

the supernatant liquid was decanted, and the solid was washed four times with acetone (50 cc. each time) and was dried *in vacuo* at 100° for thirty minutes. The dried solid was dissolved in hot, dry dioxane (100 cc.), the hot solution was filtered, and the filtrate was poured slowly into vigorously stirred, cold acetone (500 cc.). The white, flocculent precipitate was collected on a filter, washed with cold acetone, and dried at room temperature for twelve hours under high vacuum. The product weighed 8 g. (36%), and melted at 210–212°. A sample was dried for two hours at 100° under high vacuum, and was weighed out of contact with the air ("pig") and then analyzed.⁴

Anal. Calcd. for $C_{88}H_{108}O_{10}Ca$: C, 72.10; H, 9.75. Found: C, 71.83; H, 9.70.

The above process was repeated, with proportionate amounts of all materials, except for the time of refluxing, standing, etc., which was the same. The results were as follows.

α -Tocopherol, 94.3 g. (0.218 mole) gave a product (65 g., 55%) melting at 194–199°. *Anal.* Found: C, 72.39; H, 10.09.

α -Tocopherol, 100 g., gave a product (86 g., 67%) melting at 194–198°. *Anal.* Found: C, 72.27; H, 9.70; Ca, 3.37. Calcd.: Ca, 3.64.

α -Tocopherol, 4.91 (*n*-propylmagnesium chloride used in place of ethylmagnesium bromide) gave a product (4.4 g., 71%) which softened at 220°, and melted at 225°. *Anal.*

(E. E. R.). Found: C, 71.36; H, 9.65. This sample was used for the biological assays.

The above procedure gave pasty acid esters when either maleic or phthalic anhydride was substituted for succinic anhydride. These compounds, however, were not characterized further.

Summary

1. Several esters of 2,2,5,7,8-pentamethyl-6-hydroxymethylenecyclohexane have been prepared by reaction between the appropriate acid derivative and a halo-magnesium derivative of the chroman. These esters include the O-carbethoxy derivative, the acid succinate, and the chloroacetate. All of these esters are hydrolyzed with extreme ease, and it was not possible to prepare the glycine ester of the chroman by ammonolysis of the chloroacetate.

2. Calcium α -tocopheryl succinate has been prepared and characterized. This substance, a solid soluble in organic solvents and insoluble in water, exhibited a vitamin E activity approximately equal, on a molecular basis, to that of α -tocopherol itself.

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The Action of Grignard Reagents on Benzoylformanilides¹

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An investigation³ of the reactions of N-alkyl isatin derivatives with phenylmagnesium bromide showed that N-ethylisatin reacts with two moles of the Grignard reagent to form two isomeric compounds: one, 2,3-diphenyl-1-ethylindole oxide-2,3 (I), undergoes rearrangement to give the other (3,3-diphenyl-1-ethylindole) (II). These reactions suggested that analogous products might be obtained through the substitution of N-ethylbenzoylformanilide for N-ethylisatin.

However, in the case of N-ethylbenzoylformanilide, only one mole of phenylmagnesium bromide reacted, producing N-ethylbenzilanilide (III), which was found, incidentally, to be very stable toward alkaline hydrolytic agents. In an attempt to synthesize III by another method acetylbenzyl chloride was allowed to react with ethylaniline in the hope of obtaining the acetyl

derivative of III; the product, however, was found to have the empirical formula $C_{22}H_{19}ON$ instead of the $C_{24}H_{23}O_3N$ which would be required by the acetyl derivative of III, and was found to be identical with authentic samples of II. Thus, acetylbenzyl chloride and ethylaniline had reacted with the loss of acetic acid and hydrogen chloride to form 3,3-diphenyl-1-ethylindole (II).

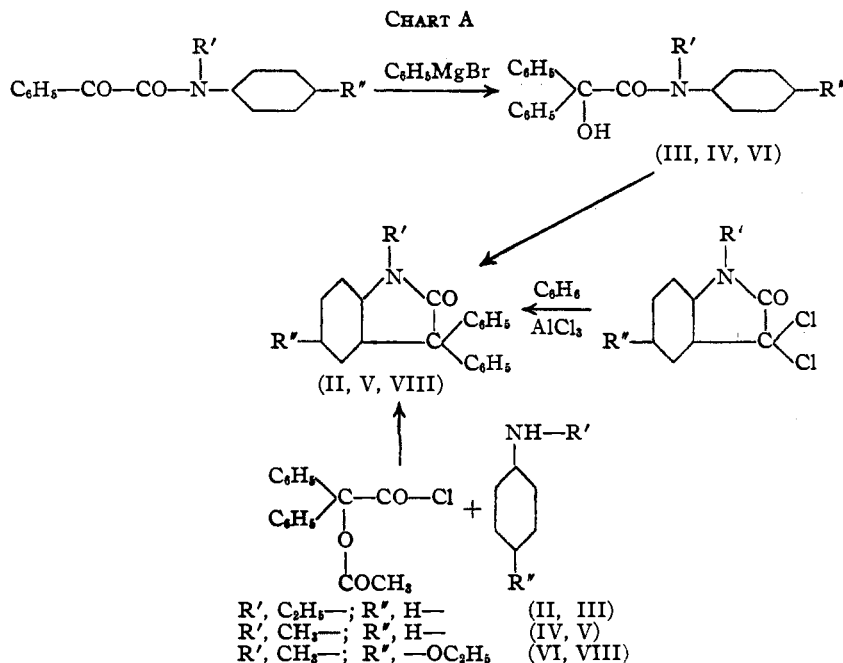
It was then found that treatment of III with reagents such as acetic anhydride, aqueous or alcoholic hydrogen chloride, or cold concentrated sulfuric acid gave rise also to the formation of II. The most rapid conversion of III to II was obtained through the use of sulfuric acid.

In an entirely similar manner N-methylbenzilanilide (IV) was prepared by the action of an excess of phenylmagnesium bromide upon N-methylbenzoylformanilide. Compound IV yielded 3,3-diphenyl-1-methylindole (V) upon being treated with acids or dehydrating agents. Also, acetylbenzyl chloride reacted with methylaniline to give V.

(1) Presented at the Detroit meeting of the American Chemical Society, September, 1940.

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(3) Myers and Lindwall, *This Journal*, **60**, 2153 (1938).



The identities of the two oxindole derivatives (II and V) produced in the above reactions were determined by comparison with samples prepared from the appropriate 3,3-dichloro-1-alkyloxindole and benzene under the conditions of the Friedel-Crafts reaction.

In an extension of the study, the preparation of N-methylbenzilic acid *p*-phenetide (VI) from N-methylphenylglyoxylic acid *p*-phenetide (VII) and phenylmagnesium bromide was attempted; the product (VI), although not obtained in pure form, yielded VIII upon being treated with acids. Compound VIII was also obtained from acetylbenzyl chloride and N-methyl-*p*-phenetidide. Attempts to establish the structure of VIII conclusively through the application of the Friedel-Crafts method to the cyclization and arylation of N-methyl-trichloroacet-*p*-phenetide have thus far been unsuccessful (Chart A).

The reaction between acetylbenzyl chloride and N-methylnaphthylamine led to the formation of a product (IX) which, by analogy to similar reactions described above, has been assigned the tentative formula 3,3-diphenyl-1-methyl- β -naphthoxindole.

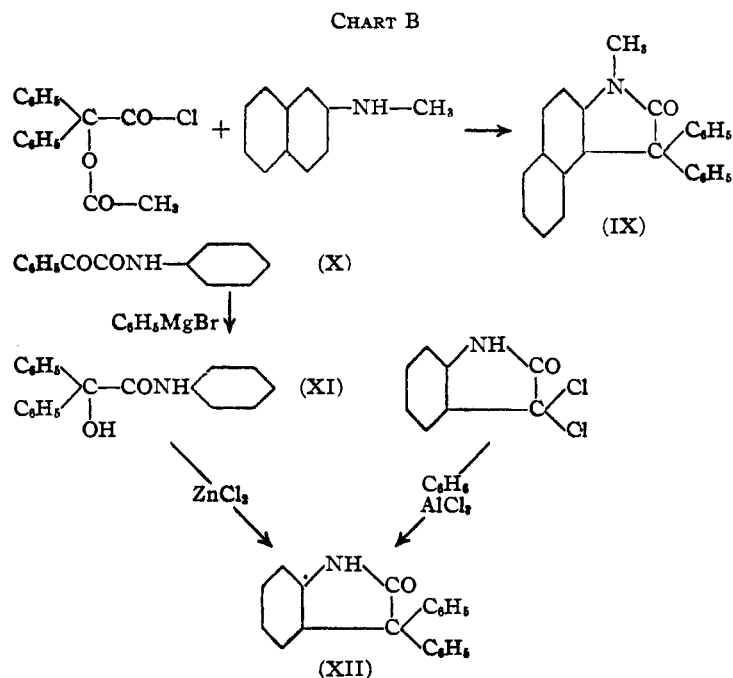
When benzoylformanilide (X) and phenylmag-

nesium bromide were allowed to react, benzilamide (XI) resulted; the identity of XI was shown by its conversion to diphenylacetic acid. Compound XI, upon being heated with anhydrous zinc chloride, yielded XII. That XII was identical with 3,3-diphenyloxindole was shown by the preparation of XII from 3,3-dichloro-oxindole by the method of Inagaki⁴ (Chart B).

Experimental

N-Methylbenzilamide (IV).—An excess of phenylmagnesium bromide (0.25 mole) was prepared in a solution of equal parts of absolute ether and benzene.

N-Methylbenzoylformanilide (12.0 g., 0.05 mole), dissolved in 100 cc. of benzene and ether, was added to the Grignard reagent over a period of forty minutes. The mixture was then held at its boiling point for thirty minutes with continued vigorous stirring. After cooling, the mixture was poured into ice and sulfuric acid and was allowed to stand



thus overnight. Most of the organic solvent mixture was then removed by evaporation, and the residual material was left in a refrigerator for several days. The oily,

(4) Inagaki, *J. Pharm. Soc. Japan*, **53**, 686 (1932).

partially crystalline product was purified by crystallization from 80% ethyl alcohol; white needles, m. p. 106–107°; yield, 81%.

Compound IV is soluble in acetone, benzene, glacial acetic acid, and ethyl alcohol; insoluble in water. When placed in cold concentrated sulfuric acid, a brilliant red color appears on the surface of the crystals, but disappears as the compound dissolves.

Anal. Calcd. for $C_{21}H_{19}O_2N$: C, 79.46; H, 6.04; N, 4.42. Found: C, 79.33; H, 6.05; N, 4.44.

N-Ethylbenzilanilide (III).—Compound III was prepared by a method similar to that used for IV. It crystallized from 95% ethyl alcohol as white prisms; m. p. 97.5–98.5°; yield, 75%.

Anal. Calcd. for $C_{22}H_{21}O_2N$: C, 79.72; H, 6.39; N, 4.23. Found: C, 79.83, 79.89; H, 6.55; N, 4.22, 4.25.

3,3-Diphenyl-1-methyloxindole (V). **Method A.**—Authentic samples of compound V were obtained from 3,3-dichloro-1-methyloxindole⁵ and benzene and aluminum chloride, or by a modified procedure using N-methyltrichloroacetanilide with benzene and aluminum chloride. Hexagonal prisms and needles after crystallization from 95% ethyl alcohol; m. p., 175.5–176.5°.

Method B.—(From IV) N-methylbenzilanilide (3.2 g., 0.01 mole) was suspended in 100 cc. of 70% ethyl alcohol and 50 cc. of 42% hydrobromic acid was added. The mixture was heated to boiling and an oil appeared, which gradually solidified. After one hour of heating the mixture was cooled and the solid matter which separated was recrystallized from ethyl alcohol; hexagonal prisms and needles; m. p. 175.5–176.5°; yield, 83%. Mixed with material from methods A and C there was no change in the melting point.

Method C.—Acetylbenzyl chloride⁵ (20 g., 0.07 mole) in 80 cc. of absolute ether was added slowly with continuous shaking and cooling to methylaniline (14.8 g., 0.14 mole) in 100 cc. of absolute ether. After standing overnight the methylaniline hydrochloride (7.5 g.) which had separated was removed. The ethereal filtrate was washed successively with dilute alkali, dilute acid, and water before being dried. Later removal of the ether left a brown oil which solidified after several days in the refrigerator. Recrystallization from ethyl alcohol yielded a mixture of hexagonal prisms and needles; m. p. 175.5–176°; yield, 51%. This product was found to be identical with samples of compound V prepared by methods A and B, by melting point methods.

3,3-Diphenyl-1-ethyloxindole (II). **Method A.**—Authentic samples of II were prepared from 3,3-dichloro-1-ethyloxindole⁵ with benzene and aluminum chloride or from N-ethyltrichloroacetanilide⁶ with benzene and aluminum chloride. Hexagonal prisms from ethyl alcohol; m. p., 158–159°.

Method B.—(From III) N-ethylbenzilanilide (1.0 g.) was suspended in 30 cc. of 50% sulfuric acid and the mixture was boiled for one-half hour. The yield of crude II was almost quantitative; hexagonal prisms from ethyl alcohol; m. p. 158–159°.

Method C.—The procedure was identical with that of "method C" above for the preparation of V. Compound

II obtained by this procedure was shown, by melting point methods, to be identical with II prepared in A and B above.

N-Methylbenzilic Acid *p*-Phenetide (VI).—An excess of phenylmagnesium bromide was prepared in a solution of equal parts of ether and benzene, and to it was added a 150 cc. benzene-ether solution of 20 g. of N-methylphenylglyoxylic acid *p*-phenetide; the addition required one hour, and during this time the Grignard solution was kept at its boiling point. After cooling the mixture, it was poured into ice and sulfuric acid and was allowed to stand thus overnight. The ethereal solution was separated and then placed with ether extracts of the residual aqueous portion; after successive washings with dilute alkali, and water, the ether solution was dried with calcium sulfate. Removal of the ether left an oil (23 g., 94%) which could not be crystallized; boiling point 120–125° (2 mm.) with decomposition.

Anal. Calcd. for $C_{23}H_{23}O_3N$: C, 76.43; H, 6.42. Found (crude): C, 76.52; H, 6.36.

3,3-Diphenyl-5-ethoxy-1-methyloxindole (VIII). **Method A.**—(From VI) a sample of crude VI (10 g.) in a solution consisting of equal volumes of 95% ethyl alcohol and 40% hydrobromic acid was boiled for one hour. Upon being cooled a crystalline material separated which was purified by successive recrystallizations from 95% alcohol and 90% acetic acid; hexagonal prisms; m. p. 186.5–187.5°; yield, 60%. Compound VIII is insoluble in water, but is soluble in benzene and acetone, slightly soluble in methyl alcohol, ethyl alcohol, and glacial acetic acid.

Anal. Calcd. for $C_{23}H_{21}O_3N$: N, 4.08. Found: N, 4.08.

Method B.—N-Methyl-*p*-phenetidine was substituted for methylaniline in the procedure for the preparation of Compound V by "Method C" (see above); hexagonal prisms; m. p. 186.5–187.5°; yield, 61%. The products of Methods A and B were shown to be identical, by melting point methods.

Anal. Calcd. for $C_{23}H_{21}O_2N$: C, 80.44; H, 6.17; N, 4.08. Found: C, 80.39; H, 6.32; N, 4.16, 3.92.

3,3-Diphenyl-1-methyl- β -naphthoxindole (IX).—Acetylbenzyl chloride (2.9 g., 0.01 mole) dissolved in 20 cc. of absolute benzene was slowly added to N-methyl- β -naphthylamine (3.1 g., 0.02 mole) dissolved in 15 cc. of absolute benzene. The mixture was boiled for one hour; upon cooling, 1.6 g. of the hydrochloride of N-methyl- β -naphthylamine separated and was removed. The benzene filtrate was washed successively with dilute alkali, dilute acid, and water; after drying, benzene was removed leaving the crude product (2.5 g., 71%) which after recrystallization from glacial acetic acid resulted in 2 g. of IX; m. p. 253–254°. Compound IX is soluble in benzene, and is slightly soluble in ether, acetone, and ethyl alcohol.

Anal. Calcd. for $C_{25}H_{19}ON$: C, 86.50; H, 5.49; N, 4.01. Found: C, 86.58; H, 6.00; N, 4.02.

Benzilanilide (XI).—An excess of phenylmagnesium bromide (0.15 mole approx.) in 125 cc. of ether was added to a solution of benzoylformanilide (0.05 mole) in 100 cc. of ether. After standing overnight the reaction mixture was poured into a mixture of ice and sulfuric acid. After several hours the white solid which had separated was re-

(5) Hurd and Williams, *THIS JOURNAL*, **58**, 962 (1936).

(6) Spiegel and Spiegel, *Ber.*, **40**, 1730 (1907).

moved and more was recovered from the benzene layer. Recrystallized from benzene as clusters of minute needles; m. p. 177–177.5°; yield 88%. Compound XI is soluble in benzene, acetone, glacial acetic acid. It is recovered unchanged after boiling for several hours with aqueous alcoholic potassium hydroxide.

Anal. Calcd. for $C_{20}H_{17}O_2N$: C, 79.17; H, 5.65; N, 4.62. Found: C, 79.66; H, 5.72; N, 4.80.

Diphenylacetic Acid from XI.—A mixture of XI (1 g.), red phosphorus (1 g.), 1 cc. of hydriodic acid (57%), and 15 cc. of glacial acetic acid was kept at its boiling point for one hour. The mixture was then poured into water, and the solid which separated was crystallized from water; m. p. 145–146°; yield, 0.6 g. (85%). Melting point methods showed this product to be identical with a known sample of diphenylacetic acid.

3,3-Diphenyloxindole (XII) (from XI).—Benzilanilide (1.0 g.) was heated with freshly fused zinc chloride (1.0 g.) at 185–190° for one-half hour. The solid mass resulting after cooling was extracted several times with hot 75% ethyl alcohol. The residue was recrystallized from benzene as stubby needles; m. p. 225–226°; yield, 0.7 g.

For purposes of identification, XII was also prepared from 3,3-dichloro-oxindole and benzene (with aluminum chloride). The products obtained by the two methods were identical.

Anal. Calcd. for $C_{20}H_{15}ON$: C, 84.18; H, 5.30; N, 4.91. Found: C, 83.82; H, 5.54; N, 4.94.

Summary

1. N-Methyl- and N-ethyl-benzoylformanilide react with phenylmagnesium bromide to yield the respective N-alkylbenzilanilides. The latter, upon treatment with acid or dehydrating agents, form the corresponding 1-alkyl-3,3-diphenyloxindoles.

2. Methyl- and ethylaniline react with acetylbenzilyl chloride to produce the respective 1-alkyl-3,3-diphenyloxindoles.

3. N-Methylphenylglyoxylic acid *p*-phenetide and phenylmagnesium bromide yield a crude product which upon treatment with acids forms 3,3-diphenyl-5-ethoxy-1-methyloxindole.

4. 3,3-Diphenyl-1-methyl- β -naphthoxindole is formed through the action of N-methyl- β -naphthylamine with acetylbenzilyl chloride.

5. Benzilanilide upon treatment with zinc chloride yields 3,3-diphenyloxindole.

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Alkanolamines. XI. Monoalkylamino Alcohols and their Esters

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This is a continuation of the work dealing with esters of substituted amino alcohols.¹ Goldberg and his co-workers^{2,3} have synthesized a number of these esters of monoalkylamino alcohols. In this present work we have prepared a series of monoalkylamino alcohols in which the carbon atom alpha to the amino group is substituted with two alkyl groups. The monoalkyl substituent on the amine nitrogen varied from ethyl to amyl in the normal series and from propyl to amyl in the iso series. The alcohols were low melting, white solids. While no regular relationship existed among the melting points of the solids, such a relationship was found to exist for the boiling points of the compounds. This is in keeping with the general rule that melting points of organic compounds do not show the same regular changes in an homologous series as do the boiling points. Further, the boiling point of an iso deriva-

tive approximated that of the next lower member of the normal series.

The monoalkyl derivatives were formed by refluxing 2-amino-2-methyl-propanol-1 with the appropriate alkyl bromide, employing ethanol as a solvent. The normal alkyl halides reacted readily. The iso alkyl halides reacted more slowly, and in the order: isoamyl > isobutyl > isopropyl. After ten to fifteen hours of refluxing the isoamyl bromide had reacted to the extent of 70% or better; the isobutyl bromide less than 40% and the isopropyl bromide approximately 20%. It was only after prolonged refluxing that the latter reacted to any appreciable extent. It is quite apparent that the iso grouping inhibits this reaction in proportion to its distance from the halide atom.

The *p*-nitrobenzoates of the amino alcohols were obtained by condensing them with *p*-nitrobenzoyl chloride, in pyridine. Temperature control is important, optimum conditions being between 30 and 40°. Formation of the esters in aqueous alkaline medium gave poor yields and

(1) C. B. Kremer, *THIS JOURNAL*, **61**, 1321 (1930).

(2) S. D. Goldberg and W. F. Whitmore, *ibid.*, **59**, 2280 (1937).

(3) S. D. Goldberg, W. F. Ringk and P. E. Spoerri, *ibid.*, **61**, 3562 (1939).