V (R = C_6H_5) resulted. Attempts to reduce the red ketone by zinc dust and acetic acid gave the lactone—this apparent anomaly was traced to the zinc acetate formed. In acetic acid solution, in less than five minutes, zinc acetate caused the red color to disappear; the lactone separated on cooling. The same change is brought about by potassium acetate in eight hours, and by hydroxylamine hydrochloride in two hours.

The 2,4-dinitrophenylhydrazone of benzalacetophenone oxide was prepared in the usual manner; it separated from methanol in orange needles, m. p. 205°.

Anal. Calcd. for $C_{21}H_{16}O_5N_4$: C, 62.6; H, 4.0. Found: C, 62.4; H, 4.0.

Summary

A number of oxidoketones have been prepared in the indene series; the reaction appears to be fairly general.

With mineral acid, most of them give isomeric glycols in the cold, and lactones when heated; the glycols are isomerized to the same lactones by warm mineral acids.

The epoxides from 2,3-diphenyl- and 2-ethyl-3-phenylindenones give bromohydrins with cold hydrogen bromide in acetic acid.

The epoxide from 2,3,5,6-tetraphenylindenone gives an isomer for which a benzcyclobutenone structure has been proposed.

The glycols are isomerized by alkaline reagents to isobenzofurans.

A mechanism has been proposed to account for certain reactions previously termed rearrangements.

The carbonyl group is still present in oxidoketones.

ROCHESTER, N. Y. RECEIVED JANUARY 13, 1943

NOTES

Conversion of 2,7-Dibromofluorene to 2,7-Dibromophenanthrene

BY WELDON G. BROWN AND BEN A. BLUESTEIN

We have previously reported[1] a synthesis of phenanthrene, starting from fluorene, in which the ring enlargement is accomplished by a Wagner rearrangement of 9-fluorenylcarbinol. A similar series of reactions, resulting in the conversion of 2,7-dibromofluorene into 2,7-dibromophenanthrene, has been carried through which it seems desirable to record as the work has been discontinued.

Experimental

2,7-Dibromo-9-formylfluorene.—Potassium ethoxide was formed from 3.9 g. (0.1 mole) of potassium and 4.6 g. (0.1 mole) of absolute alcohol in 250 cc. of dry ether. To this mixture was added 33 g. (0.1 mole) of 2,7-dibromofluorene resulting, after a few minutes refluxing, in a dark brown solution. The slow addition of 7.4 g. (0.1 mole) of ethyl formate caused the solution to become first green,

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(1) Brown and Bluestein, THIS JOURNAL, **62**, 3256 (1940).

then brown again. After refluxing for one hour, water was added, and the aqueous layer, after washing with ether, was acidified with dilute sulfuric acid. The pale yellow solid obtained in 85% yield was twice recrystallized from glacial acetic acid, m. p. 171°.

On standing the aldehyde deepens in color and becomes diminishingly soluble in aqueous alkali.

For the purposes of characterization, the acetate was prepared by the addition of acetic anhydride to a solution of the aldehyde in aqueous potassium hydroxide. It was recrystallized from a benzene–ligroin mixture, m. p. 219°.

Anal. Calcd. for $C_{16}H_{10}O_2Br_2$: C, 48.76; H, 2.56. Found: C, 49.69; H, 2.69.

2,7-Dibromo-9-fluorenylcarbinol.—To aluminum isopropoxide, prepared from 1 g. of aluminum, was added 9.5 g. of 2,7-dibromo-9-formylfluorene in 25 cc. of isopropanol. The mixture was distilled through a Vigreux column, holding the vapor temperature at 60° for about five hours, after which the remaining alcohol was removed under reduced pressure. The residue was treated with 6 *N* sulfuric acid, and the solid product was then separated by filtration. Extraction of the solid with hot alcohol, followed by precipitation from the alcoholic extract on the addition of water, yielded 5.5 g. (58%) of material which, after three recrystallizations from ligroin, melted at 154°.

Anal. Calcd. for $C_{14}H_{10}OBr_2$: C, 47.50; H, 2.85. Found: C, 47.61, H, 3.37.

The carbinol formed an acetate readily on boiling with acetic anhydride and sodium acetate, m. p. 190° (from alcohol).

2,7-Dibromophenanthrene.—One gram of 2,7-dibromo-9-fluorenylcarbinol was refluxed for thirty minutes with 1 g. of phosphorus pentoxide and 25 cc. of xylene. The xylene layer was decanted and the xylene was removed by distillation. Recrystallization of the residual solid from a xylene–ligroin mixture yielded 0.1 g. of colorless crystals, m. p. 205° (lit.[2] m. p. 2,7-dibromophenanthrene, 202°). Oxidation of the product with chromic acid in glacial acetic acid yielded 2,7-dibromophenanthraquinone, m. p. 321° (lit.[2] m. p. 323°).

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(2) Schmidt and Mezger, *Ber.*, **40**, 4560 (1907).

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Amide-Substituted Phenylarsine Oxides and Their Derivatives: A Group of Compounds of Possible Utility in the Treatment of Syphilis

BY HARRY EAGLE, RALPH B. HOGAN, GEORGE O. DOAK AND HARRY G. STEINMAN

We have previously found[1] that strongly acidic substituent groups introduced into phenylarsine oxide regularly caused a striking decrease in direct treponemicidal activity against *T. pallidum*, without a commensurate decrease in toxicity. The potential therapeutic utility of these compounds was therefore even less than that of the simple unsubstituted phenylarsine oxide. However, when the acidic group was blocked, as in ethyl or methyl esters, or as in the sulfone and phenone compounds, the treponemicidal activity was largely restored, and the ratio of treponemicidal activity: toxicity was increased as much as fourteen-fold, in several cases significantly exceeding that of the parent compound.

In the light of that finding, a series of phenylarsine oxides was prepared in which an acidic substituent group had been blocked by amide formation.[2,3] The majority of these amides have proved to be actively treponemicidal and relatively low in toxicity (first section of Table I). The ratio of treponemicidal activity: toxicity, which may be taken as a rough measure of potential therapeutic utility, was usually 2 to 6 times as favorable as that of the parent phenylarsine oxide, due primarily to the uniformly low toxicity of these compounds. As will be discussed in a following paper, some of these compounds have shown a chemotherapeutic index in the treatment of rabbit syphilis equal to or exceeding that of mapharsen, and on that basis are of potential value in the treatment and prophylaxis of syphilis. The favorable effect of amide-substitution has been so regular as to suggest that further study may disclose other related compounds of greater therapeutic utility than any of those here described.

The favorable effect of amide substituents on the toxicity of phenylarsine oxide was observed whether that amide group was attached directly to the benzene ring, as in the case of 3- and 4-$CONH_2$ and -SO_2NH_2 compounds, or through some intermediate linkages (*cf.* first section, Table I). Moreover, the integrity of the amide group was usually essential for the favorable activity: toxicity ratio: When either or both of the amide hydrogens were substituted, the compound usually developed properties apparently determined by the new terminal substituent (*cf.* 2nd and 3rd sections, Table I). Although treponemicidal activity was usually increased by such substitution, toxicity was increased to an even greater degree, giving a less favorable ratio. In this group of compounds, the activity and toxicity of the compound had thus reverted toward that of the simple unsubstituted phenylarsine oxide, or of phenylarsine oxides with such indifferent sub-

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(1) H. Eagle, R. B. Hogan, G. O. Doak and H. G. Steinman, *J. Pharmacol.*, **70**, 221 (1940).

(2) G. O. Doak, H. G. Steinman and H. Eagle, THIS JOURNAL, **62**, 3012 (1940).

(3) G. O. Doak, H. G. Steinman and H. Eagle, in preparation.