[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

AMINOKETONES DERIVED FROM FLUORENE. I. DERIVATIVES OF 2-ACYL-7-HYDROXYFLUORENE

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Received September 24, 1953

Ray and Rieveschl (1) found that esters of fluorenone-2-carboxylic acid possessed considerable topical anesthetic power and antispasmodic action. Since, in general, fluorene derivatives are usually more soluble than the corresponding fluorenone derivatives, and since the ester linkage is not essential for activity (2), Ray and MacGregor (3) prepared a series of 2′-(3-dialkylamino-1-oxopropyl)fluorenes (I, R′ = H, n = 2) to be compared with the previously reported esters. Other investigators (4–6) have also reported local anesthetic activity of fluorene derivatives. Previous experience had shown that activity was present in compounds of type I (R′ = H) when n was 1 or 2 but that the greatest activity was shown when n = 2. The substitution of an acetoxy or hydroxy group in the 7-position of the fluorene ring would be expected to modify the physiological activity of the compounds (2).

The procedure reported by Ray and Hull (7) for the preparation of 2-hydroxyfluorene (II) from 2-aminofluorene was improved by hydrolyzing 2-fluorene diazonium sulfate instead of the diazonium chloride. Esterification of 2-hydroxyfluorene with acetic anhydride in acetone and a small amount of pyridine was followed by acetylation of the 2-acetoxyfluorene by a Friedel and Crafts reaction with acetic anhydride to give crude 2-acetyl-7-acetoxyfluorene (III). The product thus prepared did not brominate smoothly nor could it be recrystallized in pure form. Hydrolysis of III to 2-acetyl-7-hydroxyfluorene (IV) in 1:1 hydrochloric acid and ethanol yielded a product which, after recrystallization from methanol, could be reesterified with acetic anhydride in acetone and pyridine to give pure 2-acetyl-7-acetoxyfluorene (III) in good yield. The Schotten-Bauman esterification of IV with benzoyl chloride yielded 2-acetyl-7-benzoyloxyfluorene.

Bromination of III in dry ether solution gave 2-bromoacetyl-7-acetoxyfluorene (V, X = Br) which, when purified, could be reacted with secondary amines in acetone solution to yield aminoketones of type I (R′ = CH_3COO, n = 1) which were isolated as the hydrochloride salts. The aminoketones of type I, where R′ = OH and n = 2, were prepared in a Mannich condensation with 2-acetyl-7-hydroxyfluorene (IV), paraformaldehyde, and secondary amine hydrochlorides. A summarized list of the aminoketones prepared in the investigation is given in Table I.

Two of the aminoketones were also prepared by a different method. When 2-acetoxyfluorene underwent a Friedel and Crafts reaction with chloroacetyl

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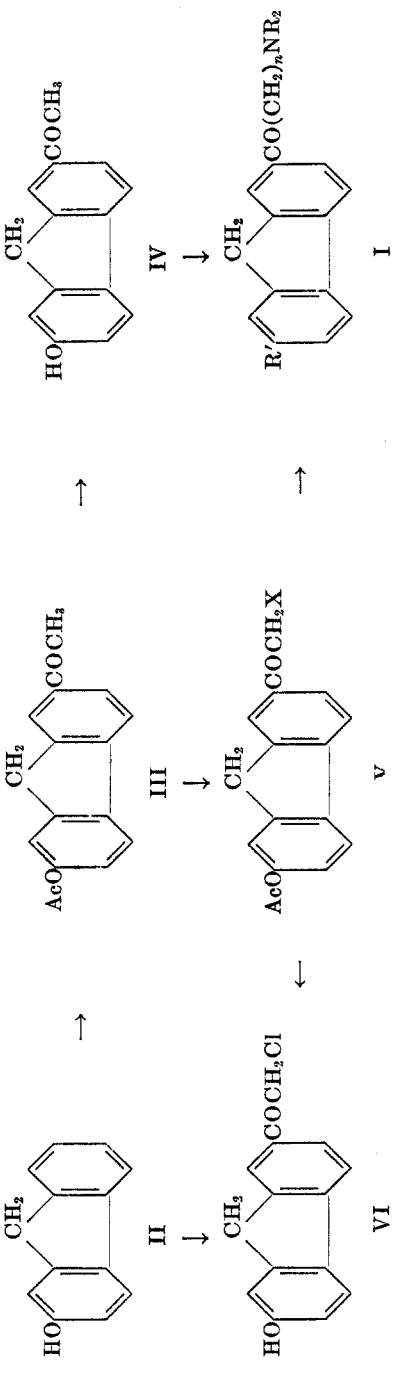
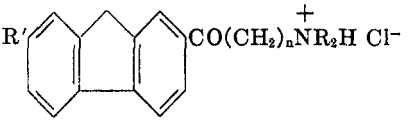

COCH3
CH2
HO
IV
CO(CH2)nNR2
CH2
R'
I
COCH2
CH2
AcO
III
COCH2X
CH2
AcO
V
COCH2Cl
CH2
HO
II
CH2
HO
VI

TABLE I

DIALKYLAMINO KETONES DERIVED FROM 2-HYDROXYFLUORENE



R′	n	—NR_2	YIELD, %	M.P., °C.[a,b]	FORMULA	ANALYSIS			
						Nitrogen[c]		Chlorine	
						Calc'd	Found	Calc'd	Found
CH_3COO	1	Piperidino	85[d]	298	$C_{22}H_{24}ClNO_3$	3.64	3.64	9.19	9.11
CH_3COO	1	Morpholino	85	250	$C_{21}H_{22}ClNO_4$	3.61	3.36	9.14	9.01
CH_3COO	1	Diethylamino	50	263	$C_{21}H_{24}ClNO_3$	3.75	3.94	9.27	9.33
CH_3COO	1	Dimethylamino	50	265	$C_{19}H_{20}ClNO_3$	4.05	4.04	10.55	10.42
HO	1	Piperidino	80[e]	298	$C_{20}H_{22}ClNO_2$	4.06	4.02	10.31	10.21
HO	2	Piperidino	80	247	$C_{21}H_{24}ClNO_2$	3.92	3.94	9.96	10.02
HO	2	Morpholino	75	250	$C_{20}H_{22}ClNO_3$	3.89	3.84	9.86	9.55
HO	2	Dimethylamino	60–80	238	$C_{18}H_{20}ClNO_2$	4.41	4.43	11.16	11.25

[a] All melting points are uncorrected. [b] Melting was accompanied by decomposition in each case. [c] By micro Kjeldahl procedure. [d] From 2-chloroacetyl-7-acetoxy fluorene. [e] From 2-chloroacetyl-7-hydroxyfluorene.

chloride, the product, 2-chloroacetyl-7-acetoxyfluorene (V, X = Cl) could be reacted with piperidine or dimethylamine to give products identical with those obtained from the bromo ketone (V, X = Br) with the same amines. Although the attempted hydrolysis of the ester linkage of V (X = Br) led to the loss of bromine from the side chain, the hydrolysis of the corresponding chloro derivative (V, X = Cl) left the chloroacetyl group intact, yielding 2-chloroacetyl-7-hydroxyfluorene (VI). Amination of VI with piperidine gave 2-N-piperidinoacetyl-7-hydroxyfluorene.

EXPERIMENTAL

2-Acetoxyfluorene. A solution of 25.0 g. (0.137 mole) of crude 2-hydroxyfluorene (7) was prepared in 300 ml. of boiling acetone. Pyridine (11.2 ml., 0.137 mole) was added to the warm solution before the addition of 14.0 ml. (0.137 mole) of acetic anhydride. The solution was refluxed on a water-bath for one hour and then poured into three times its volume of cold water. The crude product, weighing 28.8 g. (90%), melted at 114–116°, and was sufficiently pure for the acylation reaction. Recrystallization of a portion of the product from 95% ethanol yielded white needles, m.p. 130°.

Anal. Calc'd for $C_{15}H_{12}O_2$: C, 74.97; H, 5.39.

Found: C, 74.81; H, 5.20.

2-Acetyl-7-acetoxyfluorene (III). Into a two-liter, three-necked flask fitted with a 60 ml. dropping-funnel, a mercury sealed stirrer, and a long condenser terminating in a gas trap, were placed 600 ml. dry carbon disulfide and 56.0 g. (0.25 mole) of crude 2-acetoxyfluorene. With the aid of a water-bath the temperature was raised to that of gentle reflux. The flame was removed and 70.0 g. (0.53 mole) of anhydrous aluminum chloride was added. The mixture was stirred and refluxed for 30 minutes before the dropwise addition of 26.5 g. (0.255 mole) of acetic anhydride. Stirring and refluxing was continued for

an additional three hours before allowing the mixture to cool to room temperature. The olive-green precipitate was separated, dried in air, and hydrolyzed by adding it in portions to a mixture of 600 ml. of water, 200 g. of ice, and 30 ml. of concentrated hydrochloric acid. The crude product, a light tan solid (m.p. 104–106°) weighed 50.0 g. Purification was accomplished by hydrolysis and reacetylation. The pure 2-acetyl-7-acetoxyfluorene was a colorless solid when recrystallized from 50% aqueous acetic acid. Yield: 85%; m.p. 124–125°.

Anal. Calc'd for $C_{17}H_{14}O_3$: C, 73.23; H, 5.30.
Found: C, 72.94; H, 5.36.

2-Acetyl-7-hydroxyfluorene (IV). To a mixture of 100 ml. of 95% ethanol and 100 ml. of concentrated hydrochloric acid was added 50.0 g. of crude 2-acetyl-7-acetoxyfluorene. After refluxing the mixture for 45 min. it was cooled to room temperature, neutralized with concentrated ammonium hydroxide, and poured into twice its volume of cold water. The resulting precipitate was collected and was recrystallized from 80% methanol. The pure product consisted of white needles, m.p. 202°.

Anal. Calc'd for $C_{15}H_{12}O_2$: C, 74.97; H, 5.39.
Found: C, 74.66; H, 5.29.

When refluxed for one hour with equimolar quantities of acetic anhydride and pyridine in acetone the 2-acetyl-7-hydroxyfluorene could be re-esterified. When the hot solution was poured into water and the resulting solid product was recrystallized from 50% aqueous acetic acid, pure 2-acetyl-7-acetoxyfluorene (III) was obtained.

2-Bromoacetyl-7-acetoxyfluorene [V (X = Br)]. To a suspension of 21.0 g. (0.078 mole) of pure 2-acetyl-7-acetoxyfluorene in 500 ml. of dry ether was added 12.64 g. (0.073 mole) of bromine in 50 ml. of ether. The mixture was stirred vigorously and warmed on a water-bath until the reaction began, as evidenced by the disappearance of the bromine color and the complete solution of the ketone. As soon as precipitation of the bromo ketone began, the heat was withdrawn and the mixture was cooled to 0° with constant stirring. The product was collected, washed with cold ether, and dried *in vacuo*. Recrystallization from ethanol gave colorless needles, m.p. 131°; yield 65–70%.

Anal. Calc'd for $C_{17}H_{13}BrO_3$: Br, 23.2. Found: Br, 24.0.

2-Chloroacetyl-7-acetoxyfluorene [(V) (X = Cl)]. To a warm solution of 56 g. (0.25 mole) of 2-acetoxyfluorene dissolved in 600 ml. of dry carbon disulfide was added 60 g. (0.45 mole) of anhydrous aluminum chloride. After refluxing the suspension for 30 minutes, redistilled chloroacetyl chloride (19 ml., 0.25 mole) was added slowly over a period of one hour. A dark precipitate began to separate with the first few drops of the acid chloride. After refluxing the mixture for an additional two hours, it was cooled and filtered. The precipitated aluminum chloride complex was air-dried and then hydrolyzed in a solution of 30 ml. of concentrated hydrochloric acid in 800 ml. of ice-water. 2-Chloroacetyl-7-acetoxyfluorene was separated by filtration and recrystallized from 50% aqueous acetic acid; yield 49.0 g. (64%); m.p. 148°.

Anal. Calc'd for $C_{17}H_{13}ClO_3$: Cl, 11.80. Found: Cl, 12.10.

2-Chloroacetyl-7-hydroxyfluorene (VI). Hydrolysis of 49.0 g. (0.163 mole) of 2-chloroacetyl-7-acetoxyfluorene was effected by refluxing it with 500 ml. of a one to one mixture of concentrated hydrochloric acid and ethanol for one hour. The product was isolated by dilution of the reaction mixture with 1500 ml. of water and collection of the precipitate. Recrystallization from aqueous acetic acid and then from aqueous ethanol gave white needles. Yield 25%; m.p. 206°.

Anal. Calc'd for $C_{15}H_{11}ClO_2$: Cl, 13.7. Found: Cl, 13.4.

2-N-Piperidinoacetyl-7-acetoxyfluorene hydrochloride. (I, R′ = CH_3COO, n = 1) (NR_2 = $C_5H_{10}N$). The method described herein is typical of that used for the preparation of those compounds listed in Table I in which n = 1 and R′ = CH_3COO.

To a solution of 8.70 g. (0.025 mole) of 2-bromoacetyl-7-acetoxyfluorene in 100 ml. of dry acetone at reflux temperature was added a solution of 6 ml. (0.06 mole) of piperidine in 25 ml. of dry acetone. Piperidine hydrobromide began to precipitate immediately. After

30 minutes reflux the solution was cooled and diluted with 125 ml. of dry ether. The piperidine hydrobromide was separated and the filtrate was acidified with a dry ethereal solution of hydrogen chloride. The precipitated amino ketone hydrochloride was recrystallized from glacial acetic acid by the addition of ether to the warm acetic acid solution until a slight turbidity was noticed. Yield 70%, m.p. 298°. This and other compounds prepared by this method are listed in Table I.

2-N-Piperidinoacetyl-7-hydroxyfluorene hydrochloride (I, R′ = OH, n = 1, NR_2 = $C_5H_{10}N$). To a solution of 2.63 g. (0.01 mole) of 2-chloroacetyl-7-hydroxyfluorene (VI) in 20.0 ml. of dry boiling acetone was added 1.87 ml. (0.02 mole) of piperidine in 10 ml. of dry acetone. After the reaction had ceased, 100 ml. of dry ether was added to the cooled solution and the piperidine hydrochloride was separated. Enough anhydrous ethereal hydrogen chloride solution was added to the filtrate to acidify it and to cause the precipitation of the amino ketone hydrochloride. Recrystallization of the product from glacial acetic acid through the addition of ether to the acetic acid solution gave white needles. Yield 81%, m.p. 298°.

Anal. Calc'd for $C_{20}H_{21}ClNO_2$: Cl, 10.31; N, 4.06.
Found: Cl, 10.21; N, 4.02.

2′-(3-Piperidino-1-oxopropyl)-7′-hydroxyfluorene hydrochloride (I, R′ = OH, n = 2, NR_2 = $C_5H_{10}N$). The procedure described here is typical of that used for the preparation of compounds of type I in which R′ = OH and n = 2.

2-Hydroxy-7-acetylfluorene (10.9 g., 0.05 mole), 5.30 g. (0.17 mole) of paraformaldehyde, and 12.1 g. (0.1 mole) of piperidine hydrochloride were placed in a 500-ml. three-necked flask fitted with a mercury-sealed stirrer, a thermometer, and a condenser. Then 50 ml. of isoamyl alcohol was added and the mixture was refluxed for 20 to 30 min. The addition of 10 drops of concentrated hydrochloric acid hastened the depolymerization of the paraformaldehyde. The product separated from the boiling mixture in white crystalline plates. The mixture was cooled to room temperature, filtered, and to the filtrate was added dry ether until no more precipitate formed. The combined precipitates were washed with water and were recrystallized from absolute ethanol. Yield 80%, m.p. 247°.

Anal. Calc'd for $C_{21}H_{24}ClNO_2$: Cl, 9.96; N, 3.92.
Found: Cl, 10.02; N, 3.94.

SUMMARY

There is described a method for the preparation of 2-acetyl-7-hydroxyfluorene and 2-acetyl-7-acetoxyfluorene and a series of amino ketones derived from them by either the Mannich condensation or by bromination of the acetyl group followed by amination with secondary amines.

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