the residue was crystallized from ethanol to afford 7.0 Gm. (92%) of IV, identical with the previously obtained material. The analytical sample was crystallized from ethanol and melted at 162–163°.

Anal.—Calcd. for $C_{15}H_{11}NOS$: C, 71.14; H, 4.37; N, 5.53. Found: C, 70.94; H, 4.24; N, 5.75.

Procedure for the Preparation of the 5-Hydroxyimidazolidin-2-thiones VI (Table I)—Solutions of IV (2.53 Gm., 0.01 mole) in the appropriate amine (benzylamine, 2-diethylaminoethylamine, 2-morpholinoethylamine or 2-pyrrolidinoethylamine, 15 Gm. *ca.*) were heated at 100° for 8–9 hr. The mixtures were then poured into ice cold water (1000 ml.); the product which separated was collected and crystallized from aqueous ethanol. A further crystallization from ethanol or from benzene–petroleum ether afforded the pure products in the yields reported in Table I.

Procedures for the Preparation of the 4-Imidazolin-2-thiones VII (Table II)—Compound 5 was prepared as follows: a solution of 1 (3.6 Gm., 0.01 mole) in ethanol (70 ml.) was treated with 1.0 ml. of concentrated H_2SO_4, then was heated to boiling. Crystalline 5 began to separate from the hot solution. After cooling, the product was collected and recrystallized from ethanol.

Compounds 6 and 8 were prepared by the same method, from 2 and 3, respectively. The acid ethanolic solution was treated with excess 10% Na_2CO_3 to precipitate the products; these were then crystallized from aqueous ethanol.

Compound 4 could best be dehydrated to 10 by the following procedure: a solution of 4 (1.1 Gm., 3.0 mmoles) in glacial acetic acid (2.0 ml.) was refluxed for 1 hr., then was poured into cold 10% Na_2CO_3 (50 ml.). The solid was collected and recrystallized from aqueous ethanol.

The hydrochlorides 7, 9, and 11 were prepared from the corresponding bases in the conventional fashion, and were purified by crystallization from absolute ethanol.

Structure Proof of 1-Benzyl-3,4-diphenyl-4-imidazolin-2-thione (Compound 5)—Treatment of 2-benzylaminoacetophenone hydrochloride (8) (VIII) with phenyl isothiocyanate, according to the procedure described by McCombie and Scarborough (*cf.* 6) for the preparation of 1,3,4-triphenyl-4-imidazolin-2-thione, gave a 15% yield of 5; IR $\lambda_{max.}$ (nujol) 6.70, 6.91, 7.15, 7.71, 7.95, 8.30, 9.35, 10.40, 13.40, 13.59, 14.24 μ.

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Keyphrases

Imidazolthiones—synthesis
3,4-Diphenyl-4-oxazolin-2-thione—derivatives
Pharmacological screening
IR spectrophotometry—structure

New Compounds: *N*-Hydroxy- and *N*-Acetoxy-Metabolites of *N,N'*-(2,7-Fluorenylene)bisacetamide

By NELLIE W. PITZER and FRANCIS E. RAY*

The partial catalytic reduction of 2,7-dinitrofluorene (I) in dimethylformamide, ethyl acetate, and acetic anhydride has yielded: *N*-hydroxy-*N*-(2-fluorenyl-7-nitro)acetamide (VII); *N*-acetoxy-*N*-(2-fluorenyl-7-nitro)acetamide (II); *N'*-hydroxy-*N,N'*-(2,7-fluorenylene)bisacetamide (XI); *N,N'*-dihydroxy-*N,N'*-(2,7-fluorenylene)bisacetamide (VIII); and *N,N'*-diacetoxy-*N,N'*-(2,7-fluorenylene)bisacetamide (IV).

THE ISOLATION and subsequent synthesis of *N*-hydroxy-*N*-(2-fluorenyl)acetamide as a proximate carcinogenic metabolite of *N*-(2-fluorenyl)-acetamide (1) led to the undertaking of the synthesis of a similar *N*-hydroxy compound as a possible metabolite for *N,N'*-(2,7-fluorenylene)bisacetamide (VI) which is known to produce carcinoma of the glandular stomach in rats (2).

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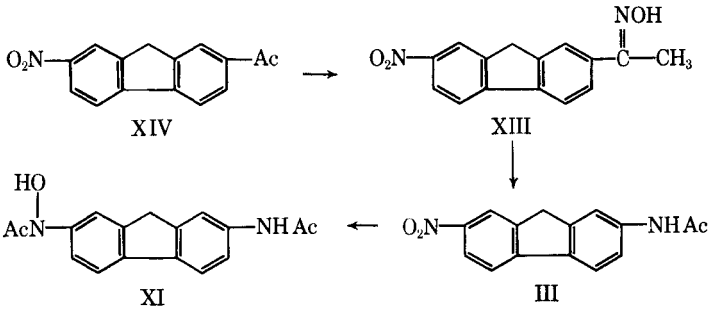
* Deceased November 25, 1966.

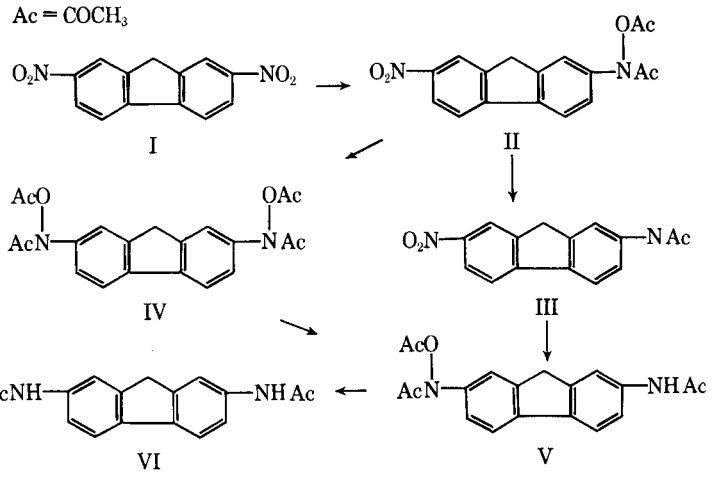
It has been reported recently that *N*-acetoxy-*N*-(2-fluorenyl)acetamide is an ultimate carcinogen of *N*-(2-fluorenyl)acetamide (3). Therefore the acetoxy esters synthesized have taken on increased biological interest.

The procedure for the catalytic partial reduction and the acetylation of 2-nitrofluorene in ethyl acetate and the subsequent hydrolysis in ammonium hydroxide (4) applied to 2,7-dinitrofluorene (I) gave a small yield of *N*-hydroxy-*N*-(2-fluorenyl-7-nitro)acetamide (VII).

After hydrolysis the ethyl acetate solution contained a mixture of reduction products. This prompted the use of *N*-(2-fluorenyl-7-nitro)acetamide (III) for catalytic reduction, as the only *N*-hy-



Scheme I



Scheme II (not isolated)

droxy derivative would then be *N'*-hydroxy-*N,N'*-(2,7-fluorenylene)bisacetamide (XI). The other probable product would be the known *N,N'*-(2,7-fluorenylene)bisacetamide (VI) (Scheme II).

A reduction of 2,7-dinitrofluorene in ethyl acetate and acetic anhydride yielded a compound, m.p. 248–249°, that was neither an *N*-hydroxy (negative to ferric chloride test) nor the known compounds, (III and VI). Microanalysis showed it to be *N,N'*-diacetoxy-*N,N'*-(2,7-fluorenylene)bisacetamide (IV) (Scheme II).

Since the one-step reduction from 2,7-dinitrofluorene (I) appeared to be unsatisfactory, due to the low solubility of I and the necessity for rapid reduction (25 min. or less), the two-step procedure with subsequent separation of products was devised.

EXPERIMENTAL

Ultraviolet spectra were obtained on a Hitachi Perkin-Elmer 139 UV-VIS spectrophotometer in 95% ethanol. Microanalyses were performed by Schwartzkopf Microanalytical Laboratories.

N'-Hydroxy-N,N'-(2,7-fluorenylene)bisacetamide (XI) from N-(2-Fluorenyl-7-nitro)acetamide (III)—*2-Acetyl-7-nitrofluorene oxime (XIII)*[1]—To a well-stirred mixture of 2.5 Gm. (0.01 mole) 2-acetyl-7-nitrofluorene (XIV) (5) heated in 150 ml. of *n*-butanol was added 1.4 Gm. (0.02 mole) of hydroxylamine hydrochloride dissolved in 3 ml. of water. Sodium acetate (1.4 Gm.) was added and the suspension heated on a magnetic stir plate for 1 hr. A few milliliters of water added near the end of the heating was necessary for complete solution. The yellow oxime (XIII) precipitated upon cooling. Yield, 2.3 Gm., 88%, m.p. 229–230°. Several recrystallizations from glacial acetic acid raised the m.p. to 236°.

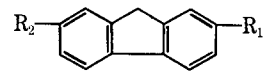
Anal.—Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.77; H, 4.49; N, 10.38.

N-*(2-Fluorenyl-7-nitro)acetamide (III)*—The oxime (XIII) (5.4 Gm., 0.02 mole) was stirred into 200 Gm. of polyphosphoric acid and heated 3 hr. on the steam bath with occasional stirring. It was then poured into ice and water to decompose the acid, filtered, and washed well with water to give an orange solid (III). Yield, 5.6 Gm., 100%, m.p. 247–252°. Several recrystallizations from glacial acetic acid and from *n*-butanol yielded 4.5 Gm., m.p. 256–257° [Lit. (6) 250–253°]. Further proof of its identity was determined by preparation of two known derivatives: 2-amino-7-nitrofluorene [XII (7, 8)] and *N,N'*-(2,7-fluorenylene)bisacetamide [VI (9)].

N' - Hydroxy - N,N' - *(2,7 - fluorenylene)bisacetamide (XI)*—To a hot solution of 4 Gm. (0.015 mole) of *N*-(2-fluorenyl-7-nitro)acetamide (III) and 250 ml. of ethyl acetate in a pressure bottle was added as quickly as possible, 15 ml. of triethylamine, 20 ml. of acetic anhydride, and 0.15 Gm. of platinum oxide.

The hot mixture was placed on the Parr pressure reaction apparatus, and hydrogen was passed in

[1] This synthesis was begun by Ru-Jen L. Han in this laboratory.



VII, R_1 = N(OH)Ac, R_2 = NO_2
VIII, R_1 = R_2 = N(OH)Ac
IX, R_1 = NHAc, R_2 = NH_2
X, R_1 = R_2 = NH_2
XI, R_2 = N(OH)Ac, R_1 = NHAc
XII, R_1 = NH_2, R_2 = NO_2

(pressure dropped from 45 p.s.i. to 41.3 p.s.i.). The mixture was filtered, the filtrate was heated and stirred with 100 ml. of water and 50 ml. of ammonium hydroxide for 1 hr. The two layers were separated, the aqueous layer extracted twice with ethyl acetate. The combined ethyl acetate layers were washed with water, evaporated almost to dryness, ether added, and extracted with 0.5 *N* sodium hydroxide. The red alkaline solution was immediately acidified with concentrated hydrochloric acid. The precipitate was filtered, dissolved in boiling water, and the solution filtered hot through coarse filter paper and allowed to cool. Yield, 0.5 Gm., 11%, m.p. 177–179°. It gave a purple color with ferric chloride solution and formed a copper chelate, m.p. 235°. $\lambda_{max.}$, mμ 303 (ε 41,500), 311–317 sh (39,800).

Anal.—Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.21; H, 5.64; N, 9.46.

N-Acetoxy and N-Hydroxy Derivatives of 2,7-Dinitrofluorene—N - *Acetoxy* - N - (2 - *fluorenyl* - 7-*nitro*)*acetamide* (*II*)—To a hot suspension of 3.8 Gm. of 2,7-dinitrofluorene (0.015 mole) and 100 ml. of dimethylformamide in a pressure bottle was added 20 ml. of acetic anhydride and 0.2 Gm. of platinum oxide. The hot mixture was placed on the Parr pressure apparatus and shaken with hydrogen (pressure dropped from 37 p.s.i. to 29 p.s.i. in less than 30 min.). The reaction mixture was filtered, the filtrate was stirred with 200 ml. of water for 1 hr., and filtered. Yield, 2.5 Gm., m.p. 160–166°. Combined runs (10 Gm.) of the crude material were extracted with benzene in a Soxhlet. Hexane, added carefully, precipitated out a red, gummy material. After most of this impurity was removed, a yellow, fluffy precipitate (II) formed spontaneously. Yield, 2.5 Gm., m.p. 174°. $\lambda_{max.}$, mμ 240–241 (ε 50,000), 336–341 (59,000).

Anal.—Calcd. for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.37; N, 8.59. Found: C, 62.65; H, 4.34; N, 9.01.

N-*Hydroxy*-N-(*2-fluorenyl-7-nitro*)*acetamide* (*VII*)—Hydrolysis of II in ammonium hydroxide gave a yellow precipitate of the *N*-hydroxy, m.p. 204°. It gave a purple color with ferric chloride and formed a copper chelate, m.p. 235°. $\lambda_{max.}$, mμ 250–262 (ε 10,170), 355–361 (18,170).

Anal.—Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.64; H, 4.60; N, 9.50.

N,N' - *Dihydroxy* - N,N' - (*2,7 - fluorenylene*)-*bisacetamide* (*VIII*) *and* N'-*Hydroxy*-N,N'-(*2,7-fluorenylene*)*bisacetamide* (*XI*)—To a hot suspension of 1.7 Gm. of *N*-hydroxy-*N*-(2-fluorenyl-7-nitro)-acetamide (VII) in 100 ml. of ethyl acetate in a pressure bottle was added 10 ml. of triethylamine, 15 ml. of acetic anhydride, 1 Gm. of 5% palladium on charcoal, and a few mg. of platinum oxide. The hot mixture was placed on the Parr pressure apparatus and shaken with hydrogen (pressure dropped from 37 p.s.i. to 35 p.s.i.). The reaction mixture was filtered and the filtrate stirred with 200 ml. of diluted ammonia for 1 hr. The products were then separated. A precipitate (VI) was filtered off. The aqueous and ethyl acetate layers of the filtrate were separated. The aqueous layer was extracted twice with ethyl acetate and discarded. The combined ethyl acetate solution was extracted: (*a*) with 5% sodium carbonate, which upon acidification with hydrochloric acid gave 0.39 Gm., m.p. 162–175°, of *N'*-hydroxy-*N,N'*-(2,7-fluorenylene)bisacetamide (XI). (*b*) With 0.5 *N* sodium hydroxide, which upon acidification yielded *N*-hydroxy-*N*-(2-fluorenyl-7-nitro)acetamide (VII). (*c*) With 5% sodium hydroxide, which upon acidification, yielded 0.18 Gm., m.p. 176–184°, of N,N'-dihydroxy - *N,N'* - (2,7 - fluorenylene)bisacetamide (VIII). A sample of VIII was prepared for analysis as follows: stirred with 0.5 *N* sodium hydroxide and filtered to remove any remaining VII and XI; dissolved in 5% sodium hydroxide, acidified, the precipitate filtered and dried; recrystallized from ethanol, m.p. 187–189°. It gave a purple color with ferric chloride and formed a copper chelate, m.p. 282°. $\lambda_{max.}$, mμ 305 (ε 34,700), 311–317 sh (30,400).

Anal.—Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.23; H, 5.47; N, 8.56.

(*d*) With concentrated hydrochloric acid. The dark green solution was poured into water to give a precipitate of 2-acetylamino-7-aminofluorene (IX), m.p. 181–184° (6). $\lambda_{max.}$, mμ 301.5 (ε 45,000).

N,N' - *Diacetoxy* - N,N' - (*2,7 - fluorenylene*)*bisacetamide* (*IV*)—2,7-Dinitrofluorene (I) was reduced in ethyl acetate and acetic anhydride at 48 p.s.i. for 1 hr. and IV was isolated from the mixture of reaction products in trace amounts on a silica gel column eluted with ethyl acetate, m.p. 248–249°.

Anal.—Calcd. for $C_{21}H_{20}N_2O_6$: C, 63.63; H, 5.09; N, 7.07. Found: C, 62.89; H, 5.03; N, 6.57.

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Keyphrases

N,N'-(2,7-Fluorenylene)bisacetamide metabolites—synthesis
N-Hydroxy, *N*-acetoxy metabolites—*N,N'*-(2,7-fluorenylene)bisacetamide
UV spectrophotometry—structure