[CONTRIBUTION NO. 669 FROM THE CHEMISTRY DEPARTMENT OF INDIANA UNIVERSITY]

The Synthesis of Spiro[cycloalkyl-1,2′-tetralins]

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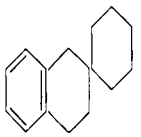
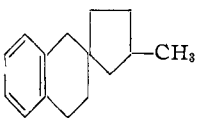
Spiro-[cycloalkyl-1,2′-tetralins] have been synthesized by the cyclization of the appropriate 2,2-disubstituted tetralins which were obtained from the alkylation of 2-carbomethoxy-1-tetralone. A study of the optimum conditions for the alkylation of the above β-keto ester is reported. The Wagner–Meerwein rearrangement of 2,2-disubstituted-1-tetralols was attempted without success.

The synthesis of spiro[cycloalkyl-1,2′-tetralins] has been accomplished by Sen-Gupta.[4] He treated the anhydrides of 1-carboxy-1-cyclohexaneacetic acid and of 1-carboxy-1-cyclopentaneacetic acid with benzene and its homologs in a Friedel–Crafts reaction. Subsequently, the steps of the Haworth synthesis led to substituted 1-tetralones which upon reduction gave the desired hydrocarbons. Of immediate interest to this publication were his syntheses of 3′,4′-dihydrospiro-[cyclohexane-1,2′-(1′H)-naphthalene] (I), and of 3-methyl-3′,4′-dihydrospiro-[cyclopentane-1,2′(1′H)naphthalene] (II).



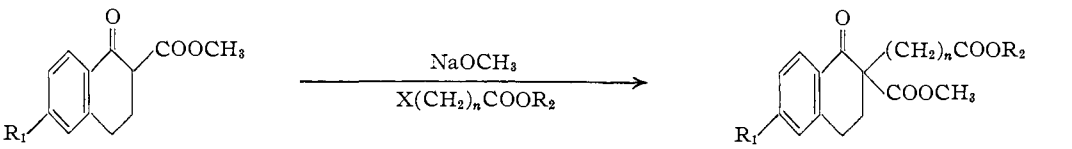
I



II

It was of interest to us to investigate a synthetic route which would lead to similar compounds having a carbonyl function in the cycloalkyl ring.

Reaction of 2-carbomethoxy-1-tetralone (IIIa) with ω-halogenated esters in the presence of sodium methoxide led to the disubstituted β-keto esters IV.



IIIa, R_1 = H
b, R_1 = OCH_3

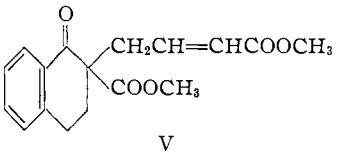
a, X = Cl, n = 0, R_2 = C_2H_5
b, X = Br, n = 1, R_2 = CH_3
c, X = Br, n = 2, R_2 = CH_3
d, X = I, n = 3, R_2 = CH_3
e, X = I, n = 4, R_2 = CH_3

IVa, R_1 = H, n = 0, R_2 = C_2H_5
b, R_1 = H, n = 1, R_2 = CH_3
c, R_1 = H, n = 2, R_2 = CH_3
d, R_1 = H, n = 3, R_2 = CH_3
e, R_1 = H, n = 4, R_2 = CH_3
f, R_1 = OCH_3, n = 0, R_2 = C_2H_5
g, R_1 = OCH_3, n = 3, R_2 = CH_3

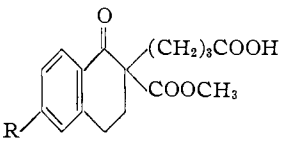
Because of the difficulties experienced in the alkylation reaction, a collateral investigation was launched to determine the best conditions for its accomplishment. As previously reported[5] the alkylation with methyl bromoacetate (n = 1) and with methyl β-bromopropionate (n = 2) proceeds satisfactorily by refluxing a mixture of the β-keto ester IIIa with sodium methoxide, methyl alcohol, benzene and the bromo ester. In the case where n = 0, the highly reactive nature of the halogen in ethyl chloroformate required that the reaction be carried out in an alcohol-free medium.[6] In the cases where n = 3 and 4 it was found that the bromo esters were very sluggish in reaction. Satisfactory yields of the disubstituted β-keto esters (IVd, e and g) could only be obtained by the use of the more reactive iodo esters in an alcohol-free medium. The most satisfactory conditions for the reaction involved slow distillation of benzene from the stirred suspension of the β-keto ester III and dry sodium methoxide in dry benzene. In this way, methanol resulting from the formation of the sodio derivative of the β-keto ester was removed as the benzene–methanol azeotrope. The mixture was then refluxed with an excess of the halogenated ester until a test portion in water did not give a color with phenolphthalein. A marked lowering of the yield was always noted if the alcohol was not removed.

It was found that anhydrous diethyl carbonate was a satisfactory substitute for benzene in the preparation of 2-carbomethoxy-1-tetralone-2-γ-crotonate (V).

Inasmuch as the 2-carbomethoxy group is hindered, saponification of the disubstituted β-keto esters with the calculated amount of base, or brief hydrolysis with a mixture of hydrochloric acid and acetic acid, gave the acid esters VI.



V



VIa, R = H
b, R = OCH_3

Extended hydrolysis was accompanied by decar-

(1) Chemistry Department, Kansas State College, Manhattan, Kansas.

(2) Portions of this material were taken from the Ph.D. dissertation of William B. Lindsey.

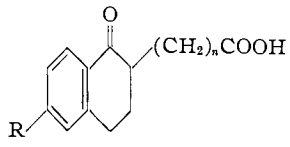
(3) Portions of this material were taken from the Master's degree dissertation of Beatrice R. Jones.

(4) S. C. Sen-Gupta, *J. Indian Chem. Soc.*, **19**, 467 (1942); *Science and Culture*, **17**, 93 (1951).

(5) W. E. Bachmann and G. D. Johnson, THIS JOURNAL, **71**, 3463 (1949).

(6) A. Pinner, *Ber.*, **22**, 2617 (1889).

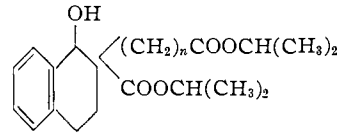
boxylation of the intermediate β-keto acid and produced the keto acid VII.



VIIa, R = H, n = 3
b, R = H, n = 4
c, R = OCH_3, n = 3

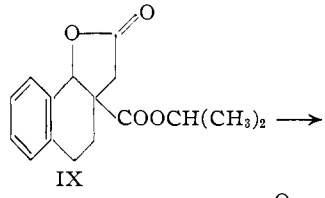
Removal of the ketonic oxygen from the disubstituted β-keto esters IV was best accomplished by the use of the Meerwein–Ponndorf reduction followed by reduction to the hydrocarbon with red phosphorus and iodine in aqueous acetic acid.[7]

The Meerwein–Ponndorf reduction was accomplished in good yield but required 1.5 to two days to go to completion. As would be expected, complete transesterification took place with the formation of the tetralols VIII. With the exception of the product VIIIa, all of the substituted tetralols

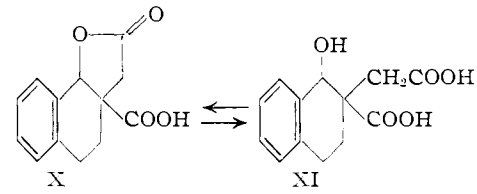


VIIIa, n = 1 c, n = 3
b, n = 2 d, n = 4

were liquids. The reduction of methyl 2-carbomethoxy-1-tetralone-2-acetate (IVb) gave 27% of the tetralol VIIIa together with 55% of the lactone IX. The ester VIIIa was converted to the lactone IX in nearly quantitative yield by heating the ester in a solution of hydrogen bromide in acetic acid. Saponification of the lactone in aqueous



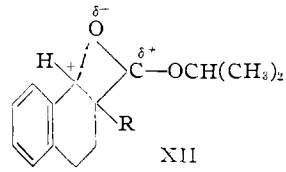
IX



X XI

potassium hydroxide gave the acid lactone X. This lactone could be converted to a dibasic acid (probably XI) by saponification in isopropyl alcohol followed by careful acidification. All attempts to crystallize the acid XI led to the formation of the acid lactone X. Models indicate that the lactone can only be formed if the acetic acid moiety and the hydroxy group are *cis* to each other.

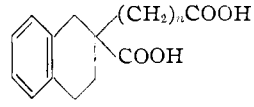
It had been hoped that the tetralols (VIII) would undergo the Wagner–Meerwein rearrangement to form 1,2-disubstituted-3,4-dihydronaphthalenes. However, none of the reagents tried (zinc chloride, sulfuric acid or potassium bisulfate) were found effective. The inability of the tetralols to rearrange may be explained on the grounds that the carbonium ion intermediate XII is stabilized by



XII

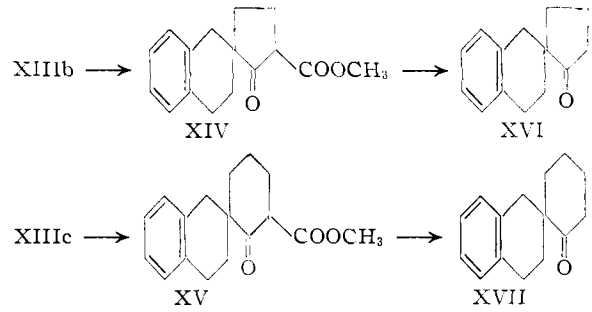
the resonance structure of the ester in the manner indicated. In addition, if the hydroxyl group and the R group of the other Meerwein–Ponndorf products are on the same side as has been shown to be the case in the sequence IX–XI, the favored rearward attack of the R group on the α-position cannot take place.

Following reduction of the tetralols VIII with red phosphorus and iodine, hydrolysis of the resulting esters gave the acids XI.



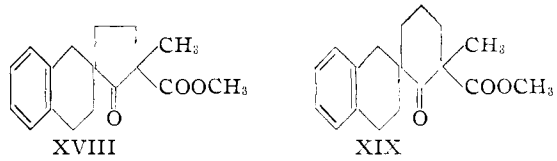
XIIIa, n = 2
b, n = 3
c, n = 4

Esterification of the acids XIII followed by a Dieckmann cyclization gave the β-keto esters of the desired spirans (XIV and XV). Two isomers were obtained in the case of XIV, about 80% of the material being the lower melting isomer. No isomers were detected in other instances because the products were liquids.



Hydrolysis of the β-keto esters (XIV and XV) gave the spiranones (XVI and XVII). Clemmensen reduction of XVII produced the spiran I whose boiling point and refractive index agreed with the values reported by Sen-Gupta.[4]

Alkylation of the β-keto esters (XIV and XV) with methyl iodide gave the disubstituted β-keto esters (XVIII and XIX).

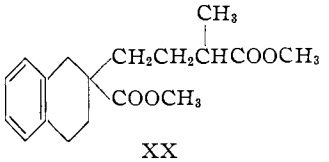


XVIII XIX

During an attempt to form the β-keto ester XIV followed by methylation in the same reaction mixture, the disubstituted β-keto ester XVIII was not obtained. Instead, a compound was obtained whose analytical data and that of its hydrolysis product best fitted the structure methyl 2-carbomethoxytetralin-2-γ-(α-methylbutyrate) (XX). This product may have resulted from fission of the initially formed β-keto ester XVIII, due to the

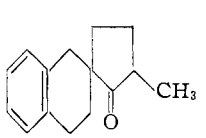
(7) C. S. Marvel, F. D. Hager and E. C. Caudle in H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 224.

prolonged refluxing time in the presence of methanol.

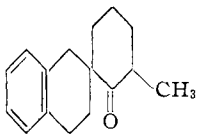


XX

Hydrolysis of XVIII and XIX produced the spiranones (XXI and XXII).



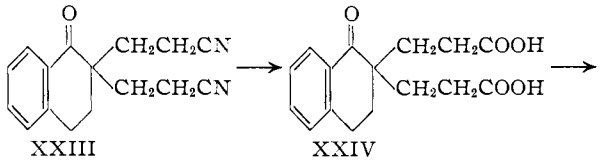
XXI



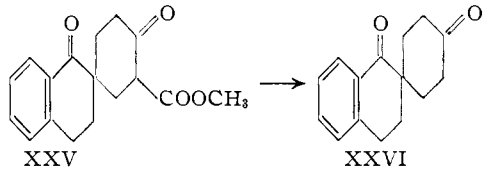
XXII

Clemmensen reduction of XXI produced the spiran II whose boiling point agreed closely with that reported by Sen-Gupta.[4]

Earlier, an alternate sequence of reactions leading to the spiran (I) had been investigated.[3] The dicyanoethylation of α-tetralone has been reported by Bruson.[8] Hydrolysis of this product XXIII gave the diacid XXIV. Esterification of XXIV



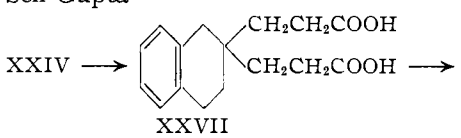
XXIII XXIV



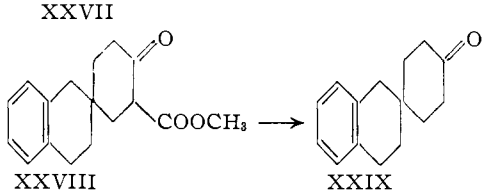
XXV XXVI

followed by a Dieckmann cyclization gave the β-keto ester XXV which upon hydrolysis was converted to the diketone XXVI.

An alternative route to the spiran stemmed from a Clemmensen reduction of XXIV which gave the diacid XXVII. Cyclization of the corresponding diester gave the product XXVIII, which upon hydrolysis gave the spiranone XXIX. Both spiranones (XXVI and XXIX) gave the spiran I upon Clemmensen reduction. The boiling point and refractive index agree with the values reported by Sen-Gupta



XXVII



XXVIII XXIX

Experimental

β-Keto Esters.—2-Carbomethoxy-1-tetralone (IIIa) was prepared according to the procedure of Bachmann and Thomas,[9] except that the crude product was distilled before crystallization, b.p. 115° (0.5 mm.). 6-Methoxy-2-carbomethoxy-1-tetralone (IIIb) was prepared by the method of the same authors.

ω-Halogen Esters.—Saturation of γ-butyrolactone with anhydrous hydrogen bromide at 150°, following the procedure of Henry,[10] gave γ-bromobutyric acid. The acid was esterified with methanol and sulfuric acid. Treatment of the ester with sodium iodide in acetone gave methyl γ-iodobutyrate.[11] Methyl δ-iodovalerate was made following the procedure of the same authors. Methyl γ-bromocrotonate was prepared by the method of Ziegler, *et al.*[12]

Alkylation Procedures.—Methyl 2-carbomethoxy-1-tetralone-2-acetate (IVb) and methyl 2-carbomethoxy-1-tetralone-2-β-propionate (IVc) were prepared by the method of Bachmann and Johnson.[5]

The alkylation reactions using ethyl chloroformate, methyl γ-iodobutyrate or methyl δ-iodovalerate were performed in the absence of methanol. The method is illustrated with the preparation of 2-carbethoxy-2-carbomethoxy-1-tetralone (IVa). Dry sodium methoxide from 1.5 g. (0.065 atom) of sodium was prepared in a three-necked flask equipped with a stirrer and a reflux condenser and protected from moisture. A solution of 11.7 g. (0.057 mole) of the β-keto ester IIIa in 60 ml. of dry benzene was added to the powdered alkoxide, and the mixture was refluxed overnight with stirring. The water was removed from the condenser jacket and the methanol–benzene azeotrope was allowed to distill slowly through the condenser until the temperature rose from 58 to 78°. The original volume was maintained bythe addition of dry benzene. Ethyl chloroformate (10.3 g., 0.095 mole) was added, and the mixture was refluxed for 30 minutes. At the end of this time, a sample of the mixture when added to water, gave no reaction with phenolphthalein. The precipitated sodium chloride was filtered with suction, washed with anhydrous ether and the filtrates were combined. The solvents and excess ethyl chloroformate were removed by distillation under reduced pressure. Crystallization was effected by chilling a methanol solution of the oily residue. There resulted 10 g. (63%) of **2-carbethoxy-2-carbomethoxy-1-tetralone (IVa)**, m.p. 48–51°. Crystallization of a sample from methanol gave colorless needles, m.p. 52.5–54°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found: C, 65.11; H, 6.00.

In like manner, the reaction of ethyl chloroformate with IIIb during 15 minutes gave 46% of **2-carbethoxy-2-carbomethoxy-6-methoxy-1-tetralone (IVf)**, m.p. 76–78°. Crystallization of a sample from methanol afforded colorless prisms, m.p. 77–78°.

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.78; H, 5.96.

From methyl γ-iodobutyrate, sodium methoxide and IIIa, after refluxing 48 hours, was obtained 79% of **methyl 2-carbomethoxytetralone-2-γ-butyrate (IVd)**, m.p. 48–49°. Crystallization of a sample from methanol gave small colorless prisms, m.p. 48–49°.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.91; H, 6.89.

From methyl γ-iodobutyrate, sodium methoxide and IIIb, after refluxing 60 hours, was obtained 81% of **methyl 2-carbomethoxy-6-methoxy-1-tetralone-2-γ-butyrate (IVg)**, m.p. 76–78°. Crystallization of a sample from methanol gave small colorless needles, m.p. 76.5–78°.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.50; H, 6.80.

From methyl δ-iodovalerate, sodium methoxide and IIIa was obtained after 5 days of refluxing, 107% of methyl 2-carbomethoxy-1-tetralone-2-δ-valerate (IVe) as a pale yellow liquid. This material could not be induced to crystallize and was used in subsequent reactions without further purification.

In like manner, except that anhydrous diethyl carbonate was substituted for benzene, methyl γ-bromocrotonate and

(8) H. A. Bruson and T. W. Riener, THIS JOURNAL, **64**, 2850 (1942).

(9) W. E. Bachmann and D. G. Thomas, *ibid.*, **64**, 94 (1942).

(10) L. Henry, *Compt. rend.*, **102**, 368 (1886).

(11) R. C. Fuson, R. T. Arnold and H. G. Cooke, Jr., THIS JOURNAL, **60**, 2273 (1938).

(12) K. Ziegler, A. Späth, E. Schaaf, W. Schumann and E. Winkelman, *Ann.*, **551**, 118 (1942).

IIIa reacted during 18 hours to form 61% of **methyl 2-carbomethoxy-1-tetralone-2-γ-crotonate (V)**, m.p. 50–53°. Crystallization of a sample from methanol afforded small colorless needles, m.p. 55–56°.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 66.90; H, 6.15.

Partial Hydrolysis of Disubstituted β-Keto Esters.—Hydrolysis of IVd with a mixture of hydrochloric acid, acetic acid and water for two hours, or saponification with one equivalent of sodium hydroxide, followed by acidification, afforded **2-carbomethoxy-1-tetralone-2-γ-butyric acid (VIa)**. A sample crystallized from methanol gave colorless platelets, m.p. 110–112°.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25; neut. equiv., 290.3. Found: C, 66.24; H, 6.36; neut. equiv., 289.0.

Similarly, partial hydrolysis of IVg or saponification with one equivalent of sodium hydroxide, afforded **2-carbomethoxy-6-methoxy-1-tetralone-2-γ-butyric acid (VIb)**. A sample crystallized from aqueous methanol gave colorless crystals, m.p. 130–131.5°.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29; neut. equiv., 320.3. Found: C, 64.17; H, 6.52; neut. equiv., 320.9.

Hydrolysis and Decarboxylation of the β-Keto Esters IV.—A mixture of 5 g. (0.016 mole) of IVd, 10 ml. of concentrated hydrochloric acid, 20 ml. of glacial acetic acid and 10 ml. of water was refluxed for 24 hours. Dilution with water gave 2.8 g. (73%) of **1-tetralone-2-γ-butyric acid (VIIa)**, m.p. 60–62°. Crystallization of a sample from 50% ethanol gave colorless needles, m.p. 63–64°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; neut. equiv., 232.3. Found: C, 72.64; H, 7.13; neut. equiv., 231.1.

By a similar procedure the β-keto ester IVe gave 81% of **1-tetralone-2-δ-valeric acid (VIIb)**, m.p. 111–112°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; neut. equiv., 246.3. Found: C, 73.05; H, 7.40; neut. equiv., 245.2.

In the same manner, the ester IVg gave **6-methoxy-1-tetralone-2-γ-butyric acid (VIIc)** as colorless platelets, m.p. 101.5–103°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; neut. equiv., 262.3. Found: C, 69.01; H, 7.03; neut. equiv., 263.0.

Meerwein–Ponndorf Reductions.—From 2.2 g. (0.08 mole) of IVb, reduced in the usual manner,[13] was obtained by chilling a petroleum ether solution of the reaction product, 1.2 g. (55%) of the **lactone of 2-carbisopropoxy-1-tetralol-2-acetic acid (IX)**, m.p. 100–102°. Crystallization of a sample from aqueous methanol gave colorless needles, m.p. 101–102°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.03; H, 6.80.

Concentration of the filtrates after removal of the lactone IX, and chilling afforded 1.0 g. (27%) of **isopropyl 2-carbisopropoxy-1-tetralol-2-acetate (VIIIa)**, m.p. 48–52°. Crystallization of a sample from petroleum ether gave small colorless prisms, m.p. 56–57°.

Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.74; H, 7.79.

The above ester VIIIa was converted in nearly quantitative yield to the lactone IX when heated with a solution of hydrogen bromide in acetic anhydride at 60–70°.

The lactone IX was saponified by refluxing with 15% aqueous potassium hydroxide for 3 hours. Acidification of the solution gave the **lactone of 2-carboxy-1-tetralol-2-acetic acid (X)**. Crystallization of a sample from aqueous methanol gave small colorless prisms, m.p. 190–192° dec.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21; neut. equiv., 232.2; sapon. equiv., 116.1. Found: C, 67.13; H, 5.37; neut. equiv., 231.9; sapon. equiv., 115.3.

Saponification of the lactone acid X with the calculated amount of potassium hydroxide in refluxing isopropyl alcohol for 3 hours followed by careful acidification of the chilled mixture with the calculated amount of 0.25 *N* hydrochloric acid gave what is probably 2-carboxy-1-tetralol-2-acetic acid (XI), m.p. 118–119° dec. All attempts to recrystallize the diacid XI resulted in the formation of the acid lactone X.

Meerwein–Ponndorf reduction of IVc, d and e gave the liquid tetralol esters, VIIIb, c and d, respectively. These were used without further purification.

Reduction of the Tetralol Esters VIII.—A mixture of 22 g. of the crude tetralol (VIIIb, c, or d), 15 g. of red phosphorus, 5 g. of iodine, 5 ml. of water and 115 ml. of glacial acetic acid was refluxed for 12 hours.[7] The phosphorus was removed by filtration and washed with glacial acetic acid. The combined filtrates were distilled under reduced pressure to remove the solvent. The oily residue was hydrolyzed in a refluxing mixture of 50 ml. of concentrated hydrochloric acid, 25 ml. of glacial acetic acid and 25 ml. of water during 24 hours. The mixture was diluted with water and extracted with ether. Extraction of the ether with 5% sodium hydroxide followed by acidification of the basic solution gave the tetralin acids XIII.

In this manner, VIIIb gave 18.6% (based on the β-keto ester IIIa) of **2-carboxytetralin-2-β-propionic acid (XIIIa)**, m.p. 91–95°. Crystallization of a sample from aqueous acetone gave colorless crystals, m.p. 125–126°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50; neut. equiv., 124.1. Found: C, 67.81; H, 6.55; neut. equiv., 125.7.

Similarly, reduction of VIIIc gave 84% (based on the β-keto ester IIIa) of **2-carboxytetralin-2-γ-butyric acid (XIIIb)**, m.p. 150–155°. Crystallization of a sample from aqueous methanol gave colorless prisms, m.p. 162–164°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; neut. equiv., 131.1. Found: C, 68.83; H, 7.06; neut. equiv., 132.2.

Esterification of XIIIb with diazomethane gave **methyl 2-carbomethoxytetralin-2-γ-butyrate**, m.p. 55–60°. Crystallization of a sample from methanol gave colorless needles, m.p. 65.5–67°.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.63; H, 7.94.

Reduction of VIIId gave 75% (based on the β-keto ester IIIa) of **2-carboxytetralin-2-δ-valeric acid (XIIIc)**, m.p. 144–153°. Crystallization of a sample from aqueous acetone gave colorless crystals, m.p. 165–166°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; neut. equiv., 138.2. Found: C, 68.84; H, 7.43; neut. equiv., 138.7.

Esterification of XIIIc with diazomethane gave the liquid methyl ester which was used without further purification.

3-Carbomethoxy-2-oxo-3′,4′-dihydrospiro-[cyclopentane-1,2′(1′H)-naphthalene] (XIV).—Dry sodium methoxide was prepared from 4.9 g. (0.21 atom) of sodium in a 500-ml., standard tapered flask, equipped with a reflux condenser protected from moisture. The air was removed from the apparatus by flushing with dry nitrogen, and a solution of 19.5 g. (0.067 mole) of the methyl ester of XIIIb in 150 ml. of dry benzene was added, and the mixture was refluxed for 3 hours. The reaction mixture was decomposed with 15 ml. of acetic acid in 75 ml. of water containing a few drops of hydrochloric acid. The mixture was extracted twice with benzene, and the combined extracts were washed with aqueous sodium bicarbonate and dried. The solvent was removed by distillation at reduced pressure, and 16.0 g. (92%) of the β-keto ester XIV was obtained as an oil which crystallized upon standing, m.p. 55–60°. Crystallization of a sample from methanol gave colorless needles, m.p. 60–61°. The compound gave a blue-violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.44; H, 7.30.

A small amount of the higher melting isomer of XIV was obtained from the residues of several reactions, m.p. 68–69°. The compound gave a blue-violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.74; H, 7.25.

2-Oxo-3′,4′-dihydrospiro-[cyclopentane-1,2′(1′H)-naphthalene] (XVI).—Hydrolysis of the β-keto ester XIV in aqueous hydrochloric acid–acetic acid[5] gave the spiranone XVI, b.p. 103–105° (0.1–0.2 mm.).

(13) A. L. Wilds in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 178–223.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.78; H, 8.05.

The 2,4-dinitrophenylhydrazone of XVI crystallized from methanol–chloroform in yellow leaflets, m.p. 159–159.5°.

Anal. Calcd. for $C_{20}H_{20}O_4N_4$: N, 14.73. Found: N, 14.89.

2-Oxo-3′,4′-dihydrospiro-[cyclohexane-1,2′H)-naphthalene] (XVII).—A mixture of 5.1 g. (0.017 mole) of the methyl ester of XIIIc and sodium methoxide from 1.8 g. (0.076 atom) of sodium in 50 ml. of dry benzene was refluxed for 36 hours. After working up the reaction mixture in a similar manner to that for the β-keto ester XIV, there was obtained 4.55 g. of the β-keto ester XV which could not be induced to crystallize. The oil gave a dark reddish-purple color with alcoholic ferric chloride.

Hydrolysis of the β-keto ester XV with aqueous hydrochloric acid–acetic acid gave 1.13 g. (32%) of the spiranone XVII, and 2.2 g. (48%) of 2-carboxytetralin-2-δ-valeric acid (XIIIc) which came from unreacted ester. The spiranone was purified by distillation, b.p. 113–115° (0.2–0.3 mm.).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 82.94; H, 8.62.

The yellow 2,4-dinitrophenylhydrazone of XVII was crystallized from methanol–chloroform; m.p. 168–169°.

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: N, 14.21. Found: 14.41.

3-Methyl-2-oxo-3′,4′-dihydrospiro-[cyclopentane-1,2′(1′H)-naphthalene] (XXI).—To a solution of 1.4 g. (0.06 atom) of sodium in 20 ml. of absolute methanol was added 3.5 g. (0.0135 mole) of the β-keto ester XIV and 20 ml. of dry benzene. After refluxing the mixture for one hour, the suspension was cooled and 10 ml. of freshly distilled methyl iodide was added. The mixture was allowed to stand 30 minutes and then was refluxed for 45 minutes. The mixture was extracted in succession with cold 5% sodium hydroxide, dilute acetic acid and 5% sodium bicarbonate. The benzene extract was dried and the solvents were removed under reduced pressure, giving 3.5 g. of the liquid β-keto ester XVIII.

Hydrolysis of XVIII in aqueous hydrochloric acid–acetic acid gave 2.5 g. (86%) of the spiranone XXI, b.p. 100–102° (0.10–0.15 mm.).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.46; H, 8.66.

The yellow 2,4-dinitrophenylhydrazone of XXI was crystallized from methanol–chloroform, m.p. 163–164.5°.

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: N, 14.21. Found: N, 14.27.

Methyl 2-Carbomethoxytetralin-2-γ-(α-methylbutyrate) (XX).—Dry sodium methoxide from 5.55 g. (0.24 atom) of sodium was prepared and powdered in a one-l. flask equipped with a condenser and protected from moisture. The air was displaced by flushing with dry nitrogen. A solution of 24 g. (0.083 mole) of methyl 2-carbomethoxytetralin-2-γ-butyrate in 600 ml. of dry benzene was added and refluxed for 12 hours. About 100 ml. of benzene was removed by distillation, the mixture was chilled, and 35 ml. of methyl iodide was added. After standing 2 hours, the mixture was refluxed for 12 hours. The benzene was removed by distillation at reduced pressure. From the oily residue, 8 g. (32%) of XX slowly crystallized, m.p. 72–75°. Crystallization from petroleum ether containing methanol gave colorless platelets, m.p. 75–75.5°.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.80; H, 7.84.

Acidic hydrolysis of a portion of the ester XX gave **2-carboxytetralin-2-γ-(α-methylbutyric) acid.** Crystallization from aqueous acetone gave colorless plates, m.p. 219–220°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; neut. equiv., 138.2. Found: C, 69.60; H, 7.34; neut. equiv., 138.7.

3-Methyl-2-oxo-3′,4′-dihydrospiro-[cyclohexane-1,2′(1′H)-naphthalene] (XXII).—The crude β-keto ester XV obtained from 5.1 g. (0.017 mole) of methyl 2-carbomethoxytetralin-2-δ-valerate was dissolved in 50 ml. of dry benzene and added to sodium methoxide made from 1.6 g. (0.67 atom) of sodium in 50 ml. of dry methanol. To the reaction mixture was added after 2 hours of refluxing, 40 ml. of methyl iodide. The reaction mixture was worked up as previously described and the liquid β-keto ester XIX was obtained, which upon acidic hydrolysis gave 2.6 g. (68%) of the spiranone XXII, b.p. 118–120° (0.2–0.3 mm.).

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.80; H, 8.85.

The yellow 2,4-dinitrophenylhydrazone of XXII was crystallized from methanol–chloroform, m.p. 167–169°.

Anal. Calcd. for $C_{22}H_{24}O_4N_4$: N, 13.72. Found: N, 13.94.

2,2-Bis-(β-carboxyethyl)-1-tetralone (XXIV).—A mixture of 2.5 g. (0.01 mole) of 2,2-bis-(β-cyanoethyl)-1-tetralone[8] (XXIII), 15 ml. of glacial acetic acid, 30 ml. of concentrated hydrochloric acid and 2 ml. of water was refluxed for 4 hours. Dilution of the solution with a mixture of 100 g. of ice and 50 ml. of water produced impure XXIV. Two crystallizations of the product from water gave 2.3 g. (79%) of colorless needles of the dibasic acid XXIV, m.p. 157–158°.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.26; H, 5.94.

3-Carbomethoxy-1′,4-dioxo-3′,4′-dihydrospiro-[cyclohexane-1,2′(1′H)-naphthalene] (XXV).—The dibasic acid XXIV was esterified with methanol and sulfuric acid. The ester could not be induced to crystallize and was used without further purification.

To dry sodium methoxide made from 0.7 g. (0.03 atom) of sodium was added 3.2 g. (0.01 mole) of the crude ester dissolved in 25 ml. of dry benzene, and the mixture was refluxed for 2 hours. The mixture was decomposed with cold, 5% hydrochloric acid, the benzene layer was separated, washed with water and dried. The solvent was removed by distillation under reduced pressure, and the oily product was induced to crystallize by chilling with Dry Ice. Two crystallizations from aqueous methanol gave 2.3 g. (80%) of colorless crystals of the β-keto ester XXV, m.p. 70–71°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.03; H, 6.39.

1′,4-Dioxo-3′,4′-dihydrospiro-[cyclohexane-1,2′(1′H)-naphthalene] (XXVI).—Hydrolysis of 2.9 g. (0.01 mole) of the β-keto ester XXV with a mixture of 10 ml. of acetic acid, 20 ml. of concentrated hydrochloric acid and 2 ml. of water for one hour, was followed by extraction of the spiranone XXVI with ether. Removal of the solvent gave an oil which crystallized while allowing a methanol solution to evaporate. Two crystallizations from methanol gave 2.0 g. (87%) of colorless prisms of the spiranone (XXVI), m.p. 79–80°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 78.62; H, 7.00.

The semicarbazone of XXVI formed colorless prisms from ethanol; m.p. 217–219°.

Anal. Calcd. for $C_{17}H_{22}O_2N_6$: N, 24.55. Found: N, 24.38.

The 2,4-dinitrophenylhydrazone of XXVI formed orange needles from ethanol; m.p. 174–175.5°.

Anal. Calcd. for $C_{27}H_{24}O_8N_8$: N, 19.04. Found: N, 19.24.

2,2-Bis-(β-carboxyethyl)-tetralin (XXVII).—Clemmensen reduction of 40 g. (0.14 mole) of the keto acid XXIV was carried out in the usual manner.[14] Two crystallizations of the crude acid XXVII from aqueous acetone gave 28.6 g. (75%) of colorless needles, m.p. 145–146°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 70.23; H, 7.40.

3-Carbomethoxy-4-oxo-3′,4′-dihydrospiro-[cyclohexane-1,2′(1′H)-naphthalene] (XXVIII).—The liquid methyl ester of XXVII was made by esterification with methanol and sulfuric acid.

In the same manner as that for the β-keto ester (XXV), 3.0 g. (0.01 mole) of the crude ester was cyclized in the presence of sodium methoxide to give 2.1 g. (78%) of colorless crystals of the β-keto ester XXVIII, m.p. 95–96°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.16; H, 7.52.

4-Oxo-3′,4′-dihydrospiro-[cyclohexane-1,2′(1′H)-naphthalene] (XXIX).—Hydrolysis of 2.7 g. (0.01 mole) of the

(14) E. L. Martin and H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 499.

β-keto ester XXVIII with aqueous hydrochloric acid–acetic acid gave 1.7 g. (80%) of the liquid spiranone XXIX, b.p. 145–146° (2 mm.).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.79; H, 8.59.

The semicarbazone of XXIX formed colorless needles from ethanol; m.p. 129–130°.

Anal. Calcd. for $C_{16}H_{21}ON_3$: N, 15.49. Found: N, 15.38.

The 2,4-dinitrophenylhydrazone of XXIX formed orange plates from ethanol; m.p. 85–86°.

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: N, 14.21. Found: N, 14.17.

The oxime of XXIX formed colorless crystals from ethanol; m.p. 104–105°.

Anal. Calcd. for $C_{15}H_{19}ON$: N, 6.11. Found: N, 6.05.

Clemmensen Reduction of the Spiranones.—Clemmensen reduction of the spiranone XXI was carried out in the usual manner.[14] The resulting spiran II was a nearly colorless liquid, b.p. 121–123° (5 mm.); $n^{20}D$ 1.5429 (reported[4] b.p. 122–125° (5 mm.)).

Clemmensen reduction of the spiranones XVII, XXVI or XXIX gave the spiran I in 30–40% yield, b.p. 122–124° (4 mm.); $n^{20}D$ 1.5476 (reported[4] b.p. 115–117° (3 mm.); $n^{20}D$ 1.5431).

BLOOMINGTON, INDIANA

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, WEIZMANN INSTITUTE OF SCIENCE]

Reduction and Benzylation by Means of Benzyl Alcohol. I. Carbon Benzylation. The Preparation of 9-Benzylfluorenes

BY YAÏR SPRINZAK

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Fluorene is readily transformed into 9-benzylfluorene by heating with benzyl alcohol in the presence of potassium hydroxide. The reaction is shown to involve condensation with benzaldehyde to form benzalfluorene, followed by reduction of the latter. The reaction has been extended to fluorene derivatives, including 2-methyl-, 2-bromo-, 2,7-dibromo-, 2-amino-, 2-hydroxy-, 4-carboxy- and 1,2,3,4-dibenzofluorene, on the one hand, and to *p*-tolylcarbinol and *p*-anisyl alcohol, on the other hand.

The reducing properties of hot benzyl alcoholic solutions of potassium hydroxide have been noted by Palfray and Sabetay[1] during their attempts to devise a method for the determination of aldehydes by means of the Canizzaro reaction. Using benzyl alcohol as a medium for this reaction, they observed that, with aromatic aldehydes[1a] such as *p*-methoxybenzaldehyde, hydrogen transfer from alcohol to aldehyde took place, as indicated by the isolation of benzoic acid instead of the expected *p*-methoxybenzoic acid

$$p\text{-}CH_3OC_6H_4CHO + PhCH_2OH \xrightarrow{KOH} p\text{-}CH_3OC_6H_4CH_2OH + PhCHO$$

$$2PhCHO + KOH \longrightarrow PRCH_2OH + PhCO_2K$$

Mastagli[2] later studied the action of the reagent in question on other types of aldehydes, as well as on ketones and α,β-unsaturated alcohols, and obtained a variety of products the formation of which could be explained readily in terms of reduction and condensation reactions, as may be illustrated by the case of β-phenylpropionaldehyde

$$PhCH_2CH_2CHO + PhCH_2OH \xrightarrow{KOH} PhCH_2CH_2CH_2OH + PhCHO$$

$$PhCH_2CH_2CHO + PhCHO \xrightarrow{KOH} PhCH{=}C(CH_2Ph)CHO \xrightarrow[KOH]{PhCH_2OH} PhCH{=}C(CH_2Ph)CH_2OH \xrightarrow[KOH]{PhCH_2OH} (PhCH_2)_2CHCH_2OH$$

It has now been found[3] that benzyl alcoholic potassium hydroxide may be used advantageously for the preparation of 9-benzylfluorene (III) and related compounds. The various methods available in the literature for the preparation of 9-benzylfluorene employ derivatives obtained from fluorene (I) by substitution in the 9-position, for example, 9-formylfluorene[4] and 9-carbethoxyfluorene,[5] which may be alkylated by benzyl chloride, with subsequent elimination of the formyl and carboxyl groups, respectively. Likewise, 9-benzylfluorene has been obtained by reduction of benzalfluorene (II), either with aluminum amalgam[6] or catalytically, in the presence of a palladium catalyst.[7] A more direct method of benzylation could, perhaps, be achieved by the interaction of benzyl chloride and 9-fluorenyllithium, obtained from fluorene and phenyllithium.[8]

In the present method, benzylation is accomplished easily by heating fluorene and benzyl alcohol in the presence of a small amount of potassium hydroxide and traces of benzaldehyde. Addition of the latter is not necessary, as it is gradually formed from benzyl alcohol by oxidation or dehydrogenation[9] under the alkaline conditions used. Although the reaction may be carried to completion by refluxing the mixture, removal of the water formed accelerates it considerably, presumably owing to the higher temperature achieved.

The conversion of fluorene to 9-benzylfluorene is considered to be the result of two consecutive reactions. In the first, fluorene condenses with benzaldehyde to yield benzalfluorene; in the second, the latter is reduced by benzyl alcohol (or potassium benzylate) to 9-benzylfluorene, the benzaldehyde

(1) L. Palfray and S. Sabetay, *Compt. rend.*, **200**, 404 (1935).

(1a) L. Palfray, S. Sabetay and P. Mastagli, *ibid.*, **203**, 1523 (1936) and reference 2.

(2) P. Mastagli, *Ann. chim.*, [11] **10**, 281 (1938).

(3) A note has been published: *Bull. Research Council Israel*, **3**, No. 1/2, 104 (1953).

(4) W. G. Brown and B. A. Bluestein, THIS JOURNAL, **65**, 1082 (1943).

(5) W. Wislicenus and W. Mocker, *Ber.*, **46**, 2772 (1913).

(6) J. Thiele and F. Henle, *Ann.*, **347**, 290 (1906).

(7) E. D. Bergmann, *Ber.*, **63**, 1617 (1930).

(8) G. Wittig, P. Davis and G. Koenig, *ibid.*, **84**, 627 (1951).

(9) See *e.g.*, M. Guerbet, *Bull. soc. chim. France*, [4] **3**, 500 (1908).