repeated recrystallization from water, it was converted to a light orange crystalline product which melted at 225–227° (with decomposition).

Anal. Calcd. for $C_{13}H_{10}N_6O_7S$: C, 39.60; H, 2.55; N, 21.31; S, 8.13. Found: C, 39.35; H, 2.73; N, 21.11; S, 8.00.

4-Methylmercapto-6-nitrobenzimidazole.—A cooled solution of the diazonium chloride of 4-amino-6-nitrobenzimidazole, prepared from 5.37 g. (0.025 mole) of the hydrochloride according to the procedure just described, was treated with 1.8 ml. of methyl mercaptan. After several minutes the light yellow diazonium salt separated. The reaction mixture was heated rapidly on the steam-bath until the evolution of nitrogen had ceased. The resulting light orange-yellow solution, after treatment with charcoal, was neutralized with sodium carbonate giving 2.73 g. (52%) of 4-methylmercapto-6-nitrobenzimidazole, m.p. 248–254°. Recrystallization from 80% alcohol gave 1.38 g. of fine yellow crystals, m.p. 277–278°.

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.93; H, 3.37; N, 20.08; S, 15.33. Found: C, 45.77; H, 3.25; N, 19.84; S, 15.51.

Picrate.—The picrate crystallized from alcohol as yellow needles melting at 229–231°. Attempts to recrystallize this material from water resulted in regeneration of the free benzimidazole. A serious amount of dissociation occurred on repeated recrystallization from both 50 and 95% alcohol. A sample, purified for analysis by recrystallization from 50% alcohol containing a small amount of picric acid, analyzed as the hemipicrate.

Anal. Calcd. for $C_8H_7N_3O_2S \cdot {}^1/_2C_6H_3N_3O_7$: C, 40.80; H, 2.65; N, 19.46. Found: C, 40.10; H, 2.56; N, 18.61, 19.33.

4-Methylmercapto-6-aminobenzimidazole Dihydrochloride.—4-Methylmercapto-6-nitrobenzimidazole (2.01 g., 0.01 mole) was reduced at 5° with stannous chloride (5.80 g.) and hydrochloric acid (20 ml.) in a manner similar to the preceding reductions. Decomposition of the tin double salt (2.84 g.) which separated, by hydrogen sulfide in 1 *N* hydrochloric acid, and treatment of the filtrate with excess acetone gave white crystals (0.61 g., 21%), m.p. 287–290°. Purification was accomplished by dissolving the product in 5 ml. of water and, after treatment with charcoal, adding 50 ml. of absolute alcohol followed by benzene to definite turbidity. After crystallization began, more benzene was added to complete the precipitation. The product obtained in this manner retained a half mole of solvent of crystallization which was not removed by drying at 100° *in vacuo*. The benzene was released upon solution of the material in water.

Anal. Calcd. for $C_8H_{11}N_3SCl_2 \cdot {}^1/_2C_6H_6$: C, 45.36; H, 4.85; N, 14.43; S, 11.01; Cl, 24.35. Found: C, 45.28; H, 4.85; N, 14.70; S, 11.13; Cl, 23.82.

Picrate.—The picrate crystallized from water as light yellow needles melting at 220–222°. After repeated recrystallization from water, the material was transformed to a deep yellow crystalline product melting at 251–252°.

Anal. Calcd. for $C_{14}H_{12}N_6O_7S$: C, 41.17; H, 2.96; N, 20.58. Found: C, 41.00; H, 3.02; N, 20.35.

PHILADELPHIA 4, PENNA.

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

Hormone Analogs. I. Preparation of Intermediate Ketones for the Synthesis of Stilbestrol Analogs[1,2]

BY TERRELL C. MYERS, RICHARD J. PRATT, ROBERT L. MORGAN, JAMES O'DONNELL AND ELWOOD V. JENSEN

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Certain 4-arylhexan-3-ones, useful for the synthesis of stilbestrol analogs, have been prepared by ethylation of the corresponding 1-arylbutan-2-ones which in turn are obtained conveniently from aromatic aldehydes, either by the glycidic ester condensation with ethyl α-bromobutyrate followed by saponification and decarboxylation, or by the amine-catalyzed condensation with 1-nitropropane followed by reduction and hydrolysis. Substitution of ethyl phenylbromoacetate for ethyl bromobutyrate in the glycidic ester process leads to a substituted desoxybenzoin, also a useful intermediate for the preparation of stilbestrol analogs.

In addition to the characteristic effects on their specific target tissues, the different types of steroid sex hormones possess the ability to inhibit or antagonize certain of the physiological actions of one another as well as to diminish the secretory activity of the pituitary gland.[3] These phenomena of inhibition and antagonism find clinical application in cases where chemical regulation of the endocrine balance is desired. In general it has been the potent members of each class of hormones which have been employed in this way, and their administration often is accompanied by undesirable side effects which arise from the primary hormonal actions of these materials. Therefore it would be of practical as well as of theoretical interest if compounds could be discovered which possess little or no primary hormonal activity, but which still have the ability to modify or regulate endocrine balance.

Whereas extensive studies have been carried out concerning the relation of molecular structure to primary hormonal activity, relatively little is known about the structural requirements for antagonism and pituitary inhibition. Accordingly an investigation has been undertaken in this Laboratory of compounds closely related in structure to the active hormones to determine whether antagonistic and pituitary-inhibiting properties depend on the same molecular features as the primary hormonal activity.

One class of substances being studied in this regard consists of compounds related in structure to stilbestrol, a synthetic estrogenic hormone which exhibits the characteristic physiological actions, both hormonal and inhibitory, of the natural steroid estrogens. A general method has been developed by which one or both of the aromatic

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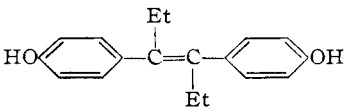
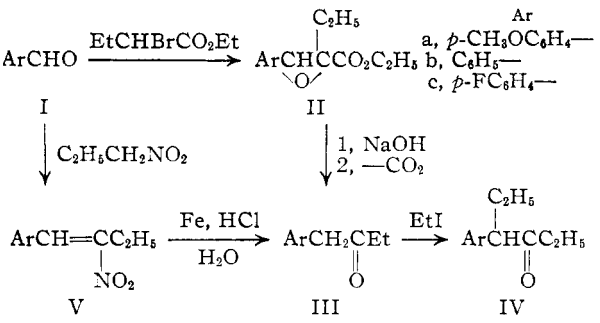
(2) This investigation was supported in part by a grant from the American Cancer Society as recommended by the Committee on Growth of the National Research Council.

(3) C. W. Emmens and A. S. Parkes, *Vitamins and Hormones*, **5**, 233 (1947); R. Courrier, *ibid.*, **8**, 179 (1950); H. Burrows, "Biological Actions of Sex Hormones," 2nd ed., Cambridge University Press, 1949; G. Pincus and K. V. Thimann, "The Hormones," Academic Press, Inc., New York ,N. Y. ,Vol. I, 1948, ch. 12, Vol. II, 1950, ch. 1, 2, 6.



Stilbestrol

rings of the stilbestrol structure can be varied as desired. This paper describes the conversion of aromatic aldehydes I to aryl-substituted hexanones IV which, as described in the following paper, can serve as precursors for the synthesis of either symmetrical or unsymmetrical diethylstilbene derivatives.

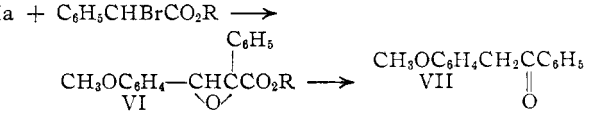


The use of 4-anisylhexan-3-one (IVa) as an intermediate for the synthesis of stilbestrol and related compounds has been described by a number of investigators.[4] Since the methods heretofore employed for the synthesis of such arylhexanones did not appear to be entirely satisfactory for general application, other possible routes to these ketones were investigated. It was found that 1-arylbutan-2-ones (III), which on ethylation furnish the hexanones (IV), can be obtained readily from the corresponding aldehydes (I) by utilization of either (a) the Darzens glycidic ester condensation[5] with ethyl α-bromobutyrate followed by hydrolysis and decarboxylation, or (b) the reaction of the aldehyde with 1-nitropropane followed by reduction and hydrolysis.[6]

In the first of these procedures, *p*-anisaldehyde (Ia) was converted to 4-anisylhexan-3-one (IVa) in 53% over-all yield, whereas from benzaldehyde (Ib) and *p*-fluorobenzaldehyde (Ic) the corresponding phenyl-(IVb) and *p*-fluorophenyl-(IVc) hexanones were produced in yields of 25 and 35%, respectively. When an attempt was made to eliminate the need for the final ethylation step by employing *p*-methoxypropiophenone instead of anisaldehyde in the condensation with ethyl α-bromobutyrate, the yield of glycidic ester was so low (*ca.* 10%) that it is preferable to start with the aldehyde.

In the second procedure, *p*-anisaldehyde (Ia) was condensed with 1-nitropropane in the presence of *n*-butylamine. The resulting 1-anisyl-2-nitrobutene-1 (Va) was subjected to reduction and hydrolysis with iron and hydrochloric acid to yield 1-anisylbutan-2-one (IIIa), which, on ethylation, gave 4-anisylhexan-3-one (IVa) in 43% over-all yield. Preliminary experiments suggest that the reduction of Va also may be carried out catalytically.

The glycidic ester procedure described above also affords a method for the preparation of substituted desoxybenzoins, compounds which have been used by a number of investigators[7,8] for the synthesis of stilbestrol and its analogs. The reaction of anisaldehyde with ethyl phenylbromoacetate gave a glycidic ester VI which on hydrolysis and decarboxylation was converted to α-(*p*-anisyl)-acetophenone (*p'*-methoxydesoxybenzoin, VII). When a similar reaction was carried out using methyl phenylchloroacetate, the glycidic ester (VI, R = Me) was obtained in a crystalline form. To our knowledge this is the first time that a glycidic ester condensation has been carried out with a halogenated ester bearing an aromatic substituent.



Experimental[9]

1-(*p*-Anisyl)-butan-2-one (IIIa) (Glycidic Ester Method).—Sodium methoxide (48 g., 0.89 mole) was added over a period of four hours to a vigorously stirred mixture of *p*-anisaldehyde (109 g., 0.80 mole) and ethyl α-bromobutyrate (156 g., 0.80 mole) in an atmosphere of dry nitrogen with cooling in an ice–salt-bath. After stirring for six hours at 0° and overnight at room temperature, 100 ml. of water was added and the organic material isolated in the usual manner.[5] The crude product was distilled *in vacuo* to yield, after a forerun of 60 g., ethyl α-ethyl-α,β-epoxy-β-anisylpropionate (IIa), 121 g., 61%, b.p. 110–120° (0.1 mm.), $n^{25}D$ 1.5132.

A solution of the glycidic ester IIa (115 g., 0.46 mole) and sodium hydroxide[10] (18.4 g., 0.46 mole) in 500 ml. of ethanol was heated under reflux for three hours in an atmosphere of nitrogen. The solution was concentrated under reduced pressure, and the residue diluted with 100 ml. of water. The aqueous solution was washed with ether and acidified with hydrochloric acid, the product was extracted with ether and the ethereal solution washed several times with water, the last portion of which contained a trace of sodium bicarbonate, and finally with saturated sodium chloride solution. The ether was evaporated, and the residual reddish oil heated for six hours at 180° in an atmosphere of nitrogen, whereupon carbon dioxide was evolved. After cooling, the reaction mixture was dissolved in 300 ml. of ether and washed with 5% sodium hydroxide, with water until neutral, and finally with sodium chloride solution. The ether was evaporated and the remaining oil distilled at reduced pressure to yield the anisylbutanone (IIIa), 75 g., 92%, b.p. 93–96° (0.5 mm.), $n^{25}D$ 1.5178; m.p. of semicarbazone derivative 153.5–155°, reported[4b] 156–157°.

Anal. (of semicarbazone) Calcd. for $C_{12}H_{17}O_2N_3$: C, 61.25; H, 7.28; N, 17.86. Found: C, 60.99; H, 7.36; N, 17.59.

Nitropropane Method.—A mixture of *p*-anisaldehyde (27.2 g., 0.20 mole), 1-nitropropane (17.8 g., 0.20 mole) and *n*-butylamine (2.0 ml.) was allowed to stand for 14 days at room temperature. The upper water layer was removed, and the residual oil was distilled through a short Vigreux column at 0.2 mm. pressure until the distillation temperature reached 105°. Then the residue and column holdup were crystallized from a mixture of ether and petroleum ether to yield 1-anisyl-2-nitrobutene-1 (Va), 21.3 g.,

(4) (a) S. Kuwada, Y. Sasagawa and M. Nisikawa, *J. Pharm. Soc. Japan*, **60**, 224A, 553 (1940); (b) F. v. Wessely, E. Kerschbaum, A. Kleedorfer, F. Prillinger and E. Zajic, *Monatsh.*, **73**, 127 (1940).

(5) M. S. Newman and B. J. Magerlein, "Organic Reactions," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 413.

(6) E. R. Shepard, J. F. Noth, H. D. Porter and C. K. Simmans, THIS JOURNAL, **74**, 4611 (1952).

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(9) Melting points and boiling points are uncorrected. Microanalyses by Micro-Tech Laboratories, Skokie, Ill.

(10) Prepared by dissolving the requisite amount of sodium in absolute ethanol containing an equal molar amount of water.

52%, m.p. 52–56°. One recrystallization furnished the analytical sample, m.p. 55–56°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.46; N, 6.76.

From the mother liquors there was obtained 1.9 g. of an acid-soluble material which appeared to be an adduct of butylamine with the nitroölefin.

When the above reaction was carried out at 60° for 48 hours the yield of Va was 40%; when *t*-butylamine was substituted for *n*-butylamine as a catalyst, the yield was only 19%.

To a stirred refluxing mixture of Va (10.4 g., 0.05 mole), iron filings (19.5 g., 0.35 mole), water (37 ml.) and ferric chloride (0.05 g.), concentrated hydrochloric acid (7.1 ml.) was added slowly over a period of 30 minutes. The mixture was stirred and heated under reflux for two hours longer and then cooled. The product was extracted with ether, washed with water and sodium bicarbonate solution, and dried over magnesium sulfate. The crude product was distilled *in vacuo* to yield the anisylbutanone (IIIa), 7.4 g., 83%, b.p. 98–101° (0.6 mm.), $n^{25}D$ 1.5176; m.p. of semicarbazone derivative 159–161° not depressed by mixture with the analyzed sample of this derivative; m.p. of 2,4-dinitrophenylhydrazone derivative 112–113°.

Anal. (of 2,4-dinitrophenylhydrazone) Calcd. for $C_{17}H_{18}O_5N_4$: C, 56.97; H, 5.06; N, 15.64. Found: C, 57.01; H, 5.07; N, 15.67.

In an experiment to determine the feasibility of catalytic reduction of the nitro compound, 101 mg. (0.49 millimole) of Va was dissolved in 15 ml. of glacial acetic acid and shaken with hydrogen in the presence of 105 mg. of 10% palladized charcoal, whereupon 1.49 millimoles of hydrogen was absorbed in 20 minutes. The catalyst was removed by filtration and the filtrate evaporated to dryness in a stream of dry nitrogen. The residue was treated with 1 ml. of concentrated hydrochloric acid and subjected to steam distillation. The distillate was collected in excess alcoholic 2,4-dinitrophenylhydrazine reagent, and the precipitate which formed was filtered and dried. Thus there was obtained 150 mg. (86%) of the 2,4-dinitrophenylhydrazone of 1-anisylbutan-2-one, m.p. 111–114°, which did not depress the melting point of the analyzed sample of this material.

4-(*p*-Anisyl)-hexan-3-one (IVa).—The anisylbutanone (IIIa) (53 g., 0.30 mole) was stirred with sodium methoxide (32.5 g., 0.60 mole) in an atmosphere of dry nitrogen, while ethyl iodide (140 g., 0.90 mole) was added over a period of one to two minutes with cooling to prevent too vigorous a reaction. After the initial reaction had subsided, the mixture was stirred under reflux on a steam-bath for one hour. If the mixture became too viscous for proper stirring, a little more ethyl iodide was added. Most of the excess ethyl iodide was removed by distillation and the residue taken up in 100 ml. of water. The product was extracted with ether and washed with sodium thiosulfate solution, water and finally saturated sodium chloride. The crude product was distilled at reduced pressure to yield the anisylhexanone (IVa), 58 g., 94%, b.p. 97–102° (0.5 mm.), $n^{25}D$ 1.5074; m.p. of semicarbazone derivative 130–131°, reported[4b] 130–132°.

Anal. (of semicarbazone) Calcd. for $C_{14}H_{21}O_2N_3$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.90; H, 8.03; N, 15.56.

1-Phenylbutan-2-one (IIIb).—The reaction of benzaldehyde (Ib) (85 g., 0.80 mole) with ethyl α-bromobutyrate (156 g., 0.80 mole) in the presence of sodium methoxide (48 g., 0.89 mole) was carried out in the manner previously described for anisaldehyde. The glycidic ester IIb distilled at 107–116° (0.20 mm.), yield 140 g., 80%.

The glycidic ester IIb (110 g., 0.5 mole) was subjected to saponification and decarboxylation in the previously described manner. In this instance considerable decomposition took place during the distillation of the reaction mixture. The crude product (32 g.) was redistilled without decomposition to yield 1-phenylbutan-2-one (IIIb), 30.4 g., 41%, b.p. 49–49.5° (0.01 mm.), $n^{25}D$ 1.5015; m.p. of semicarbazone derivative 151–153°, reported 150–153°,[11] 154–155°.[12]

4-Phenylhexan-3-one (IVb).—Treatment of IIIb (29.6 g., 0.20 mole) and sodium methoxide (21.6 g., 0.40 mole) with ethyl iodide (156 g., 1.0 mole) in the manner described above for the case of IIIa gave 4-phenylhexan-3-one (IVb), 27.1 g., 77%, b.p. 45.5–48° (0.4 mm.), $n^{25}D$ 1.5000; m.p. of semicarbazone derivative 140.5–141.5°, reported 139–140°,[13] 144°.[14]

Anal. (of semicarbazone) Calcd. for $C_{13}H_{19}ON_3$: C, 66.92; H, 8.28; N, 18.01. Found: C, 66.60; H, 8.02; N, 17.92.

1-(*p*-Fluorophenyl)-butan-2-one (IIIc).—The condensation of *p*-fluorobenzaldehyde[15] (Ic) (99 g., 0.80 mole) with ethyl α-bromobutyrate (156 g., 0.80 mole) in the presence of sodium methoxide (48 g., 0.89 mole) was carried out as described above for anisaldehyde. The glycidic ester IIc distilled at 91–95° (0.3 mm.), yield 151 g., 79%.

Saponification and decarboxylation of IIc (15 g., 0.063 mole) was carried out in the manner previously described. Considerable decomposition took place during the final stages of the distillation of the crude product and a glassy residue remained in the still-pot. The distillate (6.3 g.) was redistilled without decomposition to give the fluorophenylbutanone (IIIc), 5.9 g., 56%, b.p. 57–58° (0.2 mm.), $n^{25}D$ 1.4905.

4-(*p*-Fluorophenyl)-hexan-3-one (IVc).—Ethylation of IIIc (5.0 g., 0.03 mole) with ethyl iodide (25 g., 0.16 mole) in the presence of sodium methoxide (3.24 g., 0.06 mole) was carried out in the manner described for IIIa. Thus was obtained the fluorophenylhexanone (IVc), 4.6 g., 79%, b.p. 53–56° (0.07 mm.), $n^{25}D$ 1.4833; m.p. of semicarbazone derivative 125.5–126.5°.

Anal. (of ketone) Calcd. for $C_{12}H_{15}OF$: C, 74.20; H, 7.78. Found: C, 73.95; H, 7.82. (of semicarbazone) Calcd. for $C_{13}H_{18}ON_3F$: C, 62.13; H, 7.22; N, 16.72. Found: C, 62.26; H, 7.19; N, 16.27.

α-(*p*-Anisyl)-acetophenone (VII).—The condensation of *p*-anisaldehyde (Ia) (13.6 g., 0.10 mole) with ethyl phenylbromoacetate (24.3 g., 0.10 mole) in the presence of sodium methoxide (6.0 g., 0.11 mole) was carried out in a manner similar to that described for the reaction of this aldehyde with ethyl α-bromobutyrate. The glycidic ester (VI, R = Et) distilled at 172–174° (0.5 mm.); the yield was 20 g., 67%.

Saponification and decarboxylation of the foregoing glycidic ester (20 g., 0.067 mole) in the manner described previously furnished the anisylacetophenone (*p'*-methoxydesoxybenzoin, VII) 8.4 g., 55%, m.p. 94–95° from methanol, reported[16] m.p. 98°.

When the condensation of anisaldehyde (13.6 g., 0.1 mole) was carried out under similar conditions with methyl phenylchloroacetate (18.5 g., 0.1 mole) the ethereal solution of the crude reaction product on standing deposited crystals of the glycidic ester, m.p. 98–100°. The ethereal solution was concentrated furnishing an additional amount of the product, m.p. 97–98°; the total yield of methyl α-phenyl-α,β-epoxy-β-(*p*-anisyl)-propionate (VI, R = Me) was 20.4 g., 72%. A portion of this material, recrystallized for analysis from a benzene–hexane mixture, melted at 99–100°.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.64; H, 5.67.

Saponification and decarboxylation of the crystalline glycidic ester furnished anisylacetophenone (VII), m.p. 94–95°, identical with that obtained from the non-crystalline glycidic ester.

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(15) Obtained from the Custom Chemical Laboratories, Chicago, Illinois.

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