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°.

Acknowledgment. We are grateful to Dr. G. Ungar of our Pharmacology Division for evaluation of the estrogen activities and to A. Lawrence for his technical assistance in the preparation of the compounds.

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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.

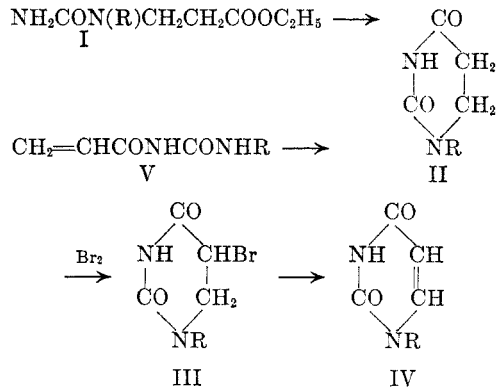
Synthesis of 1-Aryluracils[1]

NORMAN W. GABEL AND S. B. BINKLEY

Received October 15, 1957

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.

(2) R. J. Winzler, *Ann. Rev. Biochem.*, **18**, 535 (1949).

(3) G. H. Hitchings, *Am. J. Clin. Nutrition*, **3**, 321 (1955).

(4) G. W. Kenner and A. Todd, *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. 5, Chap. 7.

(5) R. Behrend, *Ann.*, **253**, 67 (1889).

(6) E. Fisher and G. Roeder, *Ber.*, **34**, 3751 (1901).

(7) J. E. Gearien and S. B. Binkley, presented at the 131st ACS National Meeting, Miami, 1957.

uracil was synthesized by Atkinson *et al.*[8] They treated propiolic anhydride with urethane to obtain *N*-propiolylurethane. The aniline addition product of this compound yielded 1-phenyluracil upon treatment with dilute alkali.

In 1951 Lieser and Kemmner[9] reported the synthesis of 1-acrylyl-3-phenylurea from acrylyl isocyanate and aniline. Several 1-acrylyl-3-arylureas (V) were prepared in this investigation in 50% yields from the arylamine and a solution of acrylyl isocyanate in anhydrous ethyl ether. These ureas were light-sensitive. The mixing of the reactants required caution because the reaction is sometimes violent and acrylyl isocyanate is a strong lachrymator.

The 1-acrylyl-3-arylureas were cyclized to 1-aryldihydrouracils (II) by refluxing for 2–3 days in *N,N*-dimethylformamide to which had been added a small amount of glacial acetic acid. The dihydrouracils were converted to 1-aryl-5-bromodihydrouracils (III) by reaction with bromine in refluxing glacial acetic acid after the method of Gearien and Binkley.[7] The 1-aryluracils (IV) were obtained by dehydrobromination with lithium chloride in *N,N*-dimethylformamide. The over-all yield of 1-phenyluracil based on aniline was 13%.

In this synthetic scheme the only reaction which has not been previously reported is the cyclization of 1-acrylyl-3-arylureas to 1-aryldihydrouracils. This reaction apparently occurs through the nucleophilic attack of the nitrogen atom (originally from the arylamine) on the β-carbon of the acrylyl portion of the urea. This is similar to the nucleophilic addition of alkylamines[7] and arylamines[10] to acrylic acid derivatives. The factors facilitating this cyclization are (*a*) the positive charge residing on the β-carbon of one of the resonance forms of acrylic acid derivatives and (*b*) the formation of a stable six-membered ring.

Although no alkyl derivatives of uracil were attempted, there is no apparent reason why they could not be synthesized by this method. If this preparative scheme can be adapted to nucleoside synthesis, it would be possible to prepare pyrimidine nucleosides with either the alpha or beta configuration at the anomeric carbon atom by starting with either an α- or β-1-amino sugar derivative.

EXPERIMENTAL[11]

Acrylyl chloride and isocyanate. Acrylyl chloride was prepared according to the procedure of Stempel, Cross, and Mariella[12] from acrylic acid and benzoyl chloride. The method of Lieser and Kemmner[9] was followed for obtaining a solution of acrylyl isocyanate in anhydrous ethyl ether from acrylyl chloride and a suspension of silver cyanate in ethyl ether.

1-Acrylyl-3-arylureas. A procedure similar to the one described by Lieser and Kemmner[9] was followed. An Erlenmeyer flask containing the acrylyl isocyanate solution was placed in an ice bath. An equimolar amount of the arylamine was added slowly while the flask was being swirled. The precipitate was washed over a Büchner funnel with ethyl ether to remove unreacted materials and was recrystallized from 95% ethanol. *1-Acrylyl-3-phenylurea*: 27 g. (0.29 mole) of aniline yielded 27 g. (50%) of 1-acrylyl-3-phenylurea; m.p. 146°. Lieser and Kemmner[9] reported 147°. *1-Acrylyl-3-α-naphthylurea:* 42 g. (0.29 mole) of α-naphthylamine yielded 34 g. (50%) of 1-acrylyl-3-α-naphthylurea; m.p. 172–174°. *1-Acrylyl-3-p-chlorophenylurea:* 16.6 g. (0.13 mole) of *p*-chloroaniline yielded 15 g. (52%) of 1-acrylyl-3-*p*-chlorophenylurea; m.p. 203°. *1-Acrylyl-3-p-ethoxyphenylurea:* 35 g. (0.25 mole) of *p*-phenetidine yielded 24 g. (41%) of 1-acrylyl-3-*p*-ethoxyphenylurea; m.p. 124°.

1-Aryldihydrouracils. Eight to sixteen grams of the 1-acrylyl-3-arylurea, 50 ml. of *N,N*-dimethylformamide, and 15–20 ml. of glacial acetic acid were added to a round-bottomed flask fitted with a reflux condensor. After refluxing the mixture for 2–3 days, the solvent was removed by heating under reduced pressure (10–20 mm.). The residue was recrystallized from dioxane to yield the dihydrouracil as clumps of colorless needles. *1-Phenyldihydrouracil:* 11 g. (0.058 mole) of 1-acrylyl-3-phenylurea yielded 9 g. (82%) of 1-phenyldihydrouracil; m.p. 182–184°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.73. Found: C, 63.18; H, 5.31; N, 14.70.

1-α-Naphthyldihydrouracil: 8 g. (0.033 mole) of 1-acrylyl-3-α-naphthylurea yielded 1.5 g. (19%) of 1-α-naphthyldihydrouracil; m.p. 250–252° dec.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: N, 11.24. Found: N, 11.21.

1-p-Chlorophenyldihydrouracil: 14 g. (0.062 mole) of 1-acrylyl-3-*p*-chlorophenylurea yielded 5.4 g. (39%) of 1-*p*-chlorophenyldihydrouracil; m.p. 224°.

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: N, 12.47. Found: N, 12.54.

1-p-Ethoxyphenyldihydrouracil: 16 g. (0.068 mole) of 1-acrylyl-3-p-ethoxyphenylurea yielded 13 g. (81%) of 1-*p*-ethoxyphenyldihydrouracil; m.p. 202–204°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.49; H, 5.96; N, 12.14.

1-Aryl-5-bromodihydrouracils. The procedure of Gearien and Binkley[7] was followed. To a refluxing solution of the 1-aryldihydrouracil in 20 ml. of glacial acetic acid was added slowly an equimolar amount of bromine dissolved in a few milliliters of glacial acetic acid. The reaction flask was cooled under running tap water and the *p*H of the contents was adjusted to *ca.* 5 with 10% sodium hydroxide. Water was then added to induce precipitation. The heavy flocculent precipitate was washed three times with distilled water over a Büchner funnel and recrystallized from dioxane. *1-Phenyl-5-bromodihydrouracil:* 2.7 g. (0.014 mole) of 1-phenyldihydrouracil yielded 2.6 g. (71%) of 1-phenyl-5-bromodihydrouracil; m.p. 192–193° dec.

Anal. Calcd. for $C_{10}H_9BrN_2O_2$: C, 44.61; H, 3.34; N, 10.41; Br, 29.74. Found: C, 44.61; H, 3.34; N, 10.46; Br, 29.95.

1-α-Naphthyl-5-bromodihydrouracil: 1.4 g. (0.006 mole) of 1-α-naphthyldihydrouracil yielded 1.8 g. (94%) of 1-α-naphthyl-5-bromodihydrouracil; m.p. 275°.

Anal. Calcd. for $C_{14}H_{11}BrN_2O_2$: Br, 25.04. Found: Br, 24.97.

1-p-Chlorophenyl-5-bromodihydrouracil: 3.9 g. (0.017 mole) of 1-*p*-chlorophenyldihydrouracil yielded 2.7 g. (53%) of 1-*p*-chlorophenyl-5-bromodihydrouracil; m.p. 211–212° dec.

Anal. Calcd. for $C_{10}H_8BrClN_2O_2$: N, 9.23. Found: N, 9.19.

(8) M. R. Atkinson, M. H. Maguire, R. K. Ralph, G. Shaw, and R. N. Warrener, *J. Chem. Soc.*, 2363 (1957).

(9) T. Lieser and K. Kemmner, *Chem. Ber.*, **84**, 4 (1951).

(10) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953).

(11) Analyses were conducted by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points are uncorrected.

(12) G. H. Stempel, R. P. Cross, and R. P. Mariella, *J. Am. Chem. Soc.*, **72**, 2299 (1950)

1-Aryluracils. The dehydrobromination of 1-aryl-5-bromodihydrouracils was accomplished by a procedure similar to the one described by Holysz.[13] A solution of equimolar amounts of lithium chloride and 1-aryl-5-bromodihydrouracil in 50 ml. of *N,N*-dimethylformamide was heated on a steam cone for 3 hr. Water was now added to the contents to bring about precipitation. The precipitate was washed with distilled water over a Büchner funnel, air-dried, and recrystallized from dioxane as fine colorless needles. The ultraviolet absorption spectrum in methanol (c = 20 μg./ml.) was obtained on a Beckman Ratio Recording Spectrophotometer. *1-Phenyluracil:* 2.3 g. (0.009 mole) of 1-phenyl-5-bromodihydrouracil yielded 0.7 g. (44%) of 1-phenyluracil; m.p. 247°; E_{max} = 11,100 at 265 mμ. Atkinson *et al.*[3] reported m.p. 247°. *1-p-Chlorophenyluracil:* 2.4 g. (0.011 mole) of 1-*p*-chlorophenyl-5-bromodihydrouracil yielded 1.1 g. (45%) of 1-*p*-chlorophenyluracil; m.p. 258°; E_{max} = 15,670 at 264 mμ.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.90; H, 3.16; N, 12.59. Found: C, 53.85; H, 3.27; N, 12.58.

Acknowledgment. This work was supported by grant number CY-3231 from the U.S. Public Health Service.

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(13) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

Action of Grignard Reagents on β-Substituted Propiomesitylenes[1]

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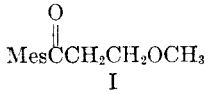
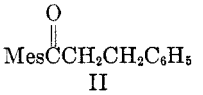
Received October 22, 1957

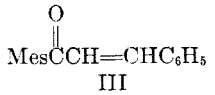
α-Hydrogen elimination reactions produced by the action of Grignard reagents on β-substituted mesityl ketones are followed by 1,4-addition of the Grignard reagent to the resulting α,β-unsaturated ketone. Thus β-methoxypropiomesitylene (I) reacts with two equivalents of phenylmagnesium bromide to give β-phenylpropiomesitylene (II).



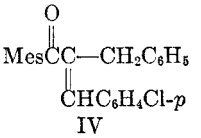
I



II



III

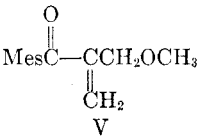


IV

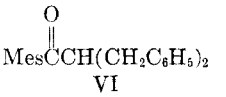
The phenylated ketone proved to be identical with that prepared by catalytic hydrogenation of benzalacetomesitylene (III) according to the method of Barnes.[3] The *p*-chlorobenzal derivative (IV) was made also.

With mesitylmagnesium bromide β-methoxypropiomesitylene (I) yielded β-mesitylpropiomesitylene previously produced by condensing β-chloropropionyl chloride with mesitylene by the method of Friedel and Crafts[4] and by catalytic hydrogenation of mesitoylmesitylacetylene.[5]

An interesting variant was furnished by 3-methoxyisopropenyl mesityl ketone (V),[6] a product of the interaction of formaldehyde, acetomesitylene, and methanol. When this unsaturated ketone was allowed to condense with phenylmagnesium bromide the product was dibenzylacetomesitylene (VI).



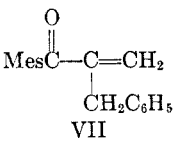
V



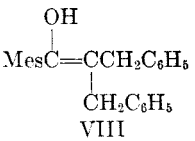
VI

This change differs from the preceding examples in that the enolate that loses the methoxide ion is formed by 1,4-addition of the Grignard reagent to an α,β-unsaturated ketone rather than by enolization of a saturated ketone. Presumably α-benzylvinyl mesityl ketone (VII) was formed as an intermediate.

In addition to the major product, dibenzylacetomesitylene, small amounts of mesitoic acid and dibenzyl ketone were isolated also. These compounds could be produced by air oxidation of the enolic form (VIII) of dibenzylacetomesitylene.



VII



VIII

EXPERIMENTAL[7]

Reaction of β-methoxypropiomesitylene (I) *with phenylmagnesium bromide.* To a refluxing solution of phenylmagnesium bromide, prepared from 62.8 g. (0.4 mole) of bromobenzene, 9.6 g. (0.4 g.-atom) of magnesium, and 200 ml. of dry ether, was added with stirring 20.6 g. (0.1 mole) of β-methoxypropiomesitylene over a period of 10 min. The heating and stirring were continued for 5 hr. The reaction mixture was cooled in an ice bath and treated with a cold dilute solution of hydrochloric acid. The organic layer, after being washed with water and dried over anhydrous sodium sulfate, was freed of solvent by distillation, and the residual yellow oil was distilled through a 12-in. Vigreux column. The small amount of forerun solidified and had the odor characteristic of biphenyl. The main fraction was β-phenylpropiomesitylene, b.p. 149–153°/0.5 mm.; n_D^{20} 1.5570; yield 16.4 g. (65%).

(1) This investigation was supported by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

(2) Socony-Vacuum Oil Co. Fellow, 1954–1955.

(3) R. P. Barnes, *J. Am. Chem. Soc.*, **57**, 937 (1935).

(4) R. C. Fuson and C. H. McKeever, *J. Am. Chem. Soc.*, 62, 2088 (1940).

(5) R. C. Fuson and J. S. Meek, *J. Org. Chem.*, **10**, 551 (1945).

(6) R. C. Fuson and C. H. McKeever, *J. Am. Chem. Soc.*, 62, 999 (1940).

(7) All melting points are corrected; all boiling points are uncorrected.