Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.33; H, 8.68.

Acetylation of **7b** with acetic anhydride–pyridine yielded diacetate **7a**: m.p. and m.m.p. 212–217°; infrared (Nujol), C═O 5.63 (s) and 5.9 (s) μ; p.m.r., 3-proton singlets at 0.85 and 0.95 (C-4 methyls), 3-proton doublets at 1.12 and 1.19 (isopropyl methyls), 3-proton singlets at 2.21 (acetate methyls), and a 1-proton singlet at 6.92 p.p.m. (aromatic hydrogen).

***In Vitro* Formation of Rosmaricine.**—A solution of 350 mg. of carnosic acid diacetate in 100 ml. of ethylene chloride saturated with 30% aqueous ammonia was allowed to stand at room temperature in the dark with occasional shaking for 5 days. The organic layer was extracted three times with 5% sulfuric acid. The combined aqueous extracts were made basic with 5% aqueous ammonia and extracted with methylene chloride. The extract was washed three times with water, dried, and evaporated. The residue was acetylated immediately with acetic anhydride–pyridine. Usual work-up gave 150 mg. of a brown solid whose chromatography on 14 g. of silica (impalpable powder) and elution with hexane–ether mixtures yielded two triacetates, 68 mg. of rosmaricine triacetate, m.p. 215–219° (lit.[4] m.p. 217–219°), and its isomer, m.p. 286–287°. These compounds were identical with the triacetates derived from direct acetylation of crude rosmaricine.

***In Vitro* Formation of Carnosol.**—A solution of 150 mg. of carnosic acid in 5 ml. of methanol was allowed to stand in the dark at room temperature for 3 weeks, whereupon crystals had separated. They were identified as carnosol by melting point, mixture melting point, and infrared (Nujol) spectral comparison.

Rosemary Oleoresin Lactones.—A methanol solution of 5 g. of oleoresin was exposed to an excess of ethereal diazomethane. Chromatography of 3 g. of the resulting methylated resin on 130 g. of silica (impalpable powder) and elution with 25-ml. fractions of hexane–ether mixtures of increasing polarity yielded first a lactone whose crystallization from methanol and subsequent sublimation afforded colorless crystals of **5d**: m.p. 171°; $[\alpha]^{23}\mathrm{D}$ −5.0° (*c* 1.24); infrared (Nujol), C═O 5.64 (s) μ; p.m.r., 3-proton singlets at 0.95 and 1.00 (C-4 methyl), 3-proton doublets at 1.19 and 1.19 (isopropyl methyls), 3-proton singlets at 3.67, 3.78, and 3.80 (methoxy methyls), 1-proton singlet at 2.20 (C-5 H), 1-proton doublet at 4.28 (J = 3.0 c.p.s., C-7 H), 1-proton doublet at 4.72 (J = 3.0 c.p.s., C-6 H), and a 1-proton singlet at 6.97 p.p.m. (aromatic hydrogen).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.74; H, 8.08.

Later fractions yielded colorless crystals of **5a**, m.p. and m.m.p. 205–208°, spectra identical with **5a** prepared by deamination of rosmaricine.

Tetrasodio Bis-β-diketones. Dicondensations with Electrophilic Compounds[1]

K. GERALD HAMPTON AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

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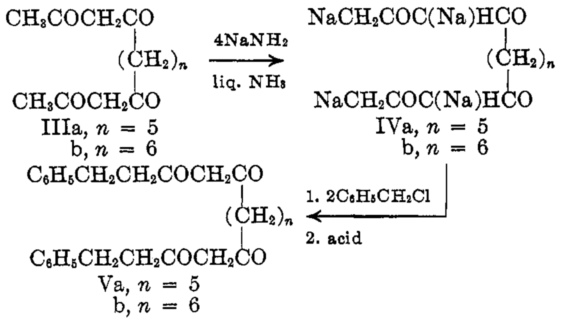
Certain bis-β-diketones of the type $(CH_3COCH_2CO)_2(CH_2)_n$ were converted by means of 4 mol. equiv. of sodamide in liquid ammonia to the corresponding tetrasodio salts, which were dialkylated with benzyl chloride to form the corresponding diterminal derivatives. One of the tetrasodio salts was also condensed at both terminal positions with methyl benzoate and benzophenone to give the corresponding diaroylation- and dialdol-type products, respectively. The diaroylation product was cyclized with ammonia to afford the dipyridone. Certain bis-β-diketones of the type $(C_6H_5COCH_2CO)_2(CH_2)_n$ were converted to their tetrasodio salts which were condensed with benzophenone or anisaldehyde to form, after treatment with methanolic acid, the dihydropyrones.

β-Diketones such as acetylacetone and benzoylacetone have previously been converted by 2 mol. equiv. of alkali amide in liquid ammonia to their dialkali salts I,[2,3] which were condensed with alkyl halides, aromatic esters, and aromatic ketones or aldehydes to form terminal derivatives. For example, I (R = CH_3, M = Na) was alkylated with benzyl chloride to give II.

$\mathrm{RCOC(M)HCOCH_2M}$ I $\quad$ $\mathrm{RCOCH_2COCH_2CH_2C_6H_5}$ II

Certain bis-β-diketones have now been converted by 4 mol. equiv. of sodamide in liquid ammonia to their tetrasodio salts, which were condensed with electrophilic compounds. Thus, bis-β-diketones IIIa, b were converted to IVa, b, which were dialkylated with benzyl chloride to afford diterminal derivatives Va, b in yields of 67 and 62%, respectively.



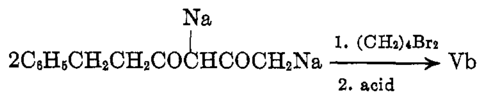
$$\begin{array}{c}\mathrm{CH_3COCH_2CO}\\ |\\ (\mathrm{CH_2})_n\\ |\\ \mathrm{CH_3COCH_2CO}\end{array} \xrightarrow[\text{liq. NH}_3]{4\mathrm{NaNH_2}} \begin{array}{c}\mathrm{NaCH_2COC(Na)HCO}\\ |\\ (\mathrm{CH_2})_n\\ |\\ \mathrm{NaCH_2COC(Na)HCO}\end{array} \xrightarrow[\text{2. acid}]{\text{1. }2\mathrm{C_6H_5CH_2Cl}} \begin{array}{c}\mathrm{C_6H_5CH_2CH_2COCH_2CO}\\ |\\ (\mathrm{CH_2})_n\\ |\\ \mathrm{C_6H_5CH_2CH_2COCH_2CO}\end{array}$$

IIIa, n = 5
b, n = 6

IVa, n = 5
b, n = 6

Va, n = 5
b, n = 6

Structures Va, b were supported by analysis and confirmed by independent synthesis (of Vb) involving twofold alkylation of disodio β-diketone VI with 1,4-dibromobutane as described recently.[4]



$$2\mathrm{C_6H_5CH_2CH_2CO}\overset{\mathrm{Na}}{\overset{|}{\mathrm{C}}}\mathrm{HCOCH_2Na} \xrightarrow[\text{2. acid}]{\text{1. }(\mathrm{CH_2})_4\mathrm{Br_2}} \mathrm{Vb}$$

VI

Tetrasodio salt IVa was treated with 1,3-dibromopropane to afford apparently poly(1,3-octanedione) (VII), the molecular weight of which indicated that n had an average value of 12–13.

$$\mathrm{+COCH_2CO(CH_2)_5+}_n$$

VII

Tetrasodio salt IVa was diaroylated with methyl benzoate to give bis-β-triketone VIII in 30% yield; this reaction was effected in the presence of sodamide.[5]

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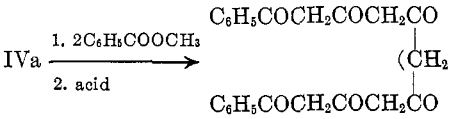
(1) Supported by the Army Research Office (Durham).

(2) (a) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958); (b) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960); (c) *ibid.*, **26**, 1716 (1961); (d) K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **30**, 61 (1965).

(3) Such multiple dialkali salts have been employed without isolation; their carbanion resonance forms have generally been represented even though other resonance forms may make more important contributions to the structure of the anions.

(4) K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965).

(5) See S. D. Work and C. R. Hauser, *ibid.*, **28**, 725 (1963).

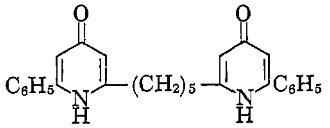


$$\mathrm{IVa} \xrightarrow[\text{2. acid}]{\text{1. } 2C_6H_5COOCH_3} \begin{array}{l} C_6H_5COCH_2COCH_2CO \\ \qquad\qquad\quad (CH_2)_5 \\ C_6H_5COCH_2COCH_2CO \end{array}$$

VIII

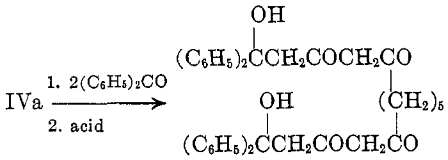
The diterminal benzoylation of bis-β-diketone IIIa was also effected with methyl benzoate and sodium hydride in refluxing 1,2-dimethoxyethane (monoglyme), but the yield of VIII was only 19%.[6]

Structure VIII was established by analysis and by cyclization with ammonia to form dipyridone IX in 87% yield. Structure IX was supported by analysis and ultraviolet spectrum, which showed λ_{max} 238 mμ (log ε 4.72), characteristic of 4-pyridones.[2b,5]



IX

Tetrasodio salt IVa underwent a twofold addition reaction with benzophenone to form diterminal adduct X in 50% yield.

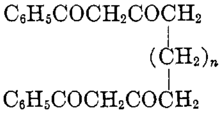


$$\mathrm{IVa} \xrightarrow[\text{2. acid}]{\text{1. } 2(C_6H_5)_2CO} \begin{array}{l} \qquad\quad OH \\ (C_6H_5)_2CCH_2COCH_2CO \\ \qquad\quad OH \qquad\ (CH_2)_5 \\ (C_6H_5)_2CCH_2COCH_2CO \end{array}$$

X

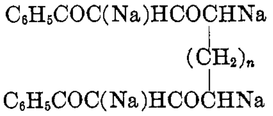
Structure X was supported by analysis, molecular weight, and infrared spectrum which showed a peak at 2.91 μ for the hydroxyl group.[2c,7]

Next, bis-β-diketones XIa, b were converted by 4 mol. equiv. of sodamide to their tetrasodio salts XIIa, b, which were condensed with benzophenone and anisaldehyde, respectively, to form presumably the corresponding diadduct. Since the adducts failed to crystallize readily, they were treated with methanolic hydrochloric acid to give apparently bisdihydropyrones XIIIa, b in over-all yields of 72 and 31%, respectively.



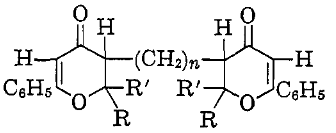
$$\begin{array}{l} C_6H_5COCH_2COCH_2 \\ \qquad\qquad\quad (CH_2)_n \\ C_6H_5COCH_2COCH_2 \end{array}$$

XIa, n = 3
b, n = 4



$$\begin{array}{l} C_6H_5COC(Na)HCOCHNa \\ \qquad\qquad\qquad (CH_2)_n \\ C_6H_5COC(Na)HCOCHNa \end{array}$$

XIIa, n = 3
b, n = 4

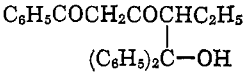


XIIIa, $n = 3$; $R,R' = C_6H_5$
b, $n = 4$; $R = H$; $R' = C_6H_4OCH_3$-p

That the product from tetrasodio salt XIIa and benzophenone was bisdihydropyrone XIIIa was supported by the n.m.r. spectrum. This spectrum showed a multiplet of peaks between 7.1 and 8.0 p.p.m. (30 protons) for the aromatic protons, a singlet at 5.80 p.p.m. (two protons) for the vinyl protons, a broad band at 3.15 p.p.m. (two protons) for the tertiary protons, and a broad peak centered at 1.22 p.p.m. (six protons) for the methylene protons. Had the product been the possible unsaturated bis-β-diketone corresponding to unsaturated β-diketone XVIII (see below), the spectrum should not have shown the peak for the tertiary protons. Had the product been the unsaturated bis-β-diketone corresponding to unsaturated β-diketone XIX, the spectrum should have shown eight methylene protons and no tertiary or vinyl protons. By analogy, the product from tetrasodio salt XIIb and anisaldehyde would be the bisdihydropyrone XIIIb.

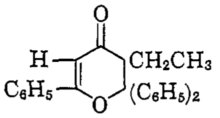
Since such an aldol-type condensation at the less acidic of two active methylene groups of a simple β-diketone has not previously been reported,[8] β-diketone XIV was converted by 2 mol. equiv. of sodamide in liquid ammonia to disodio salt XV, which was treated with benzophenone to give adduct XVI in 67% yield. The structure of this product was supported by analysis, by an infrared peak at 2.80 μ for the hydroxyl group,[2c,7] and by dehydration with methanolic acid to form apparently dihydropyrone XVII in 68% yield.

$C_6H_5COCH_2COCH_2C_2H_5$ XIV $\qquad$ $C_6H_5COC(Na)HCOC(Na)HC_2H_5$ XV

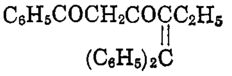


$$\begin{array}{l} C_6H_5COCH_2COCHC_2H_5 \\ \qquad\quad (C_6H_5)_2C{-}OH \end{array}$$

XVI

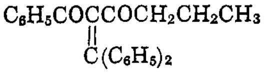


XVII



$$\begin{array}{l} C_6H_5COCH_2COCC_2H_5 \\ \qquad\qquad\ \| \\ \qquad\quad (C_6H_5)_2C \end{array}$$

XVIII



$$\begin{array}{l} C_6H_5COCCOCH_2CH_2CH_3 \\ \qquad\quad \| \\ \qquad\quad C(C_6H_5)_2 \end{array}$$

XIX

The dihydropyrone structure XVII was supported by a negative enol test with methanolic ferric chloride and by n.m.r. spectrum. This spectrum showed a multiplet of peaks between 7.1 and 8.0 p.p.m. (15 protons) for the aromatic protons, a singlet at 5.88 p.p.m. (one proton) slightly split for the vinyl proton, a quartet centered at 3.22 p.p.m. (one proton) for the tertiary proton, a multiplet centered at 1.42 p.p.m. (two protons) for the methylene group, and a triplet (three protons) centered at 0.85 p.p.m. for the methyl group. Had the product been the corresponding unsaturated β-diketone XVIII, it would presumably have given a positive enol test and its n.m.r. spectrum should not have shown the tertiary proton peak. Although the possible unsaturated β-diketone XIX would not have given an enol test, the n.m.r. spectrum should not have shown the vinyl or tertiary proton peaks while it should have shown four methylene protons. Moreover, XIX seems unlikely since condensations through dicarbanions do not generally occur at the more acidic hydrogen of the original β-diketone. Incidentally, bisdihydropyrone XIIIa also gave a negative enol test but, because of its insolubility, this observation has not been used as evidence of the structure.

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(6) In contrast to sodamide, sodium hydride may convert bis-β-diketone IIIa only to its disodio salt, as it appears to convert benzoylacetone only to its monosodio salt even though it effects the benzoylation of this β-diketone in better yield than an alkali amide: M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965).

(7) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd. Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 95.

(8) For aldol-type condensations at the terminal methyl group of simple β-diketones, see ref. 2c.

Discussion

The scope of the three types of dicondensations illustrated above could presumably be extended considerably. Thus, not only should other tetrasodio bis-β-diketones undergo such condensations, but other alkyl halides, aromatic esters, and aromatic ketones or aldehydes should also be suitable for the dialkylations, diaroylations, and dicarbonyl additions, respectively. Moreover, other types of dicondensations may be realizable. The starting bis-β-diketones used in the preparation of the tetrasodio salts such as IVa, b and XIa, b are readily synthesized by coupling two molecules of acetylacetone or benzoylacetone with 1,3-dibromopropane or higher methylene halides.[4]

Experimental[9]

Tetrasodio Bis-β-diketones IVa and b.—Tetrasodio salt IVa was prepared by addition of 0.05 mole of solid bis-β-diketone IIIa[4] from an erlenmeyer flask through Gooch tubing to a stirred suspension of 0.20 mole of sodamide[10] in commercial, anhydrous liquid ammonia. After 1 hr., the tetrasodio salt (assumed to be 0.05 mole) was employed as described below.

Similarly tetrasodio salt IVb was prepared from bis-β-diketone IIIb[4] and sodamide in liquid ammonia.

Dibenzylation of Tetrasodio Salts IVa and b.—To a stirred suspension of 0.05 mole of salt IVa in 700 ml. of liquid ammonia was added, during 15 min., 0.10 mole of benzyl chloride in 20 ml. of ether. After 2 hr., the ammonia was evaporated on the steam bath as 300 ml. of dry ether was added. The ethereal suspension was cooled (ice bath), and a mixture of 100 g. of ice and 30 ml. of cold, concentrated hydrochloric acid was added with stirring. The two layers were separated. The ethereal layer (which was combined with three ethereal extracts of the aqueous layer) was dried with anhydrous magnesium sulfate. After filtering, the ethereal solution was evaporated. The residue was recrystallized from methanol to afford 14 g. (67%) of 1,15-diphenyl-3,5,11,13-pentadecanetetrone (Va), m.p. 44.5–45.5°.

Anal. Calcd. for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 77.10; H, 7.69.

Similarly, dibenzylation of 0.05 mole of tetrasodio salt IVb in 400 ml. of liquid ammonia was effected. The product was recrystallized from methanol–ethanol to afford 13.4 g. (62%) of 1,16-diphenyl-3,5,12,14-hexadecanetetrone (Vb), m.p. 48.5–50°, undepressed on admixture with a sample of Vb prepared as described recently.[4]

Treatment of Tetrasodio Salt IVa with Trimethylene Bromide.—To a stirred solution of 0.025 mole of salt IVa in 700 ml. of liquid ammonia was added, during 10 min., 5.05 g. (0.025 mole) of 1,3-dibromopropane in 20 ml. of ether. The reaction mixture was worked up essentially as described above for the dibenzylation of salt IVa to afford, after recrystallization from benzene, 2.7 g. of apparently poly(1,3-octanedione) (VII), m.p. 87–89°, a sample of which gave a negative sodium fusion test for bromine.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63; mol. wt., 140. Found: C, 68.53; H, 8.75; mol. wt., 1800.

Dibenzoylation of Tetrasodio Salt IVa.—To a stirred suspension of 0.33 mole of sodamide in 700 ml. of liquid ammonia was added 12 g. (0.05 mole) of bis-β-diketone IIIa, followed, after 1 hr., by 15 g. (0.11 mole) of methyl benzoate in 20 ml. of ether. After 1 hr., the reaction mixture was worked up as described above for the dibenzylation of salt IVa to afford, after recrystallization from methanol, 6.6 g. (30%) of 1,15-diphenyl-1,3,5,11,13,15-pentadecanehexone (VIII), m.p. 84–85°.

Anal. Calcd. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.45; H, 6.42.

To 1 g. of bistriketone VIII suspended in 50 ml. of commercial, absolute ethanol was added commercial, anhydrous liquid ammonia until the flask was cold. The resulting solution was evaporated on the steam bath. The oily residue was dissolved in 50 ml. of absolute ethanol, and liquid ammonia was again added until the flask was cold. The solution was allowed to stand at room temperature until the ammonia evaporated (12 hr.) to precipitate 0.8 g. (87%) of crystalline dipyridone IX, m.p. 243–244°.

Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.83. Found: C, 79.06; H, 6.20; N, 6.83.

Dibenzoylation of Bis-β-diketone IIIa by Sodium Hydride.—A stirred mixture of 12.0 g. (0.05 mole) of bis-β-diketone IIIa, 13.6 g. (0.10 mole) of methyl benzoate, and 0.33 mole of sodium hydride in 200 ml. of 1,2-dimethoxyethane was refluxed for 23 hr. under nitrogen. The solvent was removed under reduced pressure. After cooling, the residue was treated with 100 ml. of ether and 100 ml. of ice water (added dropwise). The layers were separated. The aqueous layer was combined with three alkali (1 *N*) extracts of the ethereal layer and acidified with cold dilute hydrochloric acid. The resulting precipitate was collected and recrystallized from methanol to afford 4.35 g. (19%) of bistriketone VIII, m.p. 84–85°. The melting point was undepressed on admixture with a sample of VIII prepared as described above.

Dialdol Condensation of Tetrasodio Salt IVa with Benzophenone.—To a stirred solution of 0.025 mole of salt IVa in 600 ml. of liquid ammonia was added 9.1 g. (0.05 mole) of benzophenone in 50 ml. of ether. After 1 hr., the reaction mixture was poured *into a solution of 15 g. of ammonium chloride in 200 ml. of liquid* ammonia. The resulting mixture was poured back into the original three-necked reaction flask, and 250 ml. of ether was added. The ammonia was evaporated on the steam bath. The resulting ethereal suspension was cooled in ice, and a mixture of ice and hydrochloric acid was added. The ethereal layer was separated, and the aqueous layer was extracted three times with ether. The combined ethereal solution was dried with Drierite, filtered, and evaporated. The residue was recrystallized from ethanol to afford 7.52 g. (50%) of 1,1,15,15-tetraphenyl-1,15-dihydroxy-3,5,11,13-pentadecanetetrone (VII), m.p. 105–106°.

Anal. Calcd. for $C_{39}H_{40}O_6$: C, 77.46; H, 6.67; mol. wt., 605. Found: C, 77.42; H, 6.52; mol. wt., 580.

Tetrasodio Bis-β-diketones XIIa and b. Dialdol Condensations.—Tetrasodio salt XIIa (0.025 mole) was prepared from 0.025 mole of bis-β-diketone XIa[4] and 0.1 mole of sodamide in 400 ml. of liquid ammonia (stirred 30 min.) as described for tetrasodio salt IVa. To the stirred suspension of salt XIIa was added, during 5 min., 9.1 g. (0.05 mole) of benzophenone in 50 ml. of ether. After 1 hr., the reaction mixture was neutralized inversely with ammonium chloride and worked up as described above for the dialdol condensation of salt IVa with benzophenone. The oily residue obtained on evaporation of the ethereal solution of the product was dissolved in methanol, and 10 ml. of concentrated hydrochloric acid was added. The solution was refluxed for 35 min. The resulting mixture was cooled and filtered. The solid was recrystallized from chloroform–ethanol to give 12.6 g. (72%) of 1,3-bis-3-(2,3-dihydro-2,2,6-triphenylpyran-4-one)propane (XIIIa), m.p. 284–285° uncor. (taken on a Mel-Temp apparatus).

Anal. Calcd. for $C_{49}H_{40}O_4$: C, 84.94; H, 5.82. Found: C, 84.69; H, 5.84.

Similarly, tetrasodio salt XIIb was prepared and condensed with anisaldehyde to afford, after treatment of the product with methanolic acid and recrystallization from chloroform–ethanol, 4.77 g. (31%) of 1,4-bis-3-[2,3-dihydro-2-(4-methoxyphenyl)-6-phenylpyran-4-one]butane (XIIIb), m.p. 140–141°.

Anal. Calcd. *for* $C_{40}H_{38}O_6$: C, 78.15; H, 6.23. Found: C, 77.85; H, 6.43.

Disodio Salt XV. Aldol Condensation.—Disodio salt XV (0.05 mole) was prepared from 0.05 mole of 1-phenyl-1,3-hexanedione[11] (XIV) and 0.1 mole of sodamide in 400 ml. of liquid ammonia (stirred 30 min.). To the stirred suspension of salt XIV was added, during 5 min., 9.1 g. (0.05 mole) of benzophenone in 40 ml. of ether. After 1 hr., the reaction mixture was worked up as described for the dialdol condensation of salt IVa with benzophenone to give, on recrystallization of the product from meth-

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[9] Melting points were taken on a Thomas–Hoover melting point apparatus in open capillary tubes and are corrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn., Dr. I. A. Schoeller, Mikro-Labor, Kronach, West Germany, and Triangle Chemical Laboratories Inc., Chapel Hill, N. C. Infrared spectra were obtained with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method for solids. The ultraviolet spectrum was determined with a Cary Model 14 recording spectrophotometer using a 2×10^{-5} *M* solution in methanol with a 1-cm. cell. N.m.r. spectra were obtained from deuteriochloroform solutions with tetramethylsilane as internal standard using a Varian A-60 spectrometer.

[10] See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

[11] J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 284 (1945).

anol, 12.5 g. (67%) of 1-phenyl-4-(diphenylhydroxymethyl)-1,3-hexanedione (XVI), m.p. 130–131°.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.62; H, 6.50. Found: C, 80.93; H, 6.70.

A solution of 1 g. of aldol XVI in 15 ml. of methanol and 5 ml. of concentrated hydrochloric acid was refluxed for 1 hr. The resulting mixture was cooled and filtered. The solid was recrystallized from 95% ethanol to afford 0.63 g. (68%) of 2,3-dihydro-3-ethyl-2,2,6-triphenylpyran-4-one (XVII), m.p. 165–166°.

Anal. Calcd. for $C_{25}H_{22}O_2$: C, 84.71; H, 6.26. Found: C, 84.60; H, 6.33.

Alkylations of Phenylacetic, α-Alkylphenylacetic, and Diphenylacetic Esters by Means of Sodamide and Sodium Hydride[1]

WILLIAM G. KENYON, EDWIN M. KAISER, AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

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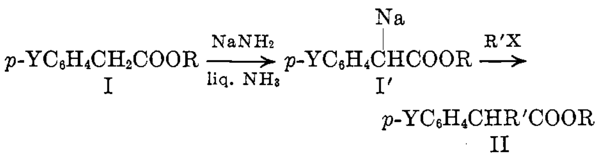
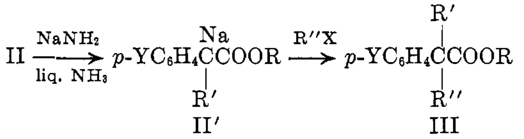
Various alkylations of ethyl and *t*-butyl phenylacetates with alkyl halides and further alkylations of the resulting α-alkylphenylacetic esters were effected by means of sodamide in liquid ammonia. The method was successful even with *p*-chloro- and *p*-methoxyphenylacetic esters and with *p*-chlorobenzyl chloride. Typical alkylations were also effected by means of sodium hydride in refluxing monoglyme. Sodamide was preferable for monoalkylations of ethyl or *t*-butyl phenylacetates, but the two reagents were about equally effective for further alkylations of α-alkylphenylacetic esters. Sodium hydride was better for dialkylation of ethyl phenylacetate with the same halide in a single operation. The present methods were superior to earlier methods. Also the present methods appear useful for the synthesis of certain mono- and dialkylarylacetic acids, which were obtained on hydrolysis of the alkylated esters. Ethyl diphenylacetate was alkylated with certain halides by means of sodamide in liquid ammonia.

Alkylations of ethyl phenylacetate with alkyl halides have recently[2,3] been effected by means of sodamide in liquid ammonia in much better yields than had been obtained previously with other reagents.[4] The method, which was applicable also to *t*-butyl phenylacetate, involved addition of the ester to a molecular equivalent of the reagent, followed by a molecular equivalent of the halide (eq. 1, Y = H, R = ethyl or *t*-butyl).



$$\underset{\text{I}}{p\text{-}YC_6H_4CH_2COOR} \xrightarrow[\text{liq. }NH_3]{NaNH_2} \underset{\text{I}'}{p\text{-}YC_6H_4\overset{Na}{C}HCOOR} \xrightarrow{R'X} \underset{\text{II}}{p\text{-}YC_6H_4CHR'COOR} \qquad (1)$$

The sodamide reagent has now been found suitable not only for other monoalkylations of I (eq. 1) but also for further alkylations of the resulting α-alkylphenylacetic esters II with the same or different halide to form III (eq. 2), none of which appear to have been reported previously with any reagent.[4]



$$\text{II} \xrightarrow[\text{liq. }NH_3]{NaNH_2} \underset{\text{II}'}{p\text{-}YC_6H_4\overset{Na}{\underset{R'}{C}}COOR} \xrightarrow{R''X} \underset{\text{III}}{p\text{-}YC_6H_4\overset{R'}{\underset{R''}{C}}COOR} \qquad (2)$$

The results are summarized in Tables I–III. The data in Tables I and II, including the yields, were based on distilled or recrystallized products, most of which were indicated to be pure by v.p.c. (single peak) or sharp melting point. The n.m.r. spectra presented in Table III are in agreement with the structures presented.

Table I shows that the yields of the five new monoalkylations (eq. 1) were 76–89%, which are comparable with those of 10 earlier cases.[2] Interestingly, the sodamide reagent was suitable with the *p*-chlorophenylacetic ester and with *p*-chlorobenzyl chloride, with which the benzyne type of reaction was possible. Also the reagent was a sufficiently strong base to produce the required intermediate I′ (see eq. 1) from the *p*-methoxyphenylacetic ester, which would presumably be less acidic than the unsubstituted ester.

Although the distilled or recrystallized products II were generally pure (see above), certain of the crude products were indicated by v.p.c. to be contaminated with small amounts (5–10%) of the corresponding dialkyl derivatives III (R′ = R″) and starting ethyl or *t*-butyl phenylacetate (I).[5] The two latter compounds presumably arose through equilibration of intermediate sodio salt I′ with sodio salt II′, which underwent further alkylation (eq. 3).

$$\text{I}' + \text{II} \rightleftharpoons \text{I} + \text{II}' \xrightarrow{R'X} \text{III}\ (R' = R'') \qquad (3)$$

Actually, with the exception of three methylation products, the alkyl derivatives II reported previously[2] and in Table I contained an R′ group that had four or more carbon atoms so that they were separated readily from the dialkyl derivative III (R′ = R″) and starting ester I by distillation or recrystallization. Even the distilled methylation products of ethyl *p*-methoxyphenylacetate and *t*-butyl phenylacetate appeared to be essentially pure; the former was indicated to be pure by n.m.r. spectrum and analysis, and the latter by v.p.c. although the n.m.r. spectrum suggested a trace of impurity (see Table III). Moreover, the distilled monomethylation product of ethyl phenylacetate that was obtained recently[2] contaminated with 2–3% of

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[1] This investigation was supported by the U. S. Army Research Office (Durham) and by Public Health Service Research Grant No. USPHS CA04455-06.

[2] W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

[3] The alkylation of ethyl phenylacetate with β-phenylethyl bromide was then effected on a 0.05-mole scale in 87% yield in 10 hr. This reaction has now been accomplished on a 0.1-mole scale in yields of 77–82% in 3 hr.

[4] See A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 284 (1957); A. L. Mndzhoyan, O. L. Mndzhoyan, E. R. Bagdasaryan, and V. A. Mnatsakanyan, *Dokl. Akad. Nauk Arm. SSR*, **30**, 97 (1960); *Chem. Abstr.*, **55**, 3508*h* (1961).

[5] The molar ratios of II:III:I from the benzylations of ethyl phenylacetate and ethyl *p*-chlorophenylacetate and from *p*-chlorobenzylation of ethyl phenylacetate were 90:7:3, 83:13:4, and 83:8:9, respectively.