TABLE I

Initial values for the second-order rate coefficients for bromide ion production, $k_2^{Br^-}$ (l. mole^{-1} sec.$^{-1}$), and for the second-order rate coefficients for acid production, $k_2^{H^+}$ (l. mole^{-1} sec.$^{-1}$), in the reaction of 2-benzyl-2-bromo-4,4-dimethyl-1-tetralone (I) with tetraethylammonium chloride in solvent acetonitrile at various temperatures, t. Some determinations were carried out in the presence of tetraethylammonium perchlorate.

t, °C.	[Bromotetralone]	[NEt_4Cl]	[NEt_4ClO_4]	$10^2k_2^{Br^-}$	$10^2k_2^{H^+}$
1.9	0.0200	0.0430			0.051
1.9	.0100	.0490			.050
1.9	.0200	.0157	0.0580		.048
26.9	.0100	.0065			.83
26.9	.0200	.0100		0.80	
26.9	.0100	.0294			.82
36.0	.0100	.0078			2.12
36.0	.0050	.0162			1.92
36.0	.0172	.0162			2.09
36.0	.0100	.0157	.0580		1.73

$k_2 = Ae^{-E/RT}$. $A = 10^{11.4}$ l. mole^{-1} sec.; $E = 18.5$ kcal./mole.

the bromotetralone I was found to be the dominant reaction.

The differing rates of chloride ion- and of bromide ion-promoted elimination indicate very strongly that the ions are entering the transition state and are not merely accelerating the self-decomposition of the bromotetralone I in solvent acetonitrile through a powerful salt effect. That this is indeed the case was confirmed by the addition of 0.1140 M tetraethylammonium perchlorate to a 0.0100 M acetonitrile solution of the bromotetralone I at 60.0°. It was found that the rate of self-decomposition[2] was not appreciably altered by the presence of weakly nucleophilic perchlorate ions. Similarly, (Table I), it was found that the addition of excess tetraethylammonium perchlorate did not appreciably affect the rates of chloride ion-promoted elimination from the bromotetralone I.

Experimental

The concentrations reported in this paper are uncorrected for expansion of the solvent from room temperature to reaction temperature. Other entities quoted which are concentration dependent are similarly uncorrected.

Materials.—Preparation of the 2-benzyl-2-bromo-4,4-dimethyl-1-tetralone has previously been described.[4]

Tetraethylammonium chloride was prepared by the neutralization of an aqueous 10% solution of tetraethylammonium hydroxide with hydrochloric acid. The residue, after evaporation to dryness, was recrystallized from acetonitrile–acetone and dried under vacuum over phosphorus pentoxide. During the preparation of solutions the salt was manipulated within a nitrogen dry atmosphere.

Tetraethylammonium perchlorate was prepared by neutralizing a 10% solution of tetraethylammonium hydroxide with perchloric acid. Filtration gave tetraethylammonium perchlorate which was recrystallized from water and dried under vacuum over phosphorus pentoxide.

The acetonitrile used was Matheson Coleman & Bell spectroquality reagent.

Kinetic Methods.—All runs were carried out in stoppered volumetric flasks. Aliquots of 4.93 ml., taken with an insulated pipet, were delivered into 30 ml. of acetone previously cooled into solid carbon dioxide–acetone slush.

Measurement of the Extent of Acid Formation.—Analysis was by titration in 30 ml. of acetone, previously rendered neutral to the lacmoid indicator against a standard solution of sodium methylate in methanol.

Measurement of the Extent of Bromide Ion Production.—Analysis was by potentiometric titration against standard aqueous silver nitrate in a titration medium consisting of 30 ml. of acetone containing about 1 ml. of 1 N nitric acid. A silver wire electrode and a potassium nitrate–agar bridge to a dip-type calomel reference electrode were used.

Product Studies.[5]—A 100-ml. solution, 0.0227 M in bromotetralone I and 0.0433 M in tetraethylammonium chloride, was allowed to react for 24 hr. at 37.0°. Two 5-ml. aliquots were removed and both indicated 100% olefin formation as determined by titration of the acid developed. The remaining solution was evaporated to dryness and the solid well washed with water. After drying 530 mg. (99% yield calculated as unsaturated ketone) of a white solid was obtained, m.p. 111–112°, the endocyclic unsaturated ketone II.[4] The mixed m.p. with an authentic sample of the unsaturated ketone II was 110–112°. The infrared and ultraviolet spectra of the product were superimposable upon those obtained for authentic samples of the endocyclic unsaturated ketone II.

Acknowledgment.—This work was supported in part by Grant G-14469 from the National Science Foundation.

(4) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

(5) Melting points were read with a calibrated thermometer. Ultraviolet absorption spectra were determined with a Cary Model 11-MS recording spectrophotometer using reagent grade methanol solutions. Infrared spectra were measured with a Perkin-Elmer Model 21 double beam recording instrument employing sodium chloride optics and matched sodium chloride cells with carbon tetrachloride solutions.

Nucleosides. II. 5′-O-Mesylthymidine and 3′-O-Mesylthymidine[1]

JEROME P. HORWITZ, JOYCE A. URBANSKI, AND JONATHAN CHUA

Rollin H. Stevens Laboratory, Detroit Institute of Cancer Research, Detroit 1, Michigan

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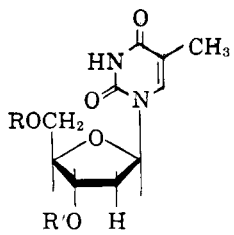
A related study required an expedient synthetic route to the title compounds. The synthesis of 5′-O-mesylthymidine (If) was modeled after the 5′-O-tosyl analog[2] which proceeds from thymidine (Ia) by a series of reactions consisting, in the main, of alternate blocking and deblocking of both alcohol functions in Ia. The successive conversion of Ia first to 5′-O-tritylthymidine (Ib), the acetylation of Ib to form 3′-O-acetyl-5′-O-tritylthymidine (Ic), and detritylation of Ic to give 3′-O-acetylthymidine (Id) constitute three key transformations in the sequence.

(1) This work was supported in part by Research Grants CY-2903 and CY-5943 from the National Cancer Institute, Public Health Service and in part by an institutional grant from the United Foundation of Greater Detroit allocated through the Michigan Cancer Foundation.

(2) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).



Ia. R = R′ = H
b. R = $(C_6H_5)_3C$, R′ = H
c. R = $(C_6H_5)_3C$, R′ = CH_3CO
d. R = H, R′ = CH_3CO
e. R = CH_3SO_2, R′ = CH_3CO
f. R = CH_3SO_2, R′ = H
g. R = $(C_6H_5)_3C$, R′ = CH_3SO_2
h. R = H, R′ = CH_3SO_2
i. R = R′ = CH_3SO_2

The tritylation of Ia in pyridine, as described by Michelson and Todd[3] is time-consuming, requiring a reaction period of one week at room temperature. It has now been found that the same transformation may be effected in 86% yield by heating the reaction mixture to 100° for half an hour. Moreover, the three steps described above may be telescoped into a single operation, affording the 3′-O-acetyl derivative (Id) in 61% over-all yield.

Mesylation of Id afforded 3′-O-acetyl-5′-O-mesylthymidine (Ie) which, on deacetylation with methanolic ammonia, gave the desired 5′-O-mesylthymidine (If), m.p. 162–164°. The identity of the latter follows from its elementary analysis together with the fact that the product, on treatment with sodium iodide, gave the known 5′-iodo-5′-deoxythymidine.[2]

It was reported in an earlier study[4] that Id, on successive mesylation and deacetylation, yields a solid, m.p. 149°, to which the structure 5′-O-mesylthymidine (If) was also assigned.[5] Repetition of the original work indicated that deacetylation, as effected by adding ethanolic ammonia to a solution of crude Ie in 95% ethanol, is, at best, incomplete. Thus, the principal product of the consecutive reactions, after two recrystallizations from ethanol, proved to be identical in every respect with Ie. Infrared studies performed on material isolated from the mother liquor, m.p. 145–150°, showed the solid to be a mixture of Ie and If.[6]

Michelson and Todd have reported that 3′-O-mesyl-5′-O-tritylthymidine (Ig), obtained from the mesylation of Ib, affords 3′-O-mesylthymidine (Ih), a water-recrystallizable solid, m.p. 116°, following a brief reflux period in 80% acetic acid. Repeated efforts to duplicate this observation led in each case to a higher melting product, 152–153° dec. with properties consistent, nevertheless, with Ih. Moreover, the material obtained in the present study, on mesylation, afforded a solid identical in every respect with Ii.[2]

The possibility of dimorphic forms of Ih was initially considered as a plausible explanation for the apparent discrepancy in melting points since the phenomenon has been observed[2] in connection with the deoxyhalogenothymidines. However, the product, Ih, obtained in the present work is virtually water-insoluble; in fact, attempts to recrystallize the solid from water resulted in wholesale decomposition.

Experimental[7]

5′-O-Tritylthymidine (Ib).—A solution of 5.0 g. (20.6 mmoles) of thymidine (Ia) in 100 ml. of dry pyridine containing 7.0 g. (25.1 mmoles) of triphenylmethyl chloride was heated at 100° with stirring for 0.5 hr. The cooled reaction mixture was poured in a thin stream into 1.5 l. of vigorously stirred ice water. The product was collected, washed with generous quantities of water, and dried in a vacuum desiccator overnight. The off-white solid crystallized from acetone–benzene; wt. 8.57 g. (86% yield), m.p. 128–130° (lit.,[3] 128°).

3′-O-Acetylthymidine (Id).—A solution of 5.0 g. (20.6 mmoles) of Ia and 7.0 g. (25.1 mmoles) of trityl chloride in 100 ml. of dry pyridine was heated at 100° with stirring for 0.5 hr. To the cooled amber solution was added 10.7 ml. (105 mmoles) of freshly distilled acetic anhydride and the reaction mixture held overnight at room temperature. The clear solution was poured slowly with vigorous stirring into 1 l. of ice water, the product collected, washed with liberal quantities of water, and dried in a vacuum desiccator (P_2O_5) overnight. The crude mixture of solids was refluxed for 10 min. in 35 ml. of 80% acetic acid and the clear solution evaporated to dryness under diminished pressure. The residue was twice evaporated first from ethanol, then benzene, and next triturated with three portions (*ca.* 25 ml.) of boiling ether. The ether-insoluble material crystallized from acetone–petroleum ether (30–60°); wt. 3.57 g. (61% yield based on Ia), m.p. 172–174° (lit.,[3] 176°).

3′-O-Acetyl-5′-O-mesylthymidine (Ie).—To a cold (0°) solution of 2.93 g. (10.3 mmoles) of Id in 60 ml. of dry pyridine was added 0.9 ml. (11.6 mmoles) of methanesulfonyl chloride and the mixture held at 0° overnight. After the addition of 1 ml. of water, the mixture was refrigerated for an additional 0.5 hr. and then poured with stirring into 300 ml. of ice water. The cloudy mixture was extracted (3 × 50 ml.) with chloroform and the combined extracts washed successively with 200 ml. of cold, 2 *N* sulfuric acid and dilute sodium bicarbonate. The dried, filtered extract was evaporated to dryness under reduced pressure and the residue crystallized from 95% ethanol in the form of irregular needles; wt. 2.2 g. (62% yield), m.p. 164.5–165°, $[\alpha]^{24}D$ −20° (EtOH, *c* 0.2), $\lambda_{max,\ min}^{95\%\ EtOH}$ (mμ) 265,231 (ε 9260, 1392).

Anal. Calcd. for $C_{13}H_{18}N_2O_8S$: C, 43.09; H, 5.01; N, 7.73. Found: C, 43.05; H, 5.03, N, 7.69.

5′-O-Mesylthymidine (If).—To 40 ml. of half-saturated methanolic ammonia was added 0.4 g. (1.1 mmoles) of Ie and the solution held at 0° overnight. The solution was

(3) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 951 (1953).

(4) R. Letters and A. M. Michelson, *ibid.*, 1410 (1961).

(5) This structural assignment was based solely on an elemental nitrogen analysis. It is pertinent to point out that the calculated nitrogen values for If and its immediate precursor, Ie, differ only by 1% (see Experimental).

(6) The observations recorded above cast serious doubt on the claim of Letters and Michelson (see reference 4) that 5,-O-mesylthymidine, m.p. 149°, is converted to 2,5,-anhydro-1-(2′-deoxy-β-D-ribofuranosyl)-thymine on treatment with sodium *t*-butoxide.

(7) All melting points are uncorrected. Analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, Model 11.

evaporated to dryness under reduced pressure and the residue crystallized as colorless rosettes of needles from ethanol; wt. 0.32 g. (90% yield), m.p. 162–164°; $[\alpha]^{25}D$ +7.8° (EtOH, *c* 0.2), $\lambda_{max,\ min}^{95\%\ EtOH}$ (mμ) 266, 234 (ε 9410, 1470).

Anal. Calcd. for $C_{11}H_{16}N_2O_7S$: C, 41.24; H, 5.04; N, 8.75. Found: C, 41.07; H, 5.01; N, 8.87.

A solution of 1.72 g. (5.34 mmoles) of If and 2.4 g. (16 mmoles) of anhydrous sodium iodide in 50 ml. of dry butanone was refluxed for 2 hr. under an atmosphere of nitrogen. The sodium mesylate was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The pale yellow residue was triturated with cold water, collected, and dried; wt. 1.67 g. (89% yield), m.p. 165–168° dec. (lit.,[2] 168° dec.) alone or when admixed with an authentic sample of 5′-iodo-5′-deoxythymidine.

Methanesulfonyl chloride[8] (0.12 ml., 1.5 mmoles) was added to a solution of 0.4 g. (1.44 mmoles) of Id in 5 ml. of pyridine and the solution held at 0° overnight. Water (1 ml.) was then added, the mixture evaporated to dryness (> 40°) under reduced pressure and a solution of the residue in chloroform was washed successively with 0.1 *N* sulfuric acid, aqueous sodium bicarbonate, and water. The dried (magnesium sulfate) extract was filtered and the filtrate evaporated to dryness under reduced pressure. The residual frothy glass was dissolved in 10 ml. of 95% ethanol, saturated ethanolic ammonia (10 ml.) was added and the solution held at 0° overnight. The solvent was removed under reduced pressure and the residue slowly crystallized at room temperature from ethanol as a colorless solid, wt. 0.21 g., m.p. 156–162°. Recrystallization from ethanol gave small, colorless arrowheads, wt. 0.15 g., m.p. 162–164° alone or when admixed with an authentic sample of Ie. Infrared absorption spectra derived from Ie and this product were essentially superimposable, both exhibiting a strong acetate peak (Nujol) at 5.74 μ.

The original alcohol filtrate was stored in a refrigerator overnight and an additional crop of material was collected; wt. 0.095 g., m.p. 145–150°. The infrared spectrum obtained with this fraction was quite similar to that derived from If with the exception that the former manifested a prominent shoulder at 5.74 μ.

3′-O-Mesylthymidine (Ih).—A solution of 3.4 g. (6.05 mmoles) of Ig[2] in 40 ml. of 80% acetic acid was refluxed for 6 min. and the clear solution evaporated to dryness under reduced pressure. The residue was twice evaporated from ethanol and then triturated with (3 × 25 ml.) boiling ether. The ether-insoluble material crystallized from ethanol as a colorless solid; wt. 1.01 g. (52% yield), m.p. 150–153° dec. A second recrystallization (Norit) from ethanol gave a colorless granular solid, m.p. 152–153° dec.; $[\alpha]^{25}D$ +9.4° (EtOH, *c* 1.15), $\lambda_{max,\ min}^{95\%\ EtOH}$ (mμ) 265, 233 (ε 9867, 2200).

Anal. Calcd. for $C_{11}H_{16}N_2O_7S$: C, 41.24; H, 5.04; N, 8.75. Found: C, 41.23; H, 5 14; N, 8.76.

To a cold solution of 0.16 g. (0.5 mmole) of Ih in 2 ml. of dry pyridine was added 0.1 ml. (1.3 mmoles) of methanesulfonyl chloride and the solution held at 0° overnight. To the clear solution was added *ca.* 0.1 ml. of water and the mixture held at 0° for an additional 0.5 hr. The clear solution was slowly poured into 50 ml. of ice water with vigorous stirring, the solid collected, washed with liberal quantities of water, and dried. A single crystallization from 95% ethanol gave rosettes of colorless needles; wt. 0.145 g. (73% yield), m.p. 166–169° dec., (lit.,[2] 168–169° dec.), $[\alpha]^{25}D$ +8.1° (acetone, *c* 1), $\lambda_{max,\ min}^{95\%\ EtOH}$ (mμ) 263, 233 (ε 8666, 1443).

An authentic sample of Ii prepared from thymidine[2] exhibited the following properties: m.p. 166–169° dec.; $[\alpha]^{23}D$ +7.9° (acetone, *c* 1), $\lambda_{max,\ min}^{95\%\ EtOH}$ (mμ) 263, 233 (ε 8670, 1140).

(8) This procedure essentially duplicates that described in ref. 4.

Synthesis of Imidazo[5, 1-*a*]isoquinoline and -β-carboline Derivatives

I. W. ELLIOTT

Department of Chemistry, Fisk University, Nashville 8, Tennessee

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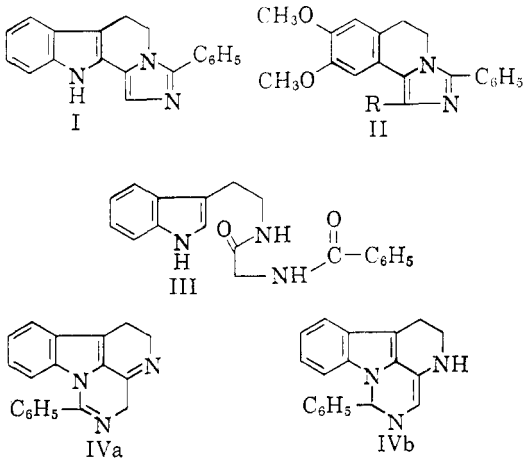
3-Phenyl-5,6-dihydroimidazo[5,1-*a*]-β-carboline (I), which represents a member of a new ring system, was prepared by a series of reactions that are analogous to the synthesis of 3-phenyl-5,6-dihydro-8,9 - dimethoxyimidazo[5,1 -*a*]isoquinoline (II).[1] The preparation of the imidazo-β-carboline derivative was undertaken to test the feasibility of extending to the indole series this double ring closure illustrated by the synthesis of II (R = H)[2] and to submit I for biological testing since II has been found to have amoebicidal properties.[1,3]



Tryptamine was condensed with ethyl hippurate to give (3-indolyl)hippuramide (III) as shown by analysis, absorption spectra and a positive Ehrlich test, which indicates that the indole ring was unsubstituted at the 2-position. The amide was dehydrated with phosphoryl chloride in toluene to afford a basic compound, $C_{19}H_{15}N_3$. The formulation of the base as I is supported by the method of synthesis, by analysis and molecular weight determination, by its chemical properties, and by absorption spectra. In contrast to the starting amide the base gives a negative Ehrlich test and forms a monohydrochloride ($C_{19}H_{16}N_3Cl$) and a monomethiodide ($C_{20}H_{18}N_3I$). The potentiometric titration of the base (I) confirms that it is a monoacidic

(1) R. Child and F. Pyman, *J. Chem. Soc.*, 36 (1931); Ring index no. 2772, A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed., American Chemical Society, Washington, D. C., 1960.

(2) In the unactivated case, the formation of an imidazo[5,1-*a*]isoquinoline from β-phenylethylhippuramide is not successful; unpublished observations.

(3) T. Kametani, H. Iida, and H. Iwakata, *J. Pharm. Soc. Japan*, **71**, 325 (1951); *Chem. Abstr.*, **46**, 4546 (1952) and earlier references.