A General Route to 2,3-Diacyl-1,4-dihydro 1,4-Disubstituted 1,4-Epoxynaphthalenes[1] and 1,4-Disubstituted 2,3-Naphthalic Anhydrides[1]

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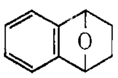
Treatment of 3,4-dicarbethoxy-2,5-dimethylfuran with benzyne generated from anthranilic acid afforded 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3a**) in 77% yield. Hydrogenation yielded 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**4**), which on treatment with concentrated sulfuric acid produced 1,4-dimethyl-2,3-naphthalic anhydride (**5**) in 82% yield. Similarly, 3,4-diacetyl-2,5-dimethylfuran yielded 3,4-diacetyl-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3b**) in 71% yield. On heating 3,6-dimethylphthalic anhydride with urea at 150°, 3,6-dimethylphthalimide was formed in 90% yield. Under similar conditions **5** was recovered unchanged. Heating **5** with urea in refluxing *N*-methylpyrrolidone for 4 hr afforded 1,4-dimethyl-2,3-naphthalimide (**7**) in 35% yield. Treatment of 3,6-dimethylphthalimide with potassium hypochlorite yielded (87%) 2-amino-3,6-dimethylbenzoic acid but **7** was unchanged under similar conditions.

A number of naphthalene derivatives have been prepared by aromatization of derivatives of 1,4-epoxy-1,2,3,4-tetrahydro (**1**) and 1,4-epoxy-1,4-dihydronaphthalenes (**2**).[2-5] Derivatives of **1** are prepared either by reaction of a dienophile with an isobenzofuran[2,6-8] or by reduction of derivatives of **2**. Aromatization is accomplished by acid-catalyzed dehydration of the adduct.[3] This method is of particular advantage for the preparation of 1,4-diarylnaphthalenes, since the required isobenzofurans are stable and readily accessible.[9] Unsubstituted and 1,4-dialkylisobenzofurans have only recently been isolated[10-12] and owing to their instability have not been used extensively as preparative intermediates.



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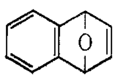

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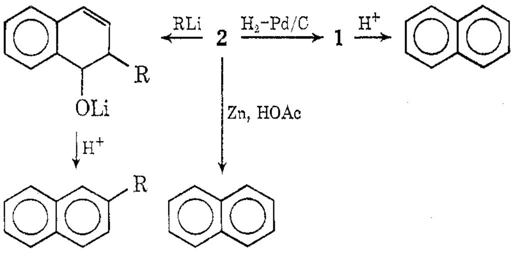
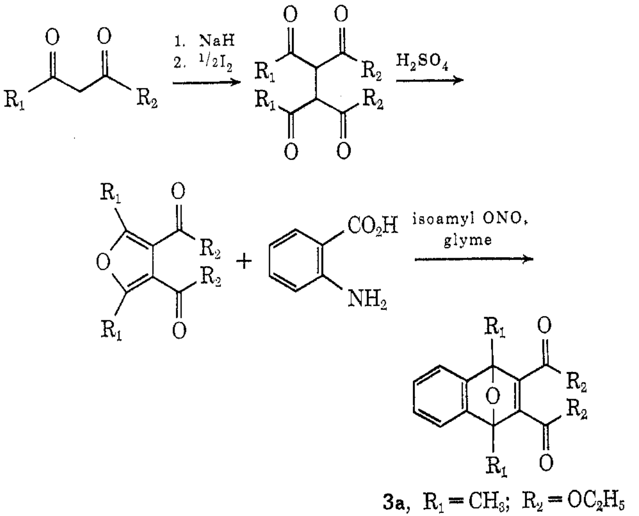
Derivatives of **2** are generally prepared by trapping benzyne with furans.[3-6,13] Aromatization of these adducts is accomplished by catalytic reduction to derivatives of **1** followed by dehydration,[3] by direct deoxygenation with metals,[13-15] or by addition of an organometallic followed by dehydration.[4]



We have found an efficient and general route to 2,3-diacyl-1,4-dihydro 1,4-disubstituted 1,4-epoxynaphthalenes *via* addition of benzyne to 3,4-diacyl 2,5-disubstituted furans. The necessary furans can be prepared in good yield by dimerization of readily available 1,3 diketones or keto esters followed by dehydration.[16] Generation of benzyne by decomposition of anthranilic acid with isoamyl nitrite in refluxing 1,2-dimethoxyethane in the presence of the furans affords benzyne adducts in good yield (see Experimental Section). The general scheme is illustrated in Scheme I. Adducts **3a** and **3b** were prepared in 58 and 52% overall yields by this process starting with ethyl acetoacetate and acetylacetone. Reduction of **3a** in ethyl acetate with H_2-Pd/C afforded 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**4**) in quantitative yield. Treatment of **4** with concentrated sulfuric acid

SCHEME I



3a, $R_1 = CH_3$; $R_2 = OC_2H_5$
b, $R_1 = R_2 = CH_3$

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[1] This work formed part of the Ph.D. Thesis of James A. Cella, The Ohio State University, 1973.

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[3] G. Wittig and L. Pohner, *Chem. Ber.*, **89**, 1334 (1956).

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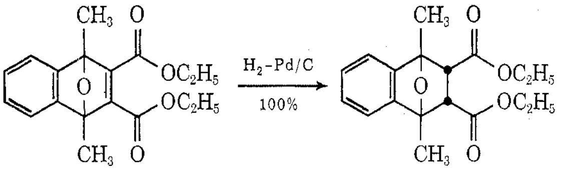
[12] U. E. Wiersum and W. J. Mijs, *Chem. Commun.*, 347 (1972).

[13] See R. W. Hoffman, "Dehydrobenzene and the Cycloalkynes," Verlag Chemie, Weinheim/Bergstr., Germany, 1967, p 209.

[14] G. Wittig, E. Knauss, and K. Niethammer, *Justus Liebigs Ann. Chem.*, **630**, 10 (1960).

[15] F. M. Beringer and S. J. Huang, *J. Org. Chem.*, **29**, 445 (1964).

[16] S. P. Mulliken, *J. Amer. Chem. Soc.*, **15**, 523 (1893).



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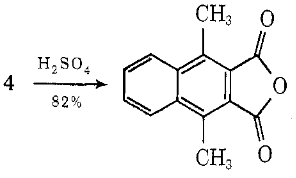
produced 1,4-dimethyl-2,3-naphthalic anhydride (**5**) in 82% yield.



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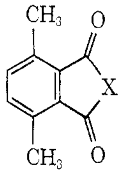
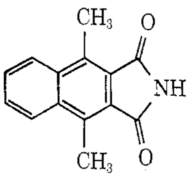
It is interesting to compare the stability of the ring system in **5** with that of 3,6-dimethylphthalic anhydride (**6a**). Anhydride **6a** reacted with 2 equiv of urea in 0.5 hr at 150° to produce imide **6b** in 90% yield. Under identical conditions **7** was recovered essentially unchanged after 1 hr. Reaction of **5** with urea required prolonged treatment in refluxing *N*-methyl-2-pyrrolidone (bp 200°) and produced **7** in 35% yield. No effort was made to optimize this yield. Moreover, **6b** was readily converted in 87% yield to 2-amino-3,6-dimethylbenzoic acid (**8**), on treatment with aqueous potassium hypochlorite and base at 50°, whereas **7** was recovered unchanged after similar treatment.



6a, X=O
b, X=NH



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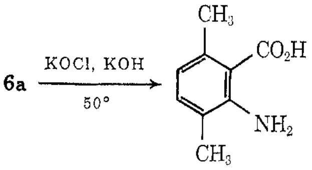

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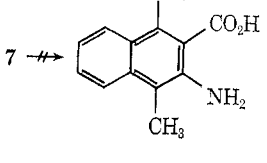
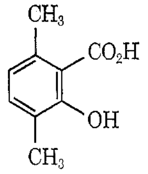


This lack of reactivity is undoubtedly due to an increased steric effect of the methyl groups caused by the buttressing effect of the peri hydrogens.[17]

Interestingly, attempted conversion of amino acid **8** to 2-iodo-3,6-dimethylbenzoic acid by diazotization followed by treatment with potassium iodide gave only 3,6-dimethylsalicyclic acid (**9**) in 94% yield. The efficient production of **9** in this reaction is probably due to hydrolysis of the β-lactone **10**. Intermediates of this type have been postulated in similar systems.[18] Formation of **10** is facilitated in this system by the steric effect of the methyl group, which forces the carboxyl group into a good conformation for participation in the loss of nitrogen.



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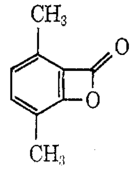

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Experimental Section

General.—All melting points and boiling points are uncorrected. Microanalyses were performed by M. H. W. Laboratories, Garden City, Mich. Ir spectra were recorded on a Perkin-Elmer Infracord using sodium chloride disks or potassium bromide pellets. Nmr spectra were recorded on an A-60 instrument, Varian Associates, Palo Alto, Calif., and are reported as δ units relative to tetramethylsilane (TMS) as an internal standard. The terms "usual work-up" or "worked up as usual" mean that, after the organic solution was washed with 3 *N* HCl or 3 *N* K_2CO_3, water, and saturated salt solution, it was dried by passage through a cone of $MgSO_4$ and the solvents were removed on a rotary evaporator.

Materials.—1,2-Dimethoxyethane was distilled from calcium hydride and stored over molecular sieves. Isoamyl nitrite and anthranilic acid were obtained from the Aldrich Co. Acetylacetone was obtained from Chemical Samples. Sodium hydride was obtained as a 50% mineral oil dispersion from Ventron and was washed with pentane prior to use.

Diethyl α,β-Diacetylsuccinate.[19]—To a suspension of 21 g (0.5 mol) of sodium hydride in 250 ml of 1:1 dimethoxyethane–ether was added 65 g (0.5 mol) of ethyl acetoacetate. After 1 hr, a solution of 63.5 g (0.25 mol) of iodine in 150 ml of dimethoxyethane was added and the resulting mixture was stirred for 0.5 hr. The mixture was diluted with water and the phases were separated. Evaporation of the solvent afforded 58.0 g (90%) of diethyl α,β-diacetylsuccinate: ir (neat) 5.79 μ (1727 cm^{-1}) (C=O); nmr (CCl_4) δ 4.36 (s, 2, COCHCO), 4.20 (q, 4, OCH_2CH_3), 2.38 (s, 6, $COCH_3$), and 1.27 (t, 6, OCH_2CH_3). This material was used directly in the next step.

3,4-Dicarbethoxy-2,5-dimethylfuran.[20]—Diethyl α,β-diacetylsuccinate (9.7 g, 37.6 mmol) was dissolved in 100 ml of cold concentrated sulfuric acid. After 5 min, the solution was poured on ice and the resulting mixture was extracted three times with ether. Combined ether extracts were worked up in the usual way to yield 7.6 g (84%) of 2,5-dimethyl-3,4-dicarbethoxyfuran: bp 127–130° (1.0 mm); ir (neat) 5.80 μ (1724 cm^{-1}) (C=O); nmr (CCl_4) δ 4.28 (q, 4, OCH_2CH_3), 2.44 (s, 6, $ArCH_3$), and 1.32 (t, 6, OCH_2CH_3); mass spectrum *m/e* 240.

Tetraacetylethane.—To a suspension of 21.0 g (0.5 mol) of sodium hydride in 400 ml of ether was added 50 g (0.5 mol) of acetylacetone. After 1 hr, 65 g (0.25 mol) of iodine in 200 ml of ether was added and the mixture was stirred for 1 hr. After addition of water, the mixture was filtered to yield 39.5 g of tetraacetylethane. Concentration of the ether afforded an additional 2.3 g. The crude material (84.5%) was of sufficient purity to be carried on to the next step. Recrystallization from ethanol afforded pure tetraacetylethane, mp 191–194° (lit.[16] mp 191°).

3,4-Diacetyl-2,5-dimethylfuran.—Tetraacetylethane (25 g, 0.13 mol) was added slowly with stirring to 100 ml of cold concentrated sulfuric acid. When all of the solid dissolved, the mixture was poured into ice water and filtered to yield 19.4 g (85.5%) of 2,5-dimethyl-3,4-diacetylfuran as long, fluffy needles, mp 58.5–60° (lit.[16] mp 63°).

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(17) F. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 552.

(18) See ref 13, p 76.

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(20) L. Knorr, *Ber.*, **17**, 2866 (1884).

Addition of Benzyne to Furans.—Solutions of 38 g (277 mmol) of anthranilic acid and 38 ml (excess) of isoamyl nitrite each in 100 ml of glyme were added simultaneously in 1.5 hr to a refluxing solution of 155 mmol of the appropriate furan in 300 ml of glyme. After addition was complete, the mixture was refluxed for 0.5 hr and then allowed to cool. The cooled solution was diluted with 300 ml of ether and stirred with 3 *N* KOH. The phases were separated and the aqueous phase was extracted with ether. The combined ether extracts were worked up in the usual way to yield the appropriate dihydronaphthalenes: 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3a**), 77% yield, bp 140–145° (0.2 mm), mp 51–52°, ir (KBr) 5.81 (1721) (C=O) and 6.13 μ (1631 cm^{-1}) (C=O), nmr (CCl_4) δ 7.10 (m, 4, ArH), 4.11 (q, 4, OCH_2CH_3), 1.88 (s, 6, $ArCH_3$), and 1.19 (t, 6, OCH_2CH_3), mass spectrum *m/e* 316; and 3,4-diacetyl-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (**3b**), 71% yield, mp 101–102°, ir (KBr) 5.89 (1698) (C=O) and 6.03 μ (1658 cm^{-1}) (C=C), nmr ($CDCl_3$) δ 7.10 (m, 4, ArH), 2.12 (s, 6, $COCH_3$), and 1.86 (s, 6, $ArCH_3$), mass spectrum *m/e* 256.

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.4; H, 6.3. Found: C, 68.2; H, 6.2.

Anal. Calcd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3. Found: C, 75.3; H, 6.2.

2,3-Dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (4).—A mixture of 4.8 g (15 mmol) of **3a** and 0.3 g of 10% palladium on carbon (Engelhardt) in 125 ml of ethyl acetate was shaken in a Parr hydrogenation apparatus (55 psi). The theoretical amount of hydrogen was consumed in 5 min. The contents were filtered through Celite and the solvent was evaporated to yield 4.9 g (100%) of **4**: mp 67–68°; ir (KBr) 5.86 μ (1706 cm^{-1}) (C=O); nmr (CCl_4) δ 7.10 (s, 4, ArH), 3.78 (q, 4, OCH_2CH_3), 3.20 (s, 2, $CHCO_2C_2H_5$), 1.76 (s, 6, $ArCH_3$), and 1.00 (t, 6, OCH_2CH_3); mass spectrum *m/e* 318.

1,4-Dimethyl-2,3-naphthalic Anhydride (5).—Crude **4** (5.0 g, 15.7 mmol) was stirred with 100 ml of concentrated sulfuric acid chilled in an ice bath. The mixture was heated slightly until most of the solids dissolved and was then poured on crushed ice. The crude product was isolated by filtration and recrystallized from acetone. This process afforded in three crops 2.95 g (82%) of 1,4-dimethyl-2,3-naphthalic anhydride: mp 283–284°; ir (KBr) 5.50 and 5.68 μ (1818 and 1761 cm^{-1}) (C=O); mass spectrum *m/e* 226.

Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.5; H, 4.4. Found: C, 74.7; H, 4.3.

3,6-Dimethylphthalimide (6b).[21]—An intimate mixture of 1.90 g of 3,6-dimethylphthalic anhydride and 1.4 g of urea was heated in an oil bath at 150° for 30 min. After a vigorous gas evolution, the mixture became solid. The solid was washed with water to yield 1.72 g (90%) of **6b**, mp 218–220°, mass spectrum *m/e* 175.

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.6; H, 5.2. Found: C, 68.3; H, 5.3.

On similar treatment of 1.0 g of **5** with 0.55 g of urea for 60 min, no **7** was obtained.

1,4-Dimethyl-2,3-naphthalimide (7).—A mixture of 10.0 g (44 mmol) of 1,4-dimethyl-2,3-naphthalic anhydride and 5.0 g (excess) of urea was refluxed in 25 ml of *N*-methyl-2-pyrrolidone for 4 hr. The cooled mixture was poured on ice and filtered. The solids were recrystallized from *N*-methyl-2-pyrrolidone to yield 3.5 g (35%) of **7**: mp >325°; ir (KBr) 5.71 and 5.88 μ (1754 and 1701 cm^{-1}) (C=O); mass spectrum *m/e* 225.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.6; H, 4.9. Found: C, 74.9; H, 4.8.

2-Amino-3,6-dimethylbenzoic Acid.—A mixture of 1.3 g of calcium hypochlorite (Sentry, 65%), 0.9 g of potassium carbonate, and 0.25 g of potassium hydroxide in 50 ml of water was shaken for 5 min and then filtered. The filtrate contained *ca.* 12 mmol of potassium hypochlorite.[22] An additional 2.0 g (50 mmol) of potassium hydroxide was added and the resulting solution was stirred while 1.6 g (9.1 mmol) of 3,6-dimethylphthalimide was added. The phthalimide dissolved rapidly and the resulting solution was slowly heated to 50°. After 30 min, the mixture was acidified with a slight excess of acetic acid. The resulting solution was extracted with several portions of ether and combined extracts were worked up as usual to yield 1.3 g (87%) of 2-amino-3,6-dimethylbenzoic acid, mp 122–123°, mass spectrum *m/e* 165.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7. Found: C, 65.3; H, 6.5.

In a similar experiment **5** was recovered unchanged.[21]

Diazotization of 8.—A solution of 0.75 g (11 mmol) of sodium nitrite in 25 ml of water was added slowly to an ice-chilled mixture of 5 ml of concentrated hydrochloric acid and 1.65 g (10 mmol) of **8** in 25 ml of water. Addition was continued at 0–5° until a positive starch iodide test was obtained. To this mixture was added a solution of 1.8 g (11 mmol) of potassium iodide in 10 ml of water. Nitrogen evolved rapidly and the mixture was warmed slightly until no more gas evolution was observed. The mixture was transferred to a separatory funnel and extracted with five 100-ml portions of ether–benzene. The combined organic extracts produced after work-up 1.5 g (94%) of 3,6-dimethylsalicylic acid (4), mp 196–198° after recrystallization from benzene.[23]

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Registry No.—**3a**, 41174-77-0; **3b**, 41174-78-1; **4**, 41174-79-2; **5**, 40682-58-4; **6b**, 15540-88-2; **7**, 41174-82-7; **8**, 15540-91-7; diethyl α,β-diacetylsuccinate, 2049-86-7; 3,4-dicarbethoxy-2,5-dimethylfuran, 19434-69-6; tetraacetylethane, 5027-32-7; 3,4-diacetyl-2,5-dimethylfuran, 10599-72-1; anthranilic acid, 118-92-3; isoamyl nitrite, 110-46-3; 3,6-dimethylphthalic anhydride, 5463-50-3; urea, 57-13-6.

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[21] This experiment was performed by Mr. John Daniel.

[22] M. S. Newman and H. L. Holmes, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 428.

[23] J. E. Joachim de Luna, French Patent 940,846 (Dec 24, 1948).