

*Anal.* Calcd. for  $C_{11}H_{14}O_3$ : C, 68.0; H, 7.2. Found: C, 68.1; H, 7.1.

$\gamma$ -(2-Methoxy-4-methylphenyl)butyric acid (VIII, R =  $CH_3$ ). The hydroxy acid (VII, 8 g., 0.04 mole) was methylated with dimethyl sulfate (15 g., 0.12 mole) in a 10% solution of sodium hydroxide (10 g., 0.24 mole) in the usual manner. After extracting the alkaline solution with ether, it was acidified with cold hydrochloric acid and the precipitate was filtered. The solid weighed 8.3 g. (almost quantitative). The methoxy acid crystallized from light petroleum ether (40–60°) as white flakes, m.p. 53°; the melting point was not raised on further recrystallization.

*Anal.* Calcd. for  $C_{12}H_{16}O_3$ : C, 69.2; H, 7.6. Found: C, 68.9; H, 7.3.

1-Methoxy-3-methyl-5-keto-5,6,7,8-tetrahydronaphthalene (IX). To a solution of the methoxy acid (VIII, 6 g.) in dry tetrachloroethane (120 ml.) was added phosphorus oxychloride (3 ml.) dropwise with shaking and the mixture was boiled for 2.5 hr. Water was added and the tetrachloroethane was distilled in steam. The semisolid residue was dissolved in ether, the ethereal layer was washed successively with water, 5% sodium carbonate solution and water, and dried over sodium sulfate. Distillation gave 3.5 g. (64%) of a pale-yellow liquid, b.p. 132–136°/2 mm.,  $n_D^{25}$  1.5596.

*Anal.* Calcd. for  $C_{12}H_{14}O_2$ : C, 75.8; H, 7.3. Found: C, 75.9; H, 7.5.

The 2,4-dinitrophenylhydrazone crystallized from glacial acetic acid as bright-red needles, m.p. 229–230°, unchanged on further crystallization.

*Anal.* Calcd. for  $C_{18}H_{18}N_4O_4$ : N, 15.1. Found: N, 15.1.

1-Methoxy-3-methyl-5,6,7,8-tetrahydronaphthalene (X). A solution of the tetralone (IX, 3.6 g.) in diethylene glycol (10 ml.) was reduced according to the Huang-Minlon method<sup>11</sup> using potassium hydroxide (3.8 g., diethylene glycol (20 ml.), and 50% solution of hydrazine hydrate (5.6 ml.). After distilling the reaction mixture in steam, the distillate was extracted with ether, the ethereal layer was dried over anhydrous sodium sulfate, and the solvent was removed. The residue was distilled to yield 2.1 g. (60%) of a colorless mobile oil, b.p. 106–108°/3 mm.,  $n_D^{25}$  1.5388.

*Anal.* Calcd. for  $C_{12}H_{16}O$ : C, 81.8; H, 9.1. Found: C, 82.2; H, 9.1.

3-Methyl-5,6,7,8-tetrahydro-1-naphthol (IV). A solution of the methyl ether (X, 1.6 g.) in glacial acetic acid (30 ml.) and 48% hydrobromic acid (12 ml.) was refluxed on an oil bath kept at 130° for 6 hr. The cooled solution was then poured into ice water and the pink solid was filtered. The naphthol weighed 1.2 g. (80%), m.p. 94°. The melting point rose to 98° after crystallization from petroleum ether (40–

60°) and remained undepressed on admixture with the sample obtained previously through cyclization.

Ethyl  $\gamma$ -phenyl- $\beta$ -methyl- $\beta$ -hydroxybutyrate (XI). The Reformatsky reaction was carried out as before using benzyl methyl ketone (20 g., 0.15 mole), ethyl bromoacetate (31.4 g., 0.188 mole), activated zinc wool (19.5 g., 0.3 atom), and dry benzene (180 ml.). Distillation gave 32 g. (97%) of a colorless oil, b.p. 140–146°/3 mm.,  $n_D^{25}$  1.4994.

*Anal.* Calcd. for  $C_{13}H_{18}O_3$ : C, 70.2; H, 8.1. Found: C, 70.2; H, 8.2.

Dehydration to the unsaturated ester (XII, R =  $C_2H_5$ ). To a solution of the  $\beta$ -hydroxy ester (XI, 8 g., 0.036 mole) in dry pyridine (18 ml.) cooled in ice, was added phosphorus oxychloride (2.8 g., 0.018 mole) dropwise with shaking. After allowing to stand overnight the mixture was warmed on the steam bath for 1 hr. and acidified with cold dilute hydrochloric acid. The organic matter was extracted with ether, the ethereal layer was separated, washed with a solution of sodium bicarbonate and water, and dried over sodium sulfate. On distillation, 7.5 g. (99%) of XII, b.p. 124–126°/1.5 mm. was obtained as a colorless oil,  $n_D^{27.5}$  1.5090.

*Anal.* Calcd. for  $C_{13}H_{16}O_2$ : C, 76.4; H, 7.8. Found: C, 76.6; H, 7.7.

Saponification to the unsaturated acids (XIII, R = H, and XIV). To a solution of potassium hydroxide (4.2 g., 0.074 mole) in ethanol (50 ml.), the unsaturated ester (XII 7.5 g., 0.037 mole) was added, and the resulting solution was refluxed for 5 hr., and then worked up as usual. Distillation gave 5 g. (77%) of the acidic material, b.p. 156–162°/3 mm. The distillate solidified to a white mass admixed with an oily material. A portion of the solid was dissolved in petroleum ether (40–60°) from which crystals were deposited, m.p. 110°. Recrystallization from the same solvent yielded the acid (XIV) as white flakes, m.p. 113°;  $\lambda_{max}^{alc}$  249  $m\mu$  ( $\log \epsilon$  4.1).

*Anal.* Calcd. for  $C_{11}H_{12}O_2$ : C, 75.0; H, 6.8. Found: C, 74.8; H, 6.6.

3-Methyl-1-naphthol (V). Phosphorus oxychloride (2 ml.) was added to a solution of the acid (XIII, 4 g.) in dry tetrachloroethane (80 ml.) and the solution was refluxed for 2.5 hr., and then distilled in steam. The residue was dissolved in ether, the ethereal layer washed with water, and evaporated. The residue was hydrolyzed with a solution of potassium hydroxide (3 g.) in ethanol (40 ml.) and worked up as usual. On distillation, the product (1 g.), b.p. 140–144°/3 mm., solidified to a yellow mass, m.p. 89–90°. Crystallization from petroleum ether (60–80°) raised the melting point to 92°, which was not depressed on admixture with the sample obtained previously.

(11) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

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[CONTRIBUTION FROM THE CHEMICAL THERAPEUTICS RESEARCH LABORATORY, MILES LABORATORIES, INC.]

## Spiro[cyclohexane-1,9'-fluoren]-4-one and Some 4-Amino Derivatives

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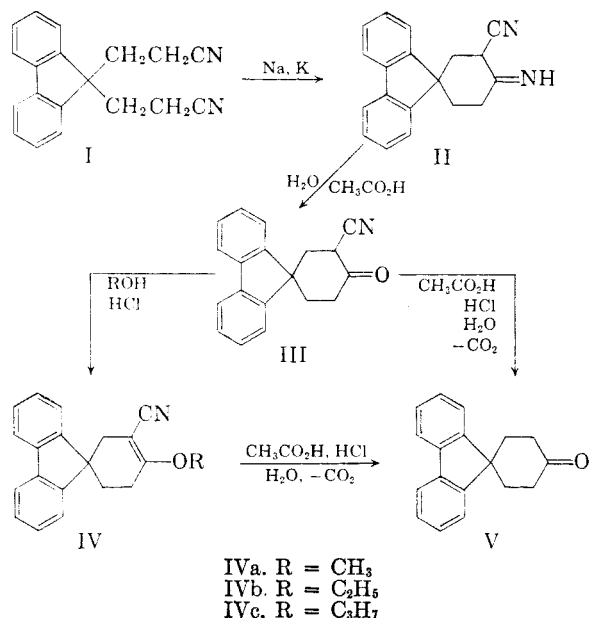
Spiro[cyclohexane-1,9'-fluoren]-4-one has been synthesized by two methods and a number of 4-amino derivatives have been prepared for pharmacological examination. The compounds showed no outstanding activity.

Spiro[cyclohexane-1,9'-fluoren]-4-one (V) was obtained by two different series of reactions, one starting with 9,9-fluorenedipropionitrile (I).<sup>1</sup> This was cyclized in the presence of metallic sodium

and a small quantity of potassium metal to give 4-iminospiro[cyclohexane-1,9'-fluorene]-3-carbonitrile in good yield. The imino compound (II) was hydrolyzed readily to the cyanoketone (III) which, on refluxing with a mixture of acetic and hydrochloric acids, was hydrolyzed with the sub-

(1) H. A. Bruson, *J. Am. Chem. Soc.*, **64**, 2457 (1942).

sequent loss of carbon dioxide to V in rather poor yield.



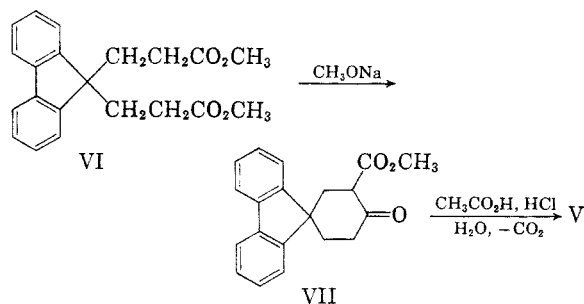
The conversion of III to V through the imido ester was attempted but III was too insoluble to allow the desired intermediate to form at the usual temperatures. When anhydrous hydrogen chloride was passed into a hot solution of III in methanol an excellent yield of the enol ether (IVa) was deposited as hard crystals. The structure of IVa was confirmed by the infrared spectrum of the compound. A band at 4.47  $\mu$  was attributed to the nitrile group; a peak at 6.09  $\mu$  corresponds to the conjugated double bond; and strong absorbance at 7.95  $\mu$  was associated with the ether grouping.

Furthermore the spectrum obtained from NMR studies is consistent with structure IVa. A sharp peak at 3.13 p.p.m. below tetramethylsilane (the reference) was assigned to the hydrogens of the enol ether on the basis of its sharpness, intensity, chemical shift, and relative area.

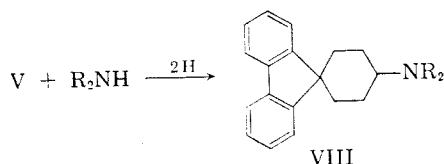
When ethanol and propanol were used in place of methanol the corresponding ethoxy (IVb) and propoxy (IVc) compounds were obtained.

IVa was hydrolyzed to V by prolonged refluxing with a mixture of acetic and hydrochloric acids. The ketone was best isolated as the thiosemicarbazone from which it was readily regenerated.

The second synthesis of V started with methyl 9,9-fluorenedipropionate (VI)<sup>2</sup> from which the keto ester (VII) was obtained in good yield by means of the Dieckmann reaction using sodium methoxide in toluene. Hydrolysis and decarboxylation of the keto ester (VII) by refluxing with a mixture of acetic and hydrochloric acids yielded the desired ketone (V).



A number of 4-amino derivatives of V were prepared by means of the Leuckart reaction (A) or by catalytic reductive alkylation (B) of the appropriate amine.



- VIIIa.  $-\text{NR}_2 = -\text{NH}_2$   
 VIIIb.  $-\text{NR}_2 = -\text{N}(\text{CH}_3)_2$   
 VIIIc.  $-\text{NR}_2 = -\text{N}$  (piperazine ring)  
 VIIIId.  $-\text{NR}_2 = -\text{N}$  (morpholine ring)  
 VIIIe.  $-\text{NR}_2 = -\text{NHCH}_3$   
 VIIIIf.  $-\text{NR}_2 = -\text{NHCH}_2\text{CH}_2\text{OH}$   
 VIIIIf.  $-\text{NR}_2 = -\text{NHCH}_2\text{CH}_2\text{Cl}$

The *N*-(2-chloroethyl) compound (VIIIIf) was obtained by treating the hydroxy derivative (VIIIIf) with thionyl chloride. In addition the dimethylamino compound (VIIIb) was quaternized with methyl chloride.

The amine derivatives were quite toxic and exhibited weak analgetic, antihistaminic and hypotensive properties.

#### EXPERIMENTAL

*4-Iminospiro[cyclohexane-1,9'-fluorene]-3-carbonitrile* (II). A finely divided suspension of sodium (12.7 g., 0.55 g.-atom) and potassium (1.3 g.) was stirred at 80° and a solution of 9,9-fluorenedipropionitrile (I) (150 g., 0.55 mole) in 300 ml. of dry toluene was added in one portion. After keeping the mixture at 80–85° for 4 hr., 150 ml. of 95% ethanol was added to destroy the unchanged metals. Then the cold mixture was treated with 700 ml. of water. The crude product (120 g., 80%) melted at 261–264°. After two recrystallizations from isopentyl alcohol the fine colorless needles melted at 264–265°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>: N, 10.29. Found: N, 10.31.  
*3-Cyanospiro[cyclohexane-1,9'-fluorene]-4-one* (III). A hot solution of II (83.3 g.) in 500 ml. of acetic acid and 25 ml. of water was poured onto 1 kg. of cracked ice. The solid material was collected, slurried with 500 ml. of hot water, and washed thoroughly with additional water. The product amounted to 80 g. (96%) and melted at 184–186°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>16</sub>NO: N, 5.13. Found: N, 5.06.  
*Preparation of the enol ethers* (IV). *4-Methoxyspiro[3-cyclohexene-1,9'-fluorene]-3-carbonitrile* (IVa). Anhydrous hydrogen chloride was passed into a solution of III (50 g.) in 500 ml. of hot methanol for 1.5 hr. while the temperature of the mixture was kept near the boiling point. Crystals began to separate after 30 min. The mixture was cooled and the product was collected and washed with methanol. The

(2) H. A. Bruson, U. S. Patent 2,339,373 (Jan. 18, 1944) [*Chem. Abstr.*, 38, 3665 (1944)].

crude enol ether (52 g., 99%) melted at 224–226°. The product melted at 226–227° after recrystallization from acetic acid.

*Anal.* Calcd. for  $C_{20}H_{17}NO$ : C, 83.59; H, 5.96; N, 4.87. Found: C, 83.39; H, 5.86; N, 4.87.

*4-EthoxySpiro[3-cyclohexene-1,9'-fluorene]-3-carbonitrile* (IVb). This compound was prepared from 5.0 g. of III and 50 ml. of absolute ethanol. The product separated on cooling and was recrystallized from absolute ethanol. The colorless crystals (1.5 g., 27%) melted at 130–131°.

*Anal.* Calcd. for  $C_{21}H_{19}NO$ : N, 4.65. Found: N, 4.59.

*4-PropoxySpiro[3-cyclohexene-1,9'-fluorene]-3-carbonitrile* (IVc). This compound was prepared in a similar way from 5.0 g. of III and 25 ml. of propanol. The crystals separated slowly from the mixture on standing at room temperature for 2 days. The product amounted to 3.2 g. (56%) and melted at 122–123°.

*Anal.* Calcd. for  $C_{22}H_{21}NO$ : N, 4.44. Found: N, 4.39.

*Methyl 4-oxospiro[cyclohexane-1,9'-fluorene]-3-carboxylate* (VII). A mixture of methyl 9,9-fluorenedipropionate (253.5 g., 0.75 mole), sodium methoxide (81.0 g., 1.5 moles) and 800 ml. of dry toluene was stirred under a nitrogen atmosphere and heated in an oil bath at 105–110°. After about 1.5 hr. the mixture suddenly solidified almost completely. The mixture was cooled and 150 ml. of acetic acid was added. Then a mixture of 50 ml. of hydrochloric acid and 500 ml. of water was added and the stirring was continued until all of the solid material had dissolved. The toluene layer was washed free of acidic materials with 10% sodium bicarbonate and dried over calcium chloride. The solid residue which remained when the solvent was removed was recrystallized from a mixture of acetone and methanol. The keto ester was obtained as colorless crystals (205 g., 90%) which melted at 122–123°.

*Anal.* Calcd. for  $C_{20}H_{19}O_3$ : C, 78.41; H, 5.92. Found: C, 78.35; H, 6.19.

*Spiro[cyclohexane-1,9'-fluorene]-4-one* (V). (A) *Hydrolysis of VII*. The keto ester (10.0 g.) was refluxed for 6 hr. with a mixture of 50 ml. of acetic acid and 25 ml. of hydrochloric acid. The supernatant liquid was decanted from the hot mixture onto 200 g. of cracked ice. The sirupy residue was extracted with another 10 ml. of hot acetic acid which was also decanted into the cold mixture. The crude material was recrystallized from ethanol to give 6.7 g. (83%) of the almost colorless ketone (V) which melted at 198–202°. After two recrystallizations from 2-propanol the product melted at 209–210°.

*Anal.* Calcd. for  $C_{18}H_{16}O$ : C, 87.06; H, 6.50. Found: C, 86.63; H, 6.52.

(B) *Hydrolysis of III*. The cyano ketone (3.0 g.) was heated under reflux for 5 hr. with a mixture of 30 ml. of acetic acid and 15 ml. of hydrochloric acid, and the hot solution was poured onto 100 g. of cracked ice. The crude product was washed with water, dried, and slurried with 15 ml. of a hot 10% sodium carbonate solution. After recrystallization from ethanol the colorless crystals of V (0.6 g., 22%) melted at 200–205°.

(C) *Hydrolysis of IVa*. The enol ether (IVa) (50 g.) was heated under reflux for 48 hr. with 500 ml. of acetic acid and 200 ml. of hydrochloric acid. Most of the acetic acid was removed by distillation and the residue was mixed with 1 kg. of ice and water. The crude ketone (44.3 g., m.p. 185–195°) was dissolved in hot ethanol and a hot solution of thiosemicarbazide (16.3 g.) in 400 ml. of ethanol was added. The mixture was kept near the boiling point for 30 min. and then cooled. The thiosemicarbazone (29.5 g.) melted at 216–217°.

*Anal.* Calcd. for  $C_{19}H_{19}N_3S$ : S, 9.98. Found: S, 9.94. The thiosemicarbazone was stirred under reflux for 18 hr. with 150 ml. of concd. hydrochloric acid. Then the mixture was cooled and diluted with 500 ml. of water. The ketone (V) was obtained as faintly yellow crystals (22.5 g., 53% based on the enol ether) which melted at 195–200°.

Samples of the crude ketone (V) obtained by methods B and C melted at 209–210° after repeated recrystallizations from 2-propanol. No depression in the melting point was observed where the materials thus purified were mixed with a sample of V prepared by method A.

(A) *Preparation of amines (VIII) by the Leuckart reaction. Spiro[cyclohexane-1,9'-fluorene]-4-amine hydrochloride* (VIIIa). A mixture of the ketone (V) (10.0 g., 0.044 mole), formamide (9.9 g., 0.22 mole), formic acid (20.2 g., 0.44 mole), and diethylene glycol (10 ml.) was heated in an oil bath, so that water and formic acid were slowly removed by distillation through a short Vigreux column. The bath temperature was raised gradually to 185° and that temperature was maintained for 4.5 hr. The mixture was cooled and diluted with 100 g. of ice and water. The solid material was collected and heated under reflux for 2 hr. with 100 ml. of ethanol and 50 ml. of hydrochloric acid. The mixture was cooled and the solid material was removed by filtration. Most of the ethanol was distilled and the residue was extracted with two 200-ml. portions of boiling water. The insoluble tarry material was discarded and the combined extracts were cooled. The hydrochloride was collected, dried and recrystallized from a mixture of methanol and 2-propanol. The colorless crystals (7.5 g., 65%) melted at 326–327°.

*Anal.* Calcd. for  $C_{18}H_{20}ClN$ : Cl, 12.41. Found: Cl, 12.27.

*N,N-Dimethylspiro[cyclohexane-1,9'-fluorene]-4-amine hydrochloride* (VIIIb). This compound was prepared in a similar manner starting with the ketone (V) (37.2 g., 0.15 mole), dimethylformamide (46.8 g., 0.75 mole), and formic acid (69.0 g., 1.5 moles). The mixture was heated at 180° for 1 hr., 190° for 1 hr., 200° for 1 hr., and finally at 210° for 2 hr. The clear solution was allowed to cool and then was heated to reflux with 600 ml. of water and 100 ml. of hydrochloric acid. The hot mixture was clarified by filtration and the hydrochloride separated from the filtrate on cooling. The crude product was recrystallized twice from a mixture of methanol and 2-propanol. The colorless crystals thus obtained (32.0 g., 68%) melted at 295–296°.

*Anal.* Calcd. for  $C_{20}H_{24}ClN$ : Cl, 11.30. Found: Cl, 11.29.

*4-(1-Piperidyl)spiro[cyclohexane-1,9'-fluorene] hydrochloride* (VIIIc). The ketone (V) (6.2 g., 0.025 mole), morphopiperidine (15.0 g., 0.125 mole), and formic acid were heated at 200° (bath temperature) for 1 hr. Then the mixture was heated under reflux at a bath temperature of 250° for 5 hr. The clear yellow solution was cooled and heated to boiling with 100 ml. of water and 10 ml. of hydrochloric acid. The salt was not appreciably soluble in the hot mixture. After cooling, the crude product was collected, dried, and recrystallized from a mixture of methanol and 2-propanol. The colorless crystals (6.7 g., 76%) melted at about 345°.

*Anal.* Calcd. for  $C_{23}H_{28}ClN$ : Cl, 10.02. Found: Cl, 9.98.

*4-(4-Morpholinyl)spiro[cyclohexane-1,9'-fluorene] hydrochloride* (VIIId). This compound was prepared in the same way as the piperidine analog starting with the ketone (V) (9.92 g., 0.04 mole), morpholine (17.4 g., 0.2 mole), and formic acid (18.4 g., 0.4 mole). The hydrochloride was obtained as colorless crystals from aqueous methanol. The product (11.5 g., 90%) melted at about 340°.

*Anal.* Calcd. for  $C_{22}H_{26}ClNO$ : Cl, 9.96. Found: Cl, 9.97.

(B) *Preparation of amines (VIII) by catalytic reductive alkylation. N-Methylspiro[cyclohexane-1,9'-fluorene]-4-amine hydrochloride* (VIIIe). Gaseous methylamine was passed into a hot mixture of the ketone (V) (7.44 g., 0.03 mole) and 50 ml. of 2-propanol until 1.0 g. (0.032 mole) of the amine had been absorbed. The clear yellow solution was added to a suspension of reduced platinum catalyst (from 0.2 g. of the oxide) in 50 ml. of 2-propanol and another 50 ml. of 2-propanol was added. The mixture was reduced under 3 atmospheres. The theoretical quantity of hydrogen was taken up in 3 hr. The catalyst and solvent were removed, and the oily free base was dissolved in a hot mixture of 100 ml. of water and 15 ml. of hydrochloric acid. The crude salt which separated on cooling was collected and recrystallized once from aqueous methanol and three times from a mixture

of methanol and 2-propanol. The colorless crystals (2.5 g., 28%) melted at 287–288°.

Anal. Calcd. for  $C_{19}H_{22}ClN$ : Cl, 11.83. Found: Cl, 11.65.

*N*-(2-Hydroxyethyl)spiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride (VIIIf). This compound was prepared by a procedure similar to that described for the methylamino analog from the ketone (V) (9.92 g., 0.04 mole) and ethanolamine (2.14 g., 0.035 mole). The colorless hydrochloride, recrystallized from a mixture of methanol and 2-propanol, amounted to 9.2 g., (80%) and melted at 290–291°.

Anal. Calcd. for  $C_{20}H_{24}ClNO$ : Cl, 10.75. Found: Cl, 10.89.

*N*-(2-Chloroethyl)spiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride (VIIIg). Compound VIIIg (8.0 g.) was mixed with 20 ml. of thionyl chloride. After the initial reaction was over the mixture was heated under gentle reflux for 3 hr. The excess thionyl chloride was evaporated under reduced pressure and the residue was diluted with 100 ml. of dry ether. The crude salt was collected and recrystallized from aqueous methanol as colorless crystals (4.3 g., 51%) which melted at about 355°.

Anal. Calcd. for  $C_{20}H_{22}Cl_2N$ : Cl, 20.36. Found: Cl, 20.24.

*N,N,N*-Trimethylspiro[cyclohexane-1,9'-fluoren]-4-ammium chloride. Compound VIIIb (11.5 g.) and 10% sodium hydroxide solution (100 ml.) were mixed and warmed. The mixture was cooled and the oily amine was extracted with ether. The extract was dried over calcium chloride and the solvent was evaporated. The solid base which remained as a residue (6.0 g.) was sealed in a glass tube with 20 ml. of methyl chloride. The amine dissolved and the quaternary ammonium salt soon began to separate. After standing overnight the almost solid mixture was crystallized from a mixture of methanol and 2-propanol. The colorless crystals (3.2 g., 27%) melted at about 290° with decomposition.

Anal. Calcd. for  $C_{21}H_{26}ClN$ : Cl, 10.81. Found: Cl, 10.85.

*Acknowledgment.* The authors wish to express their appreciation to Professor A. L. Allred of Northwestern University for the determination and interpretation of the NMR spectrum.

ELKHART, IND.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

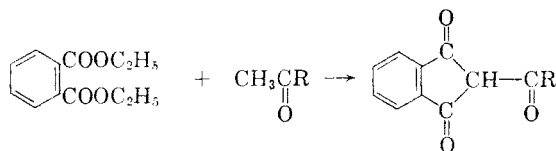
## 2-Substituted 1,3-Indandiones

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Various 2-aryl- and 2-acyl-1,3-indandiones were prepared. 3-( $\alpha$ -Hydroxy-2,3-dimethoxybenzyl)phthalide (IV) was established as a probable intermediate in the synthesis of 2-(2,3-dimethoxyphenyl)-1,3-indandione (V) from phthalide and 2,3-dimethoxybenzaldehyde. 1,3-Dioxo-2-indancarboxamide (IX) was sought because of its structural relationship with the tetracycline antibiotics. It was accessible from the corresponding nitrile but not from the ethyl ester. Fusion of the sodium enolate of this ester with ammonium acetate gave ethyl 1-imino-3-oxo-2-indancarboxylate (VIII).

In a search for improved blood anticoagulants in the 1,3-indandione series<sup>2–7</sup> we have prepared a number of new 2-substituted-1,3-indandiones. The 2-acyl derivatives listed in Table I were prepared by the sodium methoxide-catalyzed condensation of diethyl phthalate with the appropriate methyl ketone (Method A).<sup>8,9</sup>



(1) Present address: Process Development Department, American Cyanamid Co., Bound Brook, N. J.

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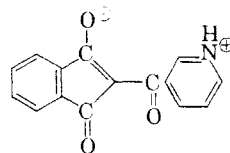
(6) W. Cavallini, E. Milla, E. Grumelli, and F. Ravenna, *Il Farmaco (Pavia), Ed. sci.*, **10**, 710 (1955); *Chem. Abstr.*, **50**, 10707 (1956).

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(8) E. Schwerin, *Ber.*, **27**, 104 (1894).

(9) L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

4-Chloroacetophenone and 4-ethylacetophenone reacted satisfactorily in refluxing benzene or toluene, but with methyl 4-chloro-1-naphthyl ketone and 4-hydroxyacetophenone it was necessary to use an excess of diethyl phthalate as the solvent. Methyl 3-pyridyl ketone was unusually reactive; the very high melting point and low solubility of the product suggest that it exists as a zwitterion such as:



It is amphoteric. As an acid it is readily soluble in dilute alkali but as a base it is so feeble that it is precipitated from aqueous solution when diluted to an acid strength less than 3*N*.

The 2-aryl-1,3-indandiones of Table I were prepared by the alkoxide-catalyzed condensation of phthalide with aromatic aldehydes (Method B).<sup>10,11</sup> Even though the yields were low this approach was found to be both versatile and convenient.

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