Anal. Calcd. for $C_{19}H_{20}O_5N_4$: C, 59.36; H, 5.24; N, 14.59. Found: C, 59.23; H, 5.29; N, 14.60.

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p-(*p*-Benzoylbenzoyl)benzoic Acid

ROBERT ZELINSKI[1] AND GEORGE O'BRIEN

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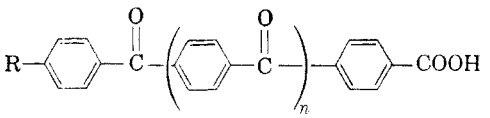
Information concerning the synthesis of linear polybenzoylbenzoic acids of type I is sparse. Koelsch and Bryan[2] prepared dibasic acids (Ia, n



Ia, R = COOH
Ib, R = H

= 1, 2, 3) by acylating toluene with acid chlorides such as those derived from terphthalic acid, *p,p'*-benzophenonedicarboxylic acid, etc., and subsequently oxidizing the end methyl groups to carboxylic acid groups. Acylation of benzene with *p,p'*-benzophenonedicarbonyl chloride gave *p*-(*p*-benzoylbenzoyl)benzoic acid as a by-product.[3] Finally, the acid catalyzed condensation of benzyl alcohol yields polymers which oxidized to a mixture of polyketones containing both ortho and para linkages.[4]

A possible route to compounds of type Ib is the Friedel-Crafts aroylation of *p*-benzylbenzoic acid by halides such as benzoyl chloride and *p*-benzoylbenzoyl chloride. In this way the preparation of *p*-(*p*-benzoylbenzyl)benzoic acid and its oxidation product, *p*-(*p*-benzoylbenzoyl)benzoic acid, was readily achieved. However, the few attempts to extend the synthesis were unsuccessful.

EXPERIMENTAL

p-(*p*-*Benzoylbenzyl*)*benzoic acid.* A solution of 0.05 mole of benzoyl chloride in 30 ml. of carbon disulfide was added with stirring to 0.04 mole of *p*-benzylbenzoic acid[5] and 0.16 mole of aluminum chloride in 30 ml. of carbon disulfide. The mixture was stirred and heated under reflux for 3 hr. after which it was hydrolyzed with ice and hydrochloric acid. The carbon disulfide was removed by steam distillation and the residue was dissolved in aqueous alkali and filtered. Acidification precipitated the crude acid which was twice recrystallized with decolorization from 150-ml. portions of methanol to give 6.6 g. (52%) of *p*-(*p*-benzoylbenzyl)-benzoic acid, m.p. 181.5–182.5°.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10; N.E. 316. Found: C, 79.50; H, 5.17; N.E. 316.

p-(*p*-*Benzoylbenzoyl*) *benzoic acid.* A solution of 3.5 g. of sodium dichromate in 5 cc. of water, 8 cc. of acetic acid, and 1.7 cc. of concentrated sulfuric acid was added dropwise over a 20-min. period to a boiling solution of 3.0 g. of *p*-(*p*-benzoylbenzyl)benzoic acid in 25 ml. of acetic acid. After 45 min. it was poured into water and the precipitate was collected. This was difficultly soluble in dilute sodium hydroxide and methanol. Crystallization from 30 ml. of dioxane gave 2.0 g. (64%) of *p*-(*p*-benzoylbenzoyl)benzoic acid, m.p. 268.5–269.5° (lit., m.p. 268°).[3]

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(1) Present address: 1653 Elm Street, Bartlesville, Okla.

(2) C. F. Koelsch and C. E. Bryan, *J. Am. Chem. Soc.*, **67**, 2041 (1945).

(3) E. Connerade, *Bull. Soc. Chim. Belg.*, **44**, 411 (1935); *Chem. Abstr.*, **30**, 1373 (1936).

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Estrogen Esters[1]

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In the steroid field the same acylating group can promote a desirable physiological response in more than one hormone category.[2,3]

This study extended our observations with the acylation of androgens[4] to the synthetic estrogens diethylstilbestrol (I) and hexestrol (II). More particularly, we were interested in varying the character of the acylating group so that the estrogenic activity inherent in I and II would be increased as well as decreased. This objective is an outgrowth of the provocative concept of Myers[5] and coworkers who have stressed the importance of the steroid sex

(1) Presented at the Meeting-in-Miniature, North Jersey Section, American Chemical Society, January 1958.

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TABLE I

BIS ESTERS OF DIETHYLSTILBESTROL AND HEXESTROL

Compound No.	Acylating Group	M.P.,[a] °C.	Yield,[c] %	Molecular Formula	Carbon[b] Calcd.	Carbon[b] Found	Hydrogen Calcd.	Hydrogen Found
1.	$ClCH_2CH_2CO$	144–145	15	$C_{24}H_{26}Cl_2O_4$	64.1	64.2	5.8	5.9
2.	$BrCH_2CH_2CO$	137–139	19	$C_{24}H_{26}Br_2O_4$[d]	53.6	54.1	4.8	5.2
3.	ICH_2CH_2CO	107–108[e]						
4.	$(CH_3)_3CCH_2CO$	123–124	52	$C_{30}H_{40}O_4$	77.6	77.7	8.7	8.7
5.	$(C_6H_5CH_2)_2CHCO$	170–172	43[ca]	$C_{50}H_{48}O_4$	84.2	84.1	6.8	6.9
			HEXESTROL					
6.	$ClCH_2CH_2CO$	132–134	15	$C_{24}H_{28}Cl_2O_4$	63.9	63.7	6.2	6.4
7.	$BrCH_2CH_2CO$	129–130[e]	14[ca]	$C_{24}H_{28}Br_2O_4$[f]	53.4	55.1	5.2	5.5
8.	ICH_2CH_2CO	108–109[e]						
9.	$(CH_3)_3CCH_2CO$	173–175	83	$C_{30}H_{42}O_4$	77.2	77.3	9.1	9.3
10.	$(C_6H_5CH_2)_2CHCO$	187–189[cb]	52	$C_{50}H_{50}O_4$	84.0	83.8	7.0	7.1

[a] All melting points are uncorrected. [b] Analyses by Drs. Weiler and Strauss, Oxford, England. [c] Unless otherwise indicated the recrystallizing solvent was ethanol; [ca] acetone-water; [cb] heptane, then ethanol. [d] Calcd.: Br, 29.7. Found: Br, 29.4. [e] The compound could not be obtained analytically pure since it apparently suffered dehydrohalogenation on treatment. [f] Calcd: Br, 29.6. Found: Br, 28.2.

hormones on chemical regulation of the endocrine balance.

In the estrogen field, in particular, a wide range of clinical utility is indicated if the primary hormonal effect on the target organs could be modified. Such applications include modification of hypercholesteremia,[6] cupremia,[7] mammary gland growth,[8] calcemia,[9] acne,[10] clinical management of the climacteric,[11] increased feed efficiency in lambs,[12] adjunct to chloropromazine therapy,[13] and protective action against toxic effects of digoxin on the myocardium.[14]

Whereas Myers[5] varied the nuclear character of I and II, we investigated different acylating groups on I and II which insured an inherently active estrogenic function as part of the completed molecule with the potential that esters more active than I and II could then be evaluated at sub-threshold doses, and those esters which were less active could be assessed as to their influence on the non-target functions described above.

The selection of acylating groups was confined to bis-β-halopropionates which were expected to enhance activity and the bis-*tert*-butylacetate and bis-α,α-dibenzylacetates which were expected to afford steric resistance to *in vivo* saponification.[4]

TABLE II

ESTROGENIC ACTIVITY[a] OF BIS-ACYLATED DIETHYLSTILBESTROL (I) AND HEXESTROL (II)

Compound No.	Dosage γ/kg.	Dosage Molar Equivalent[b] to Standard Drug	Activity
1.	1.7	1	1.75
2.	2.0	1	1.94
	1.5	0.75	1.41
	1.0	0.50	1.53
3.	2.4	1	1.98
	1.8	0.75	1.52
	1.2	0.50	0
4.	1.7	1	0.61
5.	2.7	1	0
6.	1.7	1	1.07
7.	2.0	1	1.11
8.	2.4	1	0.42
9.	1.7	1	0.51
10.	2.7	1	0

[a] Estrogenic test was done by the Allen-Doisy method. (See ref. 15). Spayed female rats were given two subcutaneous doses of the compounds and estrus evaluated by two daily vaginal smears until disappearance of the reaction. Results are expressed as per cent animals showing signs of estrus, taking into account duration of the reaction. The results of the count of cornified epithelial cells were plotted on the ordinate, as a function of time, plotted on the abscissa, and the entire area under the curve was weighted and compared to the standard compounds. Each test represents the average response of six rats. The reaction produced by 1 γ of diethylstilbestrol (I) per kg. of rat is arbitrarily taken as 1 (1 γ of hexestrol (II) so evaluated = 1.04). [b] Compounds 1–5 based on I, Compounds 6–10 based on II.

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(7) E. M. Russ and J. Raymunt, *Proc. Soc. Exptl. Biol. Med.*, **92**, 465 (1956).

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(15) C. W. Emmons, *Hormone Assay*, Academic Press, Inc., New York, N. Y., 1950, p. 396.

The compounds prepared are described in Table I, and the noted estrogenic activity as evaluated by the Allen-Doisy method[15] is shown in Table II.

The estrogenic activity tests reflect the capacity of the β-halopropionate linkage (Compounds 1–3, 6, and 7) to enhance the estrogenic response inherent in I and II. These compounds show a marked response when compared with previously assessed derivatives.[16]

The effect of the acylating group is much more pronounced in the derivatives of I than in those of II, and peak activity is found in Compound 2, the bis-β-bromopropionate of diethylstilbestrol. The use of these acylating groups in the androgen series also reflected a superiority of the β-bromo-propionate derivative.[4] The bis-*tert*-butyl acetates (Compounds 4 and 9) yielded activity below that of the parent structures, while the bis-α,α-dibenzyl acetates (Compounds 5 and 10) were inactive. It is of interest that both of these acylating groups above failed to give a hormonal response in the androgen work.[4]

EXPERIMENTAL[17]

The acid chlorides have been described.[4]

Bis(β-chloropropionate) of diethylstilbestrol (Compound 1). To a cooled (−10°) solution of 20 ml. of β-chloropropionyl chloride in 150 ml. of toluene was added dropwise with continued cooling and stirring over a 1-hr. period, a solution of 5 g. (0.0186 mole) of diethylstilbestrol in 20 ml. of pyridine and 150 ml. of toluene. After 20 hr. the reaction mixture was successively treated with water, 3*N* hydrochloric acid, water, saturated sodium bicarbonate, and water. The toluene layer was separated, dried over anhydrous magnesium sulfate, filtered, the toluene removed, and the residue recrystallized from ethanol yielded 1.37 g. (15%), m.p. 144–145°.

Bis(α,α-dibenzylacetate) of hexestrol (Compound 10). To a cooled (−10°) solution of 10 ml. of α,α-dibenzylacetyl chloride in 150 ml. of toluene was added dropwise with continued stirring and cooling, a solution of 5 g. (0.0185 mole) of hexestrol in 10 ml. of pyridine and 120 ml. of toluene. After standing 20 hr. the reaction mixture was processed as described for Compound 1. There was obtained 6.93 g. (52%) of product after successive recrystallizations from heptane and ethanol, m.p. 187–189°.

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(16) J. A. Hogg and J. Korman, *Medicinal Chemistry*, Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 34.

(17) All of the compounds described in Table I were prepared by the same general procedures and representative examples are described.

Synthesis of 1-Aryluracils[1]

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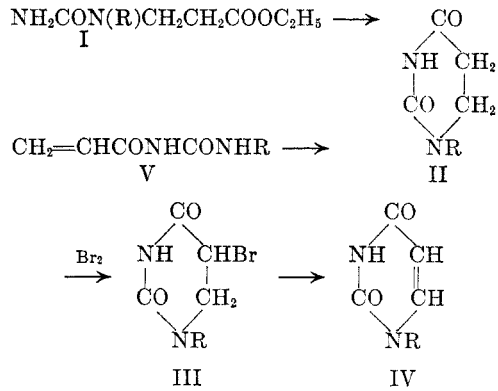
Most of the biologically active synthetic pyrimidines have been shown to effect nucleic acid metabolism.[2,3] Since all naturally occurring pyrimidine nucleosides are pyrimidines substituted with a sugar moiety in the one position, 1-aryluracils might be expected to have significant biological activity. A careful survey of the literature and an examination of the review article by Kenner and Todd[4] revealed that no synthetic preparations for 1-arylpyrimidines has been reported.

There were two general methods for synthesizing uracils substituted in the one position. Either a halogen derivative of the group to be attached is treated with a metallic salt of the pyrimidine[5] or a substituted ureidopropionic acid (I) is cyclized to a dihydrouracil (II), brominated in the five position (III), and dehydrobrominated to the uracil (IV).[6,7] The former method is obviously inapplicable for substitution by an aromatic group and the latter was found to be unsuitable after many unsuccessful attempts to synthesize I having an aromatic group.



To obtain the 1-aryluracils it was necessary to develop a new synthetic preparation which, it is hoped, can also be adapted to nucleoside synthesis since there is no satisfactory method for the introduction of the carbohydrate group into the one position of the pyrimidine ring.

While this investigation was in progress, 1-phenyl-

(1) Based upon a dissertation submitted by N. W. Gabel in partial fulfillment of the requirements for the M. S. degree in The Graduate College at the Chicago Professional Colleges of the University of Illinois.

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