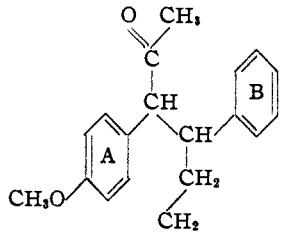
3-(*p*-Methoxyphenyl)-4-phenyl-2-hexanone and Derivatives

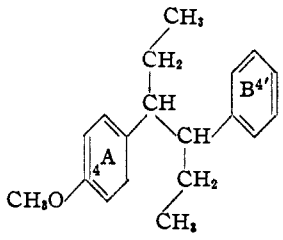
BY DANIEL R. SATRIANA, ATHANASIOS LOTER AND MANUEL M. BAIZER

Hager and Burgison[1] have reported the synthesis of 4,4′-bis-(acetoxyacetyl)-α,α′-diethylstilbene as part of a study of synthetic analogs of the adrenal cortical hormones.

In related work whose objective is the preparation of "open model" aromatic compounds which have a keto group in a position corresponding formally to the 11-oxygen function of corticosterone and its important derivatives (*e. g.*, Kendall's compounds A, E and F), we have prepared and characterized one of the *dl*-forms of 3-(*p*-methoxyphenyl)-4-phenyl-2-hexanone (I) and certain of its derivatives.



I



II

Brownlee and Duffin[2] claim the successful introduction of an acetyl or substituted acetyl group into the 4′-position of II by a Friedel–Crafts reaction between II and an appropriate acyl halide; 4-methoxy-4′-glycolyl-α,α′-diethyldibenzyl, so prepared, is claimed to have corticosterone-like activity.[3]

When I in carbon disulfide was treated with acetylglycolyl chloride and excess anhydrous aluminum chloride,[4] 83% of starting material was recovered unchanged and no other identifiable product was obtained. With chloroacetyl chloride, I yielded *ca.* 35% of a halogen-containing product (III) melting at 78–80°. However, analysis of III indicated that the desired product, if formed at all, was present in only small quantity.

The presence of a carbonyl group is known to impede the Friedel–Crafts reaction.[5] In view of the fact, however, that compounds in which the carbonyl group is separated (by one or more methylenes) from the ring-to-be-substituted have been successfully acylated,[6] the deactivation of ring B of I is surprising. Investigation of the reactivity of the other *dl*-form of I might clarify the respective roles of the carbonyl group and of steric factors in this impedance.

Acknowledgment.—We wish to express our appreciation to Dr. W. G. Bywater, S. B. Penick and Co., for many helpful discussions.

Experimental

***p*-Methoxy-α-cyanostilbene (IV).**—This compound was obtained in 67.5% yield by the condensation of benzaldehyde and *p*-methoxybenzyl cyanide.[7]

α-(*p*-Methoxyphenyl)-β-phenylvaleric Acid (V).—The reaction of IV with ethylmagnesium bromide followed the procedure used by Hunter and Korman[8] in a similar case. The mixture of isomeric α-(*p*-methoxyphenyl)-β-phenylvaleronitriles was obtained in 98–100% crude yield. A mixture of 23.5 g. of sodium hydroxide, 46.5 ml. of water and 78.3 g. of these nitriles was heated under reflux for 46 hours. The reaction mixture was diluted with 700 ml. of water and filtered hot. The filtrate was chilled, acidified with dilute hydrochloric acid and extracted with three 150-ml. portions of ether. The combined ethereal extracts were extracted with three 150-ml. portions of 2.5% sodium hydroxide. Acidification of the alkaline solution caused the precipitation of 11.6 g. of crude V, m.p. 174–177°; ether extraction of the filtrate followed by evaporation of the ether and recrystallization of the residue (56 g.) from 95% ethanol yielded an additional 14 g. of similar material. Recrystallization of crude V from 95% ethanol provided the analytical sample, m.p. 180–181°.

Anal.[9] Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.03; H, 7.25.

From the alcoholic mother liquors there was isolated *ca.* 12 g. of the other isomeric acid, which, after two recrystallizations from 95% ethanol, melted at 147–148°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.04; H, 7.19.

3-(*p*-Methoxyphenyl)-4-phenyl-2-hexanone (I).—The acid chloride from 19.9 g. (0.07 mole) of V was allowed to react in dry benzene with dimethylcadmium prepared from 12.84 g. (0.07 mole) of anhydrous cadmium chloride.[10] After a two-hour reflux period, the reaction mixture was cooled and poured into 250 ml. of dilute hydrochloric acid. The organic layer was separated; the aqueous solution was extracted with three 100-ml. portions of ether. The organic solutions were combined, washed with water, dried and distilled to dryness. The residue was heated under reflux for 90 minutes with 250 ml. of 1% sodium hydroxide. The solution was cooled and extracted three times with ether. From the alkaline solution 4.9 g. of crude V was recovered. The ether solution on evaporation to dryness yielded 15.9 g. of solid which after recrystallization from 95% ethanol gave 5.9 g. of I, m.p. 95–99°. An additional 0.7 g. of I was recovered from the alcoholic mother liquor by evaporating to dryness and distilling the residue at 168–170° (4 mm.). The sample for analysis was recrystallized from 95% ethanol; m.p. 104–105°.

Anal.[9] Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.90. Found: C, 80.36; H, 8.13.

The dinitrophenylhydrazone was prepared in the usual manner,[11] and recrystallized from 90% ethanol; m.p. 145–147°.

Anal.[9] Calcd. for $C_{25}H_{26}O_5N_4$: C, 64.86; H, 5.67; N, 12.12. Found: C, 65.17; H, 5.89; N, 11.67.

3-(*p*-Hydroxyphenyl)-4-phenyl-2-hexanone.—A mixture of 2.0 g. of I, 20 ml. of glacial acetic acid and 8.0 ml. of 48% hydrobromic acid was heated under reflux for 6 hours, cooled and poured into water. The aqueous solution was extracted with three 75-ml. portions of ether. The combined ether extracts were washed with water, sodium bicarbonate and then water. Washings were discarded. The ethereal solution was extracted with 5% sodium hydroxide, the alkaline solution acidified and extracted with ether.

(1) G. P. Hager and R. M. Burgison, *J. Am. Pharm. Assn., Sci. Ed.*, **39**, 7 (1950).

(2) G. Brownlee and W. M. Duffin, U. S. Patent 2,376,415, May 22, 1945.

(3) W. R. Biggerstaff and A. L. Wilds, THIS JOURNAL, **71**, 2132 (1949), synthesized the very closely related 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-hexane and found it inactive at 2-mg. daily doses in life-maintenance tests on adrenalectomized rats; *cf.* W. C. J. Ross, *J. Chem. Soc.*, 538 (1945).

(4) In this and subsequently attempted Friedel-Crafts reactions a large excess of catalyst was used in order to compensate for the quantity that was expected to be bound by the keto-group of I. *Cf.* Gilman, "Organic Chemistry, an Advanced Treatise," Vol. I, second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 184.

(5) Berliner, in Adams, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 233.

(6) W. Borsche and F. Sinn, *Ann.*, **553**, 260 (1942).

(7) J. B. Niederl and A. Ziering, THIS JOURNAL, **64**, 885 (1942).

(8) J. H. Hunter and J. Korman, *ibid.*, **70**, 3424 (1948).

(9) Schwarzkopf Microanalytical Laboratory, Middle Village, L. I., N. Y.

(10) *Cf.* W. R. Biggerstaff and A. L. Wilds, THIS JOURNAL, **71**, 2136 (1949).

(11) Shriner and Fuson, "Identification of Organic Compounds," second edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

The ethereal solution, upon washing, drying, and evaporating left 1.21 g. of solid which, after recrystallization from ethanol–benzene–ligroin, yielded 0.18 g. of the phenolic ketone, m.p. 184–186°.

Anal.[9] Calcd. for $C_{18}H_{20}O_2$: C, 80.58; H, 7.53. Found: C, 80.52; H, 7.83.

The acetoxy derivative was prepared in the usual manner.[12]

Anal.[9] Calcd. for $C_{20}H_{22}O_3$: C, 77.41; H, 7.15. Found: C, 77.59; H, 7.54.

Attempts to Acylate I by a Friedel-Crafts Reaction. (a) **With Acetylglycolyl Chloride.**—A solution of 2.00 g. of I (0.007 mole) and 1.06 g. (0.007 mole) of acetylglycolyl chloride in 50 ml. of carbon disulfide was chilled to 5°. Over a period of 20 minutes 2.77 g. (0.021 mole) of anhydrous aluminum chloride was added with mechanical stirring. The mixture was allowed to come to room temperature and then heated under reflux for 5 hours. It was then cooled and poured into 40 ml. of 10% hydrochloric acid. The layers were separated, the aqueous solution was extracted twice with carbon disulfide. The combined organic layers were dried and evaporated. The residue (1.8 g.), after recrystallization from ethanol, yielded 1.66 g. of solid, m.p. 98–100°, giving no depression in a mixture melting point with I.

(b) **With Chloroacetyl Chloride.**—The reaction was carried out as described above. The residue (1.8 g.) remaining after the evaporation of the carbon disulfide was heated *in vacuo* to distill out unchanged I. The residual sirup, after several crystallizations from alcohol–water, yielded 0.88 g. of III, m.p. 78–80°, giving a positive Beilstein halogen test. Analysis showed 3.50% of chlorine instead of the anticipated 9.88%.

(12) Reference 11, p. 138.

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Some Amides of Tuberculostearic Acid

BY DAVID A. SHIRLEY AND GUSTAV A. SCHMIDT[1]

Tuberculostearic acid or 10-methyloctadecanoic acid is a naturally occurring fatty acid of unique structure isolated by Anderson and Chargaff[2] from the human tubercle bacillus. In an earlier paper[3] we have described an improved method of synthesis of *dl*-tuberculostearic acid.

As a part of a general program of examination of certain derivatives of long chain fatty acids as anti-tubercular chemotherapeutic agents, we have introduced the *dl*-tuberculostearic acid fragment into several biologically active amines such as *p*-aminosalicylic acid and 4,4′-diaminodiphenyl sulfone.

Biological evaluation of these amides is being conducted by the Eli Lilly Co. of Indianapolis and we are grateful to Dr. R. G. Jones for arranging the tests.

We would also like to express appreciation to the Research Corporation of New York for a grant which supported this work.

Experimental[4]

***p,p′*-Bis-(10-methyloctadecanamido)-diphenyl Sulfone.**—Four grams (0.0135 mole) of *dl*-10-methyloctadecanoic acid was converted to the acid chloride by thionyl chloride as mentioned previously.[3] To the acid chloride was added a solution of 1.6 g. (0.0065 mole) of *p,p′*-diaminodiphenyl sulfone in 15 ml. of pyridine. The mixture was refluxed for 4 hours, cooled and poured into 200 ml. of water. The precipitated solid was dissolved in acetone, decolorized with charcoal and recrystallized from ethanol to give 4.5 g. of product melting in the range 80–86.5°. Two additional recrystallizations from ethanol and one from a mixture of benzene and petroleum ether (b. p. 60–80°) gave 1.0 g. (20%) of the amide melting at 86.5–88°.

Anal. Calcd. for $C_{50}H_{84}N_2O_4S$: N, 3.46; C, 74.4; H, 10.2. Found: N, 3.48, 3.54; C, 74.2; H, 10.2.

***p*-(10-Methyloctadecanamido)-salicylic Acid.**—The acid chloride from 2.0 g. (0.0068 mole) of 10-methyloctadecanoic acid was added to a solution of 1.0 g. (0.0067 mole) of *p*-aminosalicylic acid in 20 ml. of pyridine. After standing 1 hour, the reaction mixture was poured into excess water and acidified with hydrochloric acid. The precipitated material solidified on standing and was separated and recrystallized once from ethanol, two times from 70% aqueous ethanol and two times from benzene to give 1.4 g. (48%) of the amide melting at 170–172°.

Anal. Calcd. for $C_{26}H_{43}NO_4$: N, 3.23; C, 72.2; H, 9.93. Found: N, 3.30; C, 72.0; H, 9.95.

1,4-Bis-(10′-methyloctadecanamido)-benzene.—The acid chloride from 2.5 g. (0.0084 mole) of 10-methyloctadecanoic acid and 0.4 g. (0.0037 mole) of *p*-phenylenediamine was treated in general accordance with the procedures used above except an overnight reflux period was used. There was obtained 1.0 g. (40%) of the diamide, m. p. 155–156°.

Anal. Calcd. for $C_{44}H_{80}N_2O_2$: N, 4.19; C, 79.1; H, 12.0. Found: N, 4.14; C, 79.1, 78.9; H, 12.1, 12.1.

4-(*p*-Nitrobenzenesulfonamido)-acetanilide.—Nine grams (0.0407 mole) of *p*-nitrobenzenesulfonyl chloride was added to a solution of 5.5 g. (0.037 mole) of *p*-aminoacetanilide in 30 ml. of anhydrous pyridine. After standing 1 hour, the mixture was poured into excess water and the precipitated solid (8.0 g.) recrystallized three times from ethanol. The product melted at 242–242.5° and weighed 6.0 g. (48%).

Anal. Calcd. for $C_{14}H_{13}N_3O_5S$: N, 12.54. Found: N, 12.60.

4-(*p*-Nitrobenzenesulfonamido)-aniline.—The acetanilide derivative above (1.6 g. or 0.0048 mole) was hydrolyzed by a two hour reflux with 30 ml. of 6*N* hydrochloric acid and 15 ml. of ethanol. The mixture was filtered and the filtrate neutralized with sodium acetate. The precipitated amine (1.1 g. or 80%) was recrystallized once from ethanol to give small plates, m. p. 201–202°.

Anal. Calcd. for $C_{12}H_{11}N_3O_4S$: N, 14.33. Found: N, 14.40.

4-*p*-Nitrobenzenesulfonamido)-1-(10′-methyloctadecanamido)-benzene.—Reaction of 1.0 g. (0.0034 mole) of the above amine with the acid chloride from 1.4 g. of 10-methyloctadecanoic acid in general accordance with the procedures used above gave 0.8 g. (42%) of the amide, m. p. 170.5–172°. The product was recrystallized four times from ethanol and once from a 1:1 mixture of benzene and hexane.

Anal. Calcd. for $C_{31}H_{47}N_3O_5S$: N, 7.35. Found: N, 7.55.

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Replacement of Vitamin B_{12} by Desoxynucleotides in Promoting Growth of Certain Lactobacilli

BY WILLIAM SHIVE, MARGARET E. SIBLEY AND LORENE L. ROGERS[1]

Thymidine,[2a,b] hypoxanthine desoxyriboside[3] and other purine desoxyribosides[4,5,6] replace vitamin

(1) Frederick G. Cottrell Research Fellow, 1949–1950.

(2) Anderson and Chargaff, *J. Biol. Chem.*, **85**, 77 (1929).

(3) Schmidt and Shirley, THIS JOURNAL, **71**, 3804 (1949).

(4) All melting points reported were taken on a Fisher melting point block and are uncorrected.

(1) Eli Lilly and Co. Post-doctorate Fellow.

(2) (a) Shive, Ravel and Eakin, THIS JOURNAL, **70**, 2614 (1948); (b) Wright, Skeggs and Huff, *J. Biol. Chem.*, **175**, 475 (1948).

(3) Shive, papers presented at Conference on Development and Uses of Antimetabolites, New York Acad. Sci., Feb., 1949, *Ann. N. Y. Acad. Sci.*, **52**, 1212 (1950).

(4) Kocher and Schindler, *Intern. Z. Vitaminforschl.*, **20**, 441 (1949).

(5) Kitay, McNutt and Snell, *J. Biol. Chem.*, **177**, 993 (1949).

(6) Hoff-Jorgensen, Abstr. 1st Intern. Congr. Biochem., 292 (Cambridge, 1949).