[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Some Sulfanilamide Derivatives of the Isoquinoline Series[1]

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Several 1-alkyl-2-sulfanilyl-1,2,3,4-tetrahydroisoquinolines have been prepared. The intermediate 1-alkyl-1,2,3,4-tetrahydroisoquinolines were obtained by ring closure of the β-acylaminoethylbenzenes followed by reduction. These and related compounds are described.

The pharmacological importance of many sulfanilamide derivatives containing a nitrogen heterocycle suggested that the isoquinoline nucleus, present in a variety of alkaloids of pronounced physiological activity and low toxicity, might profitably be incorporated in such a compound. To this end a series of 1-alkyl-2-sulfanilyl-1,2,3,4-tetrahydroisoquinolines and 5-sulfanilamidoisoquinoline have been synthesized. The alkyl groups in the former have been so chosen as to give representative members of the series from the parent compound with no alkyl substituent to the derivative with an alkyl substituent of 13 carbons. Alkyl groups with both even and odd numbers of carbon atoms are represented. The hexyl and heptyl derivatives afford an example of adjacent members of the homologous series. The effect of the length of the alkyl chain in this series is apparent not only in the differing solubilities but also in the basicities. For example the 1-ethyl derivative gives a hydrochloride with concentrated acid while the 1-hexyl and higher derivatives do not.

The 1-alkyl-2-sulfanilyl-1,2,3,4-tetrahydroisoquinolines were prepared by the hydrolysis of the acetyl derivative obtained by the Schotten–Baumann condensation of the tetrahydroisoquinoline with acetylsulfanilyl chloride. In the case of the parent compound with no 1-alkyl substituent, *p*-nitrobenzenesulfonyl chloride was used in place of the acetylsulfanilyl chloride and the resulting nitro compound converted to the amine by reduction. The 1-(*n*-hexyl) compound was prepared by both of these routes. The necessary 1-alkyl-tetrahydroisoquinolines were obtained by the Bischler–Napieralski ring closure of the appropriate β-acylaminoethylbenzene to the 3,4-dihydroisoquinoline, followed by reduction. The unsubstituted 1,2,3,4-tetrahydroisoquinoline was obtained by the reduction of isoquinoline.

The preparation of 5-sulfanilamidoisoquinoline has been reported elsewhere[3] since this investigation was completed. However, as a study of certain steps of the synthesis has been made and two different routes compared, the results are reported here.

Experimental[4]

Preparation of β-Acylaminoethylbenzenes.—The acid chlorides, prepared from the acid and thionyl chloride, were condensed with β-phenylethylamine by the Schotten–Baumann reaction. Results are summarized in Table I. Potassium carbonate was used as hydrogen chloride acceptor in all cases with the exception of the preparation of β-undecanoylaminoethylbenzene where pyridine was used. Pyridine is apparently the preferable agent as the yield in this case was quantitative. The crude amides were used without further purification in the preparation of the dihydroisoquinoline with the exception of β-propionylaminoethylbenzene, which was distilled. Analytical samples were purified by crystallization from a variety of solvents.

TABLE I

β-ACYLAMINOETHYLBENZENES

Acyl group	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found
Propionyl[a]	72	57–57.5[b]			
Heptanoyl[c]	80	43–44	$C_{15}H_{23}NO$	6.01	6.04
Octanoyl	94	54–54.5	$C_{16}H_{25}NO$	5.67	5.76
Undecanoyl	100	68	$C_{19}H_{31}NO$	4.84	4.74
Tetradecanoyl	79	80	$C_{22}H_{37}NO$	4.23	4.28

[a] B.p. 141–143° (0.5 mm.). [b] Given as 50–51°, E. Späth, F. Berger and W. Kuntara, *Ber.*, **63**, 137 (1930). [c] B.p. 187–189° (0.5 mm.).

Preparation of 1-Alkyl-3,4-dihydroisoquinolines.—The β-acylaminoethylbenzenes were closed to the 1-alkyl-3,4-dihydroisoquinolines by the method of Bischler and Napieralski.[5] The results are summarized in Table II. This is the only reaction in the synthesis of the 1-alkyl-2-sulfanilyl-1,2,3,4-tetrahydroisoquinolines in which good yields were not obtained. Two factors were responsible. One was the lack of a group such as alkoxy in the 3 or 4 position to activate the benzene ring. The other is that the reaction was carried out with relatively large quantities of material so that neither uniform heating nor mechanical stirring of the thick, viscous, semi-solid material which formed during the reaction were possible. Various modifications of the usual procedure were employed in an attempt to overcome the detrimental effect of the large quantities, but they had little effect on the yields.

Preparation of 1,2,3,4-Tetrahydroisoquinolines.—The 1-alkyl-1,2,3,4-tetrahydroisoquinolines were prepared by the reduction of the 3,4-dihydro compounds with hydrogen in the presence of Adams platinum oxide catalyst. The reduction went readily and in excellent yield. Results are summarized in Table II. 1,2,3,4-Tetrahydroisoquinoline itself was prepared by the reduction of isoquinoline. Sodium and alcohol, tin and hydrochloric acid, and hydrogen in the presence of Adams catalyst were all effective.

Preparation of 2-Acetylsulfanilyl and 2-(*p*-Nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinolines.—These compounds were prepared by the Schotten–Baumann reaction of the base with the appropriate sulfonyl chloride. An example is described below. Table III contains a summary of the results.

1-(*n*-Tridecyl)-2-acetylsulfanilyl-1,2,3,4-tetrahydroisoquinoline.—To 3.7 g. (0.0159 mole) of acetylsulfanilyl chloride was added a solution of 5 g. (0.0159 mole) of 1-(*n*-tridecyl)-1,2,3,4-tetrahydroisoquinoline and 3.8 g. (0.0481 mole) of dry pyridine in 30 ml. of absolute acetone. Reaction was evidenced by warming of the reaction mixture. The solution, protected from moisture, was refluxed on an air-bath for 6 hours during continuous stirring, allowed to stand overnight, then poured into 4 volumes of cold water. The product precipitated as a brown oil which slowly crystallized on standing in a freezing-bath. The tan powder partially oiled on the filter. The crude yield was 7.65 g. (95%).

Purification was difficult because the product persisted in coming out of solution as an oil, and when obtained in the solid state all attempts to dry *in vacuo* caused it to revert to a sirup. Purification was accomplished by crystallization

(1) From the dissertation presented by George E. Hall for the degree of Doctor of Philosophy, Yale University, 1942.

(2) Mount Holyoke College, South Hadley, Mass.

(3) J. J. Craig and W. E. Cass, THIS JOURNAL, **64**, 783 (1942).

(4) All experimentally determined temperatures are corrected.

(5) Bischler and Napieralski, *Ber.*, **26**, 1903 (1893).

TABLE II

1-ALKYL-3,4-DIHYDROISOQUINOLINES AND 1-ALKYL-1,2,3,4-TETRAHYDROISOQUINOLINES

Alkyl group	Yield, %	B.p. at 0.5 mm., °C.	n^tD	t, °C.	Chloroplatinate M.p., °C.	Chloroplatinate Formula	Platinum, % Calcd.	Platinum, % Found[a]
Dihydroisoquinolines								
Ethyl[b]	41	74–78	1.5751	27	210[c]	$(C_{11}H_{13}N)_2 \cdot H_2PtCl_6$	26.81	26.98
n-Hexyl[d]	55	129–137	1.5328	21	184	$(C_{15}H_{21}N)_2 \cdot H_2PtCl_6$	23.24	23.23
n-Heptyl[e]	50	144	1.5309	23	181–183	$(C_{16}H_{23}N)_2 \cdot H_2PtCl_6$	22.49	22.50
n-Decyl	49	165–167	1.5183	25	152–153	$(C_{19}H_{29}N)_2 \cdot H_2PtCl_6$	20.50	20.50
n-Tridecyl	35	190	1.5160	21	137[f]	$(C_{22}H_{35}N)_2 \cdot H_2PtCl_6$	18.83	18.77
Tetrahydroisoquinolines								
Ethyl	91	75–78	1.5550	24	182[c]	$(C_{11}H_{15}N)_2 \cdot H_2PtCl_6$	26.64	26.49
n-Hexyl[g,h]	86	134[i]	1.5240	22.5	152–153[f]	$(C_{15}H_{23}N)_2 \cdot H_2PtCl_6$	23.13	23.03
n-Heptyl[j]	91	137–139[i]	1.5208	22.5	166–167	$(C_{16}H_{25}N)_2 \cdot H_2PtCl_6$	22.39	22.32
n-Decyl	91	165–167	1.5101	29	141–142	$(C_{19}H_{31}N)_2 \cdot H_2PtCl_6$	20.42	20.44
n-Tridecyl	98	203–205	1.5070	23.5	121.5–123	$(C_{22}H_{37}N)_2 \cdot H_2PtCl_6$	18.76	18.78

[a] Average of two values differing not more than 0.20. [b] Picrate, m.p. 196–196.5°. Reported, 190–192° *in vacuo*, reference,[b] Table I. [c] With frothing. [d] Picrate, m.p. 84.5°. *Anal.* Calcd. for $C_{15}H_{21}N \cdot C_6H_3N_3O_7$: N, 12.61. Found: N, 13.01. [e] Picrate, m.p. 77–78°. [f] Sintering began several degrees lower. [g] Hydrochloride, m.p. 123–123.5°. [h] 2-Phenylcarbonamido derivative, m.p. 77.5°. *Anal.* Calcd. for $C_{22}H_{28}N_2O$: N, 8.33. Found: N, 8.25. [i] At 1 mm. [j] 2-(*p*-Nitrobenzoyl) derivative, m.p. indefinite, about 225°, with decomposition beginning about 210°. *Anal.* Calcd. for $C_{23}H_{28}N_2O_3$: N, 7.37. Found: N, 8.06.

TABLE III

N-ARYLSULFONYL-1,2,3,4-TETRAHYDROISOQUINOLINES

1-Substituent	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2-Acetylsulfanilyl-1,2,3,4-tetrahydroisoquinolines					
Ethyl	91	156.5–157.5	$C_{19}H_{22}N_2O_3S$	7.82	7.79
n-Hexyl	77	102–103	$C_{23}H_{30}N_2O_3S$	6.76	6.68
n-Heptyl	81	[a]	$C_{24}H_{32}N_2O_3S$	6.34	6.51
n-Tridecyl	95	56–58	$C_{30}H_{44}N_2O_3S$	5.47	5.76
2-(*p*-Nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinolines					
Hydrogen	83	179	$C_{15}H_{14}N_2O_4S$	8.81	8.80
n-Hexyl	77	56–57	$C_{21}H_{26}N_2O_4S$	6.97	6.92
2-Sulfanilyl-1,2,3,4-tetrahydroisoquinolines					
Hydrogen	44	177–178[b]	$C_{15}H_{16}N_2O_2S$	9.72	9.63
Ethyl	100	134–134.5	$C_{17}H_{20}N_2O_2S$	8.86	8.86
n-Hexyl	78[c]	58–58.5	$C_{21}H_{28}N_2O_2S$	7.53	7.42
n-Heptyl		67–67.5	$C_{22}H_{30}N_2O_2S$	7.25	7.37
n-Tridecyl	98	70.5–71.5	$C_{28}H_{42}N_2O_2S$	5.96	5.89

[a] Indefinite, depending upon rate of heating. In range 50–75°. [b] Reported 179–180.5° (reference 7) and 174° (reference 8). [c] By hydrolysis of the acetyl compound. Reduction of the nitro compound gave a 70% yield.

in sequence from dilute alcohol, ligroin, dilute alcohol and methanol. The colorless acetyl compound melted at 56–58°.

Preparation of 2-Sulfanilyl-1,2,3,4-tetrahydroisoquinolines.—These compounds may be prepared either by the hydrolysis of the acetyl derivative or by the reduction of the corresponding nitro compound. Both routes were tested in the preparation of the 1-(*n*-hexyl) compound. The yields in the preparation of the acetyl and the nitro derivatives were the same (77%), but the hydrolysis of the former gave a 78% yield, while the reduction of the latter gave only 70%, presumably due to poisoning of the Adams platinum oxide catalyst by the sulfur compound. The route through the acetyl compound was chosen for the other 1-alkyl sulfanilyl compounds. The results are summarized in Table III. An example of the hydrolysis is given below.

Both the 1-alkyl-2-acetylsulfanilyl-1,2,3,4-tetrahydroisoquinolines and the free amines showed a marked tendency to form oils and were difficult to obtain in crystalline form. This reluctance to crystallize was characteristic of the pure as well as the crude products, increasing to a maximum at the *n*-decyl derivative. Neither 1-(*n*-decyl)-2-sulfanilyl-1,2,3,4-tetrahydroisoquinoline, the intermediates in its preparation, nor its derivative with phenyl isothiocyanate or with diethylacetyl isocyanate could be crystallized. Both the lower members and the higher member have been crystallized and purified to give sharp melting points and accurate analyses.

The reduction of the nitro compound to 2-sulfanilyl-1,2,3,4-tetrahydroisoquinoline was accomplished with zinc and ammonium chloride in 44% yield. Since this work was completed, two reports of this compound have been made by other investigators; Sargent and Small[6] through the acetyl derivative, Holliman and Mann[7] by a radically different route.

1-(*n*-Tridecyl)-2-sulfanilyl-1,2,3,4-tetrahydroisoquinoline.—To 1.1 g. (0.00215 mole) of 1-(*n*-tridecyl)-2-acetylsulfanilyl-1,2,3,4-tetrahydroisoquinoline were added 16 ml. of a mixture of equal weights of alcohol and concentrated hydrochloric acid. The solution was refluxed for 30 minutes, then cooled in an ice-bath. The amine came out as an emulsion which soon crystallized to a tan precipitate; yield, 0.99 g. (98%). The product was purified by crystallization, twice from ether, from dilute alcohol, and again from ether; m.p. 70.5–71.5°.

Preparation of 5-Sulfanilaminoisoquinoline.—This compound was obtained both by the reduction of the corresponding nitro compound and by the hydrolysis of its N-acetyl derivative.

In the preparation of 5-nitroisoquinoline from isoquinoline, the procedure of Claus and Hoffmann[8] in which fuming nitric and sulfuric acids were used as the nitrating reagent was found to be preferable to that of LeFèvre and LeFèvre,[9] who used potassium nitrate dissolved in sulfuric acid. In contrast to the earlier investigators[8,9] who reported quantitative yields, the best yield was 77%, in agreement with the 74% yield of Fieser and Martin.[10]

The reduction of the nitro compound to 5-aminoisoquinoline was accomplished in 84% yield with stannous chloride in hydrochloric acid. The fine, almost colorless needles melted at 130° (reported m.p.: 128°,[8,11] 128–129°,[3] 154°[12]). Tin and hydrochloric acid, iron with a trace of acetic acid, ammonium polysulfide, zinc and ammonium chloride, and sodium hydrosulfite in basic solution were tried for the reduction of the nitro compound. The above procedure gave much the best results. A yield of 80% has since been reported by catalytic reduction.[3]

5-Acetylsulfanilamidoisoquinoline was obtained by the condensation of the amino compound with acetylsulfanilyl chloride; yield 82%; m.p. 290° with darkening (reported, 284–288° (dec.)[3]). Condensation of the amino compound with *p*-nitrobenzenesulfonyl chloride gave 5-(*p*-nitroben-

(6) L. J. Sargent and L. Small, *J. Org. Chem.*, **11**, 179 (1946).
(7) F. G. Holliman and F. G. Mann, *J. Chem. Soc.*, 737 (1942).
(8) A. Claus and K. Hoffmann, *J. prakt. Chem.*, **47**, 252 (1893).
(9) C. Q. LeFèvre and R. W. LeFèvre, *J. Chem. Soc.*, 1475 (1935).
(10) L. F. Fieser and E. L. Martin, THIS JOURNAL, **57**, 1840 (1935).
(11) A. Claus and C. Gutzeit, *J. prakt. Chem.*, **52**, 18 (1895).
(12) P. Fortner, *Monatsh.*, **14**, 146 (1893).

zenesulfonamido)-isoquinoline as fine white crystals; yield 43%; m.p. 270° with darkening (*Anal.* Calcd. for $C_{15}H_{11}N_3O_4S$: N, 12.78; S, 9.72. Found: N, 12.9; S, 9.34).

5-Sulfanilamidoisoquinoline was obtained in 80% yield by the hydrolysis of the acetyl compound. Recrystallization gave fine white needles melting at 224° (reported, 223–224.5°[3]). Reduction of 5-(*p*-nitrobenzenesulfonamido)-isoquinoline gave only a 34% yield of crude product.

NEW HAVEN, CONN. RECEIVED JULY 12, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND NUTRITION, SCHOOL OF MEDICINE AND THE LABORATORIES OF THE ALLAN HANCOCK FOUNDATION, UNIVERSITY OF SOUTHERN CALIFORNIA]

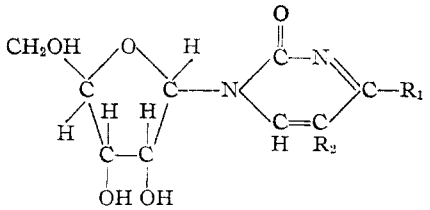
Uridine and Cytidine Derivatives[1]

BY MARTIN ROBERTS AND DONALD W. VISSER

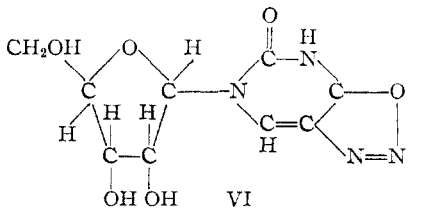
The preparation of the new compounds 5-methyluridine, 5-methylcytidine, 5-aminouridine, diazouridine and an improved method for the preparation of 5-hydroxyuridine is described. These compounds are of interest because of their structural similarity to uridine and cytidine which are utilized for nucleic acid biosynthesis.

It has been shown previously[2] that 5-chlorouridine (I) reversibly inhibits the growth response of *Neurospora* mutant, 1298, produced by uridine or cytidine. It was of interest, therefore, to prepare other derivatives of the pyrimidine nucleosides and test them in biological systems. Compounds of this type may provide a means of studying nucleic acid metabolism and may also have chemotherapeutic applications.

A method for the synthesis of 5-methylcytidine (II), 5-methyluridine (III), 5-aminouridine (IV), 5-hydroxyuridine (V) and diazouridine (VI) are reported in this paper. Results of the biological studies will be reported elsewhere.



I, R_1 = OH, R_2 = Cl
II, R_1 = NH_2, R_2 = CH_3
III, R_1 = OH, R_2 = CH_3
IV, R_1 = OH, R_2 = NH_2
V, R_1 = OH, R_2 = OH



VI

5-Methylcytosine has been reported as a constituent of nucleic acids,[3,4] and a thymine pentoside has been isolated from sponges.[5] It seemed desirable, therefore, to synthesize the related compounds, 5-methylcytidine (II) and 5-methyluridine (III), especially since these nucleosides are also structurally similar to thymidine. 5-Methylcytidine (II) was prepared from 2,4-diethoxy-5-methylpyrimidine using a modification of the procedure of Howard, *et al.*[6] Acid hydrolysis of the intermediate condensation product yielded 5-methyluridine (III).

The synthesis of 5-aminouridine (IV) was particularly desirable since the compound was not only of interest as a possible antimetabolite, but also could be used to synthesize other compounds by substitution through diazotization. Coupling with diazotized *p*-nitroaniline in the 5-position of uridine and then reduction of the resulting azo dye to the amine was a possible scheme of synthesis[7] which proved to be impractical. An orange azo dye could be separated from the other products of the reaction by means of chromatography using alumina as an absorbent, but the yield was very low. Johnson, *et al.*,[8] comment that substitution on the N_1 of pyrimidines prevents diazo compounds from coupling.

5-Aminouracil has been prepared from 5-bromouracil by heating with aqueous ammonia at 180°,[9] however, under these conditions 5-bromouridine decomposed excessively. When the temperature was lowered to 55° very little decomposition resulted and 5-aminouridine (IV) was readily isolated in good yield.

Repeated attempts to prepare 5-hydroxyuridine (V), as described by Levene and LaForge,[10] failed to give a crystalline product. A modification of the procedure, however, resulted in 5-hydroxyuridine (V) which melted 20° higher than reported by these workers.

Diazouridine (VI) was prepared from 5-aminouridine using the method of Johnson, *et al.*,[11] for the synthesis of diazouracil from aminouracil. The structure of VI is assumed to be similar to the one postulated for diazouracil.

(1) Supported by a grant from the Research Corporation. This material was taken from a thesis presented by Martin Roberts to the Graduate School, University of Southern California, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Presented in part at the Federation Meetings, April, 1951. Contribution No. 287 from the Department of Biochemistry and Nutrition.

(2) T. K. Fukuhara and D. W. Visser, *J. Biol. Chem.*, **190**, 95 (1951).

(3) T. B. Johnson and R. D. Coghill, THIS JOURNAL, **47**, 2838 (1925).

(4) W. E. Cohn, *ibid.*, **72**, 2811 (1950).

(5) W. Bergman and R. J. Feeney, *ibid.*, **72**, 2809 (1950).

(6) G. A. Howard, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 1052 (1947).

(7) B. Lythgoe, A. R. Todd and A. Topham, *ibid.*, 315 (1944).

(8) T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 163 (1908).

(9) H. L. Wheeler and T. B. Johnson, THIS JOURNAL, **31**, 603 (1909).

(10) P. A. Levene and F. B. LaForge, *Ber.*, **45**, 616 (1912).

(11) T. B. Johnson, O. Baudisch and A. Hoffman, *ibid.*, **64B**, 2629 (1931).