tion gave 1.5 g. of Δ^{16}-pregnenol-3(β)-one-20, m. p. 188–190°, when crystallized from ether–pentane after sublimation, yield 47%.

Dihydropseudotigogenin (4.16 g.) upon acetylation and oxidation gave 1.8 g. of Δ^{16}-*allo*-pregnenol-3(β)-one-20, m. p. 202–204°, yield 60%.

Dihydropseudo-*epi*-tigogenin (4.16 g.) upon acetylation and oxidation gave 1.7 g. of Δ^{16}-*allo*-pregnenol-3(α)-one-20, m. p. 219–222°, yield 56%.

Reduction of Δ^{16}-Pregnenol-3(α)-one-20 with Sodium and Ethyl Alcohol.—To a solution of 300 mg. of Δ^{16}-pregnenol-3(α)-one-20 in 75 cc. of absolute alcohol was added 5 g. of sodium in small pieces. After the sodium was in solution, water was added and the product was crystallized from acetone, m. p. 242–243°. Mixed with pregnanediol-3(α),20(α), m. p. 242°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 80.0; H, 11.2.

Upon refluxing with acetic anhydride it gave a diacetate which was crystallized from acetic anhydride and from methanol, m. p. 175–176°. It gave no depression in melting point when mixed with an authentic sample of the diacetate of pregnanediol-3(α),20(α), m. p. 175°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.4; H, 10.1.

Reduction of Δ^{16}-Pregnenol-3(α)-one-20 with Palladium.—A solution of 300 mg. of Δ^{16}-pregnenol-3(α)-one-20 in 25 cc. of ether and 25 cc. of alcohol containing 1 g. of palladium–barium sulfate catalyst was shaken under an atmosphere of hydrogen for two hours. The solution was filtered and the solvent was removed. The residue was crystallized from alcohol–water, m. p. 145–147°. Mixed with pregnanol-3(α)-one-20, m. p. 145–147°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.0; H, 10.0.

It gave an acetate with acetic anhydride which was crystallized from aqueous alcohol, m. p. 112–114°. When mixed with an authentic sample it gave no depression in melting point.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.8; H, 10.1. Found: C, 76.6; H, 10.1.

Reduction of Δ^{16}-Pregnenol-3(α)-one-20 with Platinum Oxide Catalyst.—A solution of 300 mg. of Δ^{16}-pregnenol-3-(α)-one-20 in 50 cc. of acetic acid containing 300 mg. of platinum oxide catalyst was shaken with hydrogen at 45 pounds pressure for two hours. The solution was filtered and the solvent removed *in vacuo*. The product was crystallized from alcohol, m. p. 230–232°. Mixed with an authentic sample of pregnanediol-3(α),20(β), m. p. 231°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.6; H, 11.2.

Oxidation of Δ^{16}-Pregnenol-3(α)-one-20 to Δ^{16}-Pregnenedione-3,20.—To a solution of 100 mg. of Δ^{16}-pregnenol-3(α)-one-20 in 20 cc. of glacial acetic acid was added a solution of 60 mg. of chromic anhydride in 2 cc. of dilute acetic acid. It was allowed to stand for one hour at room temperature. Water was added and the product was extracted with ether. The ethereal solution was washed with a 2% sodium hydroxide solution and the solvent removed. The residue was crystallized from acetone, m. p. 200–202°. Mixed with Δ^{16}-pregnenedione-3,20, m. p. 200–202°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 79.9; H, 9.6.

Summary

An improved method for the oxidation of the acetylated pseudosapogenins to the four compounds, Δ^{16}-pregnenol-3-one-20 isomeric at C-3 and C-5 is described.

STATE COLLEGE, PENNA. RECEIVED AUGUST 17, 1940

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Alkamine Esters of 4-Acetylferulic and 3,4-Dimethoxycinnamic Acids[1]

BY L. S. FOSDICK AND A. C. STARKE, JR.

Since the preparation of procaine,[2] alkamine esters of various acids have been shown to possess local anesthetic properties.

Shriner and Keyser[3] noted that most effective anesthetics of the ester type have a carbonyl group conjugated with double bonds. The conjugation of the carbonyl group with an aromatic nucleus would not be lost by the insertion of an ethylene group and perhaps might increase the anesthetic activity in the case of cinnamate derivatives. It has been shown[4] that the alkamine esters of phenylacetic acid, which would not have the conjugated system, are almost inactive.

The use of apothesine[5] and apocaine as local anesthetics[6] has suggested that the cinnamate derivates should be further investigated. Alkamine esters of *p*-methoxycinnamic acid[7] and aminocinnamic acid[8] have local anesthetic activity.

(1) Abstract of a thesis submitted to the faculty of the Graduate School of Northwestern University by A. C. Starke in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

(2) Einhorn and Uhlfelder, *Ann.*, **371**, 131 (1909).

(3) Shriner and Keyser, THIS JOURNAL, **60**, 286 (1938).

(4) Pyman, *J. Chem. Soc.*, **111**, 167 (1917).

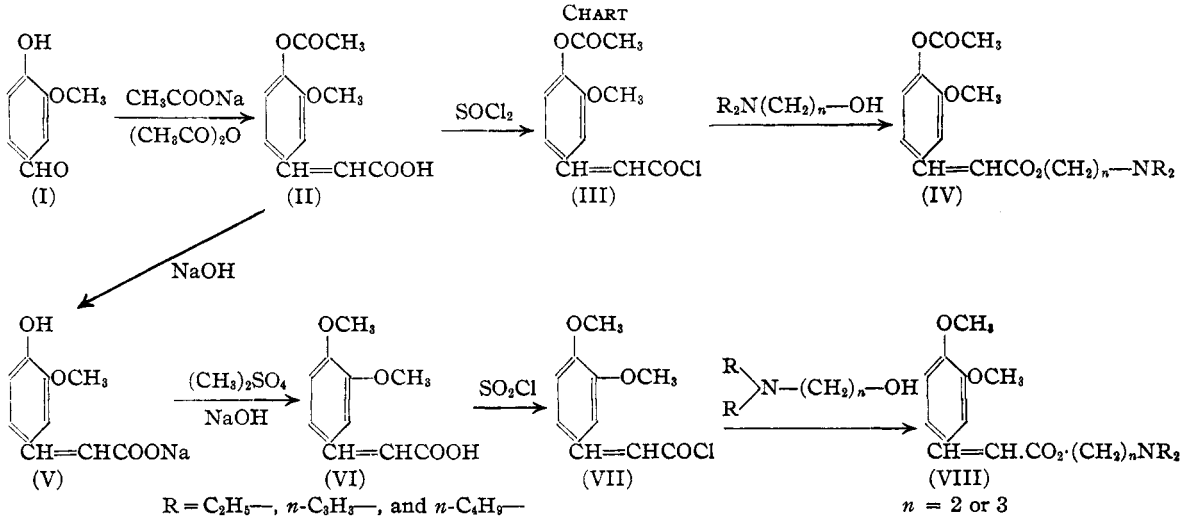
(5) Wildman and Thorp, U. S. Patent 1,193,649.

(6) Meeker and Frazier, *J. Pharmacol.*, **22**, 375 (1923).

(7) Brill, THIS JOURNAL, **54**, 2484 (1932).

(8) Meister, Lucius and Brüning, German Patent 187,593.

CHART



The alpha derivatives of cinnamic acids have been investigated, and their esters were found to produce anesthesia.[9]

The present investigation was concerned with the synthesis of the alkamine esters of 4-acetylferulic (3-methoxy-4-acetoxycinnamic acid) and 3,4-dimethoxycinnamic acids. These were prepared by the series of reactions shown in the accompanying chart. Vanillin (I) was condensed with acetic anhydride in the presence of sodium acetate and pyridine by the Perkin[10] reaction, to form acetylferulic acid (II). This was treated with thionyl chloride to form the acid chloride, acetylferuloyl chloride (III), which was esterified by the appropriate amino alcohol to yield the alkamine ester of acetylferulic acid (IV).

Acetylferulic acid (II) also was used as a starting product in the formation of the alkamine esters of 3,4-dimethoxycinnamic acid. It was saponified with sodium hydroxide to yield the sodium salt of ferulic acid (V), from which the free acid was recovered by acidification. The ferulic acid was methylated by the use of dimethyl sulfate in alkaline solution, yielding the methyl ester of 3,4-dimethoxycinnamic acid. Upon saponification of this ester with sodium hydroxide, and acidification of the reaction mixture, 3,4-dimethoxycinnamic acid (VI) was recovered. This was converted into the acid chloride (VII) which was treated with the appropriate amino alcohol to yield the alkamine ester of 3,4-dimethoxycinnamic acid (VIII).

A study of the pharmacology of beta-diethylaminoethyl 4-acetylferulate hydrochloride and beta-diethylaminoethyl 3,4-dimethoxycinnamate-hydrochloride was undertaken in this Laboratory. The results indicated that these compounds were not topically active toward the rabbit's cornea, but they were more active than procaine, as shown by the goldfish and the human intradermal wheal tests. The LD_{50} of the compounds were 185 and 106 mg./kg. of mouse, respectively. Hence these compounds are as toxic as cocaine, and much more toxic than procaine. No tissue necrosis was noted.

Experimental

4-Acetylferulic Acid.—Tiemann and Nagai's[11] method for the synthesis of acetylferulic acid by the Perkin[10] reaction was employed. Vanillin (100 g.) and freshly fused sodium acetate (100 g.) were well mixed, then acetic anhydride (500 g.) and pyridine (1 cc.) were added. The mixture was heated under reflux for eight to ten hours in an oil-bath, maintained at 160–170°. While still warm, the mixture was poured over cracked ice, at which time a brown oil separated out. The mixture was stirred and heated until dissolution of the oil took place, and it was allowed to cool overnight in an ice-box. A yellow solid that was precipitated on standing was then filtered off, pressed dry of the filtrate, and washed with water and alcohol. The light yellow solid (64% of theoretical yield) was recrystallized several times from dilute acetic acid, m. p. 194–196°.

Ferulic Acid.—Acetylferulic acid was hydrolyzed by heating with excess 20% sodium hydroxide solution on a steam-bath until dissolution had taken place. The solution was cooled and then filtered. The filtrate was slowly added to an ice–hydrochloric acid mixture. The resulting yellow precipitate (86% of theoretical yield) was filtered off and air dried, m. p. 167–168°.

3,4-Dimethoxycinnamic Acid.—The method of Perkin and Schiess[12] was used. Ferulic acid (73 g.) was dissolved

(9) Lott and Christiansen, *J. Am. Pharm. Assoc.*, **28**, 499 (1939); McIntyre and Sievers, *J. Pharmacol.*, **63**, 369 (1938).

(10) Perkin, *J. Chem. Soc.*, **31**, 388 (1877).

(11) Tiemann and Nagai, *Ber.*, **11**, 647 (1878); **9**, 54, 416 (1876).

(12) Perkin and Schiess, *J. Chem. Soc.*, **85**, 164 (1904).

TABLE I

	Compound	Appearance	M. p., °C.	Yield,[a] %	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	
1	4-Acetylferoyl chloride	Yellow solid	133–134	82	$C_{12}H_{11}O_4Cl$	...	...	...	[b]	.. ..
2	β-Diethylaminoethyl 4-acetylferulate hydrochloride	White powder	185–186	51	$C_{18}H_{26}O_5NCl$	3.8	3.9	3.8	9.6	9.8 9.8
3	β-Di-*n*-propylaminoethyl 4-acetylferulate hydrochloride	White powder	178–179.5	36	$C_{20}H_{30}O_5NCl$	3.5	3.3	3.3	8.9	8.9 8.9
4	β-Di-*n*-butylaminoethyl 4-acetylferulate hydrochloride	White powder	193.5–195	28	$C_{22}H_{34}O_5NCl$	3.3	3.4	3.5	8.3	8.4 8.5
5	γ-Diethylaminopropyl 4-acetylferulate hydrochloride	White powder	155–157	45	$C_{19}H_{28}O_5NCl$	3.6	3.7	3.7	9.2	9.0 9.0
6	γ-Di-*n*-propylaminopropyl 4-acetylferulate hydrochloride	White powder	153–154	74	$C_{21}H_{32}O_5NCl$	3.4	3.4	3.5	8.6	8.6 8.5
7	γ-Di-*n*-butylaminopropyl 4-acetylferulate hydrochloride	White powder	148–149	67	$C_{23}H_{36}O_5NCl$	3.2	3.3	3.3	8.0	8.1 8.1
8	3,4-Dimethoxycinnamoyl chloride	Greenish-tan solid	80–82	64	$C_{11}H_{11}O_3Cl$	...	...	...	15.7	15.9 15.8
9	β-Diethylaminoethyl 3,4-dimethoxycinnamate hydrochloride	Light tan powder	162–163	50	$C_{17}H_{26}O_4NCl$	4.1	4.1	4.2	10.4	10.3 10.4
10	β-Di-*n*-propylaminoethyl 3,4-dimethoxycinnamate hydrochloride	White powder	124–127	10	$C_{19}H_{30}O_4NCl$	3.8	[c]		9.5	9.5 9.6
11	β-Di-*n*-butylaminoethyl 3,4-dimethoxycinnamate hydrochloride	Fluffy white powder	116–117	40	$C_{21}H_{34}O_4NCl$	3.5	4.3	3.5	8.9	9.0 8.8
12	γ-Diethylaminopropyl 3,4-dimethoxycinnamate hydrochloride	White powder	142–144	60	$C_{18}H_{28}O_4NCl$	3.9	4.0	4.0	9.9	9.8 9.7
13	γ-Di-*n*-propylaminopropyl 3,4-dimethoxycinnamate hydrochloride	White powder	138–139	46	$C_{20}H_{32}O_4NCl$	3.6	3.6	3.7	9.2	9.0 9.1
14	γ-Di-*n*-butylaminopropyl 3,4-dimethoxycinnamate hydrochloride	White powder	98–99	50	$C_{22}H_{36}O_4NCl$	3.4	3.3	3.3	8.6	8.3 8.3

[a] Based on the acid. [b] Synthesized by Ogawa, *Bull. Chem. Soc. Japan*, **2**, 20 (1927). [c] Not determined.

in the calculated amount of 2 *N* sodium hydroxide solution (30.1 g. of NaOH in 375 cc. of water). Dimethyl sulfate (94.7 g.) was added slowly over a period of one hour, while the mixture was vigorously stirred, and continued for an additional hour. An oil, the methyl ester of the desired acid, separated out. Four hundred cc. of 10% sodium hydroxide solution was added, the mixture was refluxed for three hours, cooled, filtered, and acidified by pouring into an ice–hydrochloric acid mixture. The yellow precipitate was filtered off and dried. The resulting mass was ground to a powder and washed with 500 cc. of hot water. The undissolved portion was filtered off and dried. The solid was recrystallized from dilute acetic acid, yielding 52.5 g. (67% of the theoretical yield) of a light yellow powder, m. p. 179.5–180.5°.

Acid Chlorides.—4-Acetylferuloyl chloride and 3,4-dimethoxycinnamoyl chloride were made by treatment of the respective acids with excess thionyl chloride. After about thirty minutes of refluxing of the mixtures, the acids were found to be dissolved in the reaction medium. The unreacted thionyl chloride was distilled off under vacuum. Anhydrous benzene was added, and the reaction mixture was again subjected to vacuum distillation. This was repeated two or three times to make sure that all of the thionyl chloride had been distilled off. The acid chlorides were soluble in hot benzene and insoluble in cold benzene. The crude acid chlorides were used in the subsequent esterification. It was found that the acid chlorides could be purified by recrystallization from benzene, but this procedure was considered unnecessary in the synthesis of the alkamine esters.

Amino Alcohols.—The various amino alcohols necessary in the synthesis of the alkamine esters were synthesized by the method of Adams and co-workers.[13] Yields from 43 to 90% were obtained in the various reactions. It was found that the use of a steel bomb improved the yields.

Alkamine Esters.—The acid chlorides from the respective acids (12 to 15 g.) were dissolved in 100 cc. of anhydrous benzene and combined with an equimolecular quantity of the amino alcohol in 50 cc. of benzene. Upon mixing, the solution became warm from the heat of reaction. In the lower members of the two series, a precipitate formed immediately. The mixtures were refluxed for one to two hours or until a precipitate was formed on cooling. The mixtures became markedly darker in color during the heating.

The precipitate was removed by filtration, washed well with anhydrous ether and recrystallized twice from absolute alcohol–ether mixtures. During the purification, the alcoholic solutions were treated with activated charcoal (Norit). Anhydrous ether was added to the clear saturated alcoholic solution until a cloudiness was observed. The mixture was then placed in an ice-box until complete precipitation had occurred. The precipitate was recovered by filtration. The results of these syntheses are shown in the accompanying table.

An attempt to isolate the free bases of the lower members of the alkamine-ester series was unsuccessful. Due to the difficulties encountered and their negligible practical importance, no further attempts to isolate the free bases were made. The isolation of the higher members of the series was more successful, but no attempts were made to determine the physical constants of the resulting oils.

Summary

3,4-Dimethoxycinnamoyl chloride has been prepared.

Some alkamine-ester hydrochlorides of 4-acetylferulic acid have been prepared.

(13) Burnett, Jenkins, Peet, Dreger and Adams, THIS JOURNAL, **39**, 2248 (1937).

Some alkamine-ester hydrochlorides of 3,4-dimethoxycinnamic acid have been prepared.

A pharmacological study of the first member of each series of alkamine esters, indicates that they are slightly more active than procaine as local anesthetics, but are as toxic as cocaine. Hence, their usefulness is doubtful.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 26, 1940

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Sulfanilamide Compounds. V. Arylidine Derivatives of N^4-Acetyl-N^1-(4-amino)-phenyl-sulfanilamide and N^1-(4-Amino)-phenyl-sulfanilamide

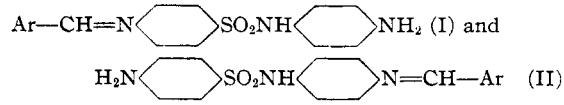
BY H. G. KOLLOFF AND JAMES H. HUNTER

In 1937 Whitby[1] reported that 4,4'-diaminobenzenesulfonanilide [N^1-(4-amino)-phenylsulfanilamide], in the form of its tartrate, was slightly more effective than sulfanilamide against experimental streptococcal infections in mice. In this respect Bauer and Rosenthal[2] found the free base to be approximately twice as active as sulfanilamide and of about the same order of toxicity; against experimental pneumococcal infections it was inferior to sulfanilamide. Gross, Cooper, and Lewis[3] concluded that N^1-(4-amino)-phenylsulfanilamide was as good as, or better than, sulfanilamide as an antistreptococcal agent in experimental infections while Webster and Powers[4] described its N^4-acetyl derivative as being moderately effective.

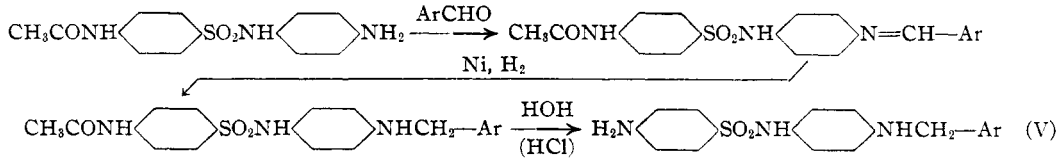
Consideration of these reports led us to extend our investigations[5,6] of N^4-arylidine derivatives of certain N^1-substituted sulfanilamides to the preparation and biologic evaluation of a number of mono- and di-arylidine derivatives of N^1-(4-amino)-phenylsulfanilamide as well as several N^4-acetyl-N^1-(4-arylidineamino)-phenylsulfanilamides.

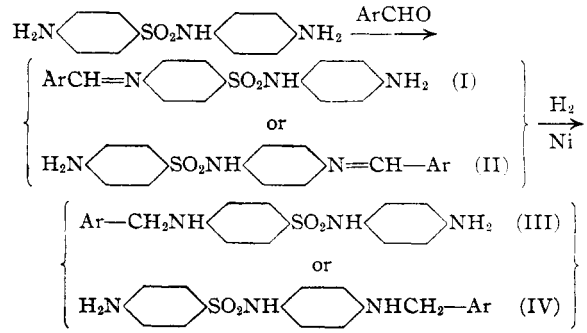
N^4-Acetyl-N^1-(4-amino)-phenylsulfanilamide and N^1-(4-amino)-phenylsulfanilamide were prepared by reduction of the corresponding nitro derivatives[4] according to the procedure of Webster and Powers.[4] When condensed with the appropriate aldehyde after the previously described[5] general procedure, these substituted sulfanilamides readily yielded their mono-arylidine derivatives. In a like manner the di-arylidine derivatives of N^1-(4-amino)-phenylsulfanilamide were obtained from the latter and slightly more than two equivalents of the requisite aldehyde. At present, all attempts to prepare the di-benzylidine derivative of this substituted sulfanilamide have resulted in the formation of the mono-benzylidine compound rather than the expected product.

It is apparent that interaction of molecular equivalents of an aldehyde and N^1-(4-amino)-phenylsulfanilamide can yield a mono-arylidine derivative of two possible structures, *i. e.*



We have shown that compounds 8 and 9 of Table I have the type II structure by means of the following scheme





If (I) is the correct structural type, then com-

(1) Whitby, *Lancet*, **1**, 1518 (1937).
(2) Bauer and Rosenthal, *Pub. Health Reports*, **53**, 40 (1938).
(3) Gross, Cooper and Lewis, *Proc. Soc. Exptl. Biol. Med.*, **38**, 375 (1938).
(4) Webster and Powers, THIS JOURNAL, **60**, 1553 (1938).
(5) Kolloff and Hunter, *ibid.*, **62**, 158 (1940).
(6) Kolloff and Hunter, *ibid.*, **62**, 1647 (1940).