concentrated to small volume. On cooling the monohydrochloride separated out. It was recrystallized from absolute ethanol; yield 20 g. (92%). The dihydrochloride melted at 192–193°. A sample of the monohydrochloride converted to the free base distilled at 124–130° (3–4 mm.).

3-Acetamido-4-(N⁴-acetylsulfanilamido)-anisole (36).—Fifteen grams (0.05 mole) of 4-(N⁴-acetylsulfanilamido)-3-aminoanisole and 45 cc. (0.5 mole) of acetic anhydride were heated on a steam-bath for about fifteen minutes. The product which crystallized out on cooling was filtered off, washed with water and recrystallized from a 70–30 acetone–alcohol mixture; yield 90%.

Acknowledgment.—The authors wish to thank Mr. J. F. Alicino of this Institute for the microanalyses reported.

Summary

Seven isomeric aminosulfanilanisides together with some of their derivatives have been described.

3-Amino-4-sulfanilamidoanisole (or using the aniside nomenclature 2′-aminosulfanil-*p*-aniside[8]), its N⁴-acetyl derivative, and its sodium acetaldehyde bisulfite derivative, have been found to have definite antimalarial activity.

(8) This compound is identified as SN 374 in the forthcoming monograph, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor.

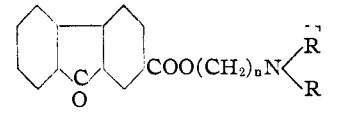
NEW BRUNSWICK, N. J. RECEIVED AUGUST 16, 1946

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

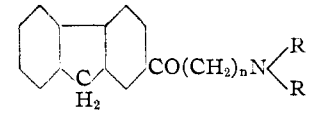
Alkylamine Derivatives of Fluorene

BY FRANCIS EARL RAY AND IAN R. MACGREGOR[1]

Derivatives substituting both the aliphatic 9-carbon[2,3] and the aromatic carbons[4,5] of fluorene have been found to have therapeutic properties.



I



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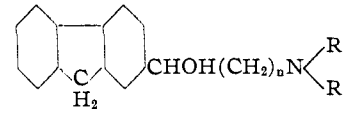

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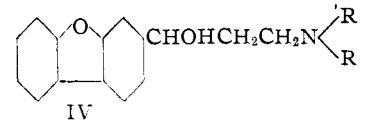
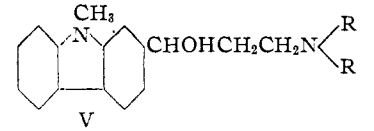


IV



V

Ray and Rieveschl[4] found that esters of fluorenone-2-carboxylic acid of the type I possessed considerable topical anesthetic power and antispasmodic action. As is well known,[6] the ester linkage is not essential for activity. We therefore decided to replace the ester linkage with the keto, as in II, or hydroxy, as in III, group. Fluorene was selected instead of fluorenone because of its greater solubility. Previous experience suggested that the activity might be expected to reach a maximum when $n = 2$. Hydroxy compounds of type III would be analogous to the derivatives of dibenzofuran, of the type IV, and 9-methylcarbazole, of the type V, which showed analgesic activity in cats.[7]

Ketones, of the type II, in which $n = 1$ were prepared by the side chain bromination of 2-acetylfluorene and its subsequent reaction with a mono- or dialkylamine. Those ketones in which $n = 2$ were obtained by means of the Mannich[8] reaction from 2-acetylfluorene, paraformaldehyde and a primary or secondary amine hydrochloride. When ammonium chloride was substituted for the amine hydrochloride, a tertiary amine, VI, resulted, while methylamine hydrochloride yielded a small amount of the tertiary amine VII in addition to the desired product.

$(C_{13}H_9COCH_2CH_2)_3N\cdot HCl$ (VI) $(C_{13}H_9COCH_2CH_2)_2NCH_3\cdot HCl$ (VII)

No cyclization of the kind reported by Mannich and Ball[9] was observed.

Secondary amines reacted well with the exception of diethylamine. This agrees with the observations of Kermack and Muir[10] who found that diethylamine was so inert that it failed to react with ethyl methyl ketone and formaldehyde,

(1) Abstracted from a thesis submitted to the Graduate School, University of Cincinnati, by I. R. MacGregor in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Lehmann and Knoefel, *J. Pharmacol.*, **74**, 217, 274 (1942); **76**, 194 (1942).

(3) Burtner and Cusie, THIS JOURNAL, **65**, 262, 1582 (1943).

(4) Ray and Rieveschl, *ibid.*, **65**, 836 (1943).

(5) Bielschosky and Green, *Nature*, **149**, 526 (1942).

(6) Goodman and Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., N. Y., 1941, pp. 185–225.

(7) Nelson, *J. Pharmacol.*, **65**, 424 (1939); Eddy, *ibid.*, **68**, 159 (1936).

(8) "Organic Reactions," **1**, 327 (1942).

(9) Mannich and Ball, *Arch. Pharm.*, **264**, 65 (1926).

(10) Kermack and Muir, *J. Chem. Soc.*, 3089 (1931).

TABLE I

Compound, R-fluorene hydrochlorides	M. p., °C.	Formula	Analyses, % Calcd.	Found
2′-(3-Methylamino-1-oxopropyl)-	217–218	$C_{17}H_{18}ONCl$	Cl, 12.36	12.50
2′-(3-Dimethylamino-1-oxopropyl)-	187–188	$C_{18}H_{20}ONCl$	Cl, 11.74	11.69
2′-(3-Ethylamino-1-oxopropyl)-	225–226	$C_{18}H_{20}ONCl$	N, 4.64	4.51
2′-(3-Monoethanolamino-1-oxopropyl)-	201–202	$C_{18}H_{20}O_2NCl$	N, 4.42	4.69
			Cl, 11.15	11.16
2′-(3-Allylamino-1-oxopropyl)-	214–215	$C_{19}H_{20}ONCl$	N, 4.49	4.79
2′-(3-Di-*n*-propylamino-1-oxopropyl)-	150–151	$C_{22}H_{29}ONCl$	Cl, 9.91	9.75
2′-(3-Benzylamino-1-oxopropyl)-	239–240	$C_{23}H_{22}ONCl$	N, 3.85	3.98
2′-(3-*n*-Octylamino-1-oxopropyl)-	184–185	$C_{25}H_{32}ONCl$	N, 3.63	3.66
			Cl, 9.20	9.15
2′-(3-Piperidino-1-oxopropyl)-	212–213	$C_{21}H_{24}ONCl$	Cl, 10.31	10.34
2′-(3-Piperidino-1-oximidopropyl)-	217–218	$C_{21}H_{25}ON_2Cl$	Cl, 9.80	9.98
2′-(3-Morpholino-1-oxopropyl)-	226–227	$C_{20}H_{22}O_2NCl$	N, 4.08	4.13
ω-Piperidino-2-acetyl-	273–274	$C_{20}H_{22}ONCl$	Cl, 10.81	10.94
ω-Morpholino-2-acetyl-	263–264	$C_{19}H_{20}O_2NCl$	Cl, 10.75	10.56
2′-(3-Piperidino-1-aminopropyl)-·2HCl	262–263	$C_{21}H_{28}N_2Cl$	N, 7.07	7.15
Tri-3-(1,2′-fluoryl-1-oxopropyl)-amine·HCl	248–249	$C_{48}H_{40}O_3NCl$	N, 1.96	2.04
(a) Free base	213	$C_{48}H_{39}O_3N$	Mol. wt. 678	675
Potassium 2′-(3-piperidino-1-oxopropyl)-fluorene-7′-sulfonate	300	$C_{21}H_{23}O_4NSK$	S, 7.56	7.55
Sodium 2′-(3-morpholino-1-oxopropyl)-fluorene-7′-sulfonate	300	$C_{20}H_{20}O_5NSNa$	S, 7.81	7.84
2′-(3-Piperidino-1-oxopropyl)-fluorenone hydrochloride	231–232	$C_{21}H_{22}O_2NCl$	Cl, 9.96	9.76
ω-Bromo-2-acetylfluorene	144–145	$C_{15}H_{11}OBr$	Br, 27.86	27.67
ω-Bromo-2-acetylfluorenone	211–212	$C_{15}H_9O_2Br$	Br, 26.55	26.25

All melting points are uncorrected. All fluorene compounds were white and all fluorenone compounds were pale yellow. The oximes, however, were white.

while Levy and Nisbet[11] reported that diethylamine did not react with 2-acetylfuran and formaldehyde.

In the present investigation the heterocyclic amines piperidine and morpholine reacted especially well giving good yields of compounds with considerable local anesthetic activity. These were, unfortunately, rather insoluble in water.

The compounds resulting from the condensation of diethanolamine with 2-acetylfluorene and paraformaldehyde; and of di-*n*-octylamine with 2-acetylfluorene and paraformaldehyde were secondary amines, VIII, in which R = $HOCH_2CH_2$— and $CH_3(CH_2)_6CH_2$—. Apparently one alkyl

$$C_{13}H_9CO(CH_2)_2—\overset{H}{N}—R\cdot HCl \qquad \text{VIII}$$

group was eliminated from nitrogen under the conditions used in bringing about the condensation.

The alcohols, III, were obtained by catalytic reduction of the ketones with hydrogen and platinum oxide catalyst. The reaction was quite slow at pressures of 2 to 4 atmospheres.

The oximes showed less topical anesthetic action than the ketones, nor was the solubility increased to any great degree by oximation, *cf.* ref. 4. 2′-(3-Piperidino-1-aminopropyl)-fluorene dihydrochloride was prepared by catalytic reduction of the corresponding oxime. This compound while more soluble than the ketone or oxime was without local anesthetic action on the tongue.

(11) Levy and Nisbet, *J. Chem. Soc.*, 1053–1056 (1938).

To increase its solubility 2′-(3-piperidino-1-oxypropyl)-fluorene was sulfonated. While increased solubility in water resulted, the sulfonate was without topical anesthetic effect. Similar results were obtained with the morpholino derivative.

Experimental

2-Acetylfluorene was prepared by the method of Ray and Rieveschl.[4] The amine hydrochlorides were prepared by passing hydrogen chloride into an ethereal solution of the amine.

2′-(3-Piperidino-1-oxopropyl)-fluorene Hydrochloride.—This preparation is typical of those carried out by the Mannich reaction. In a three-necked flask were placed 42.6 g. (0.2 mole) of 2-acetylfluorene, 36.4 g. (0.3 mole) paraformaldehyde, 28.5 g. (0.3 mole) of piperidine and 120 cc. of *i*-amyl alcohol and the mixture refluxed for one hour. After cooling, the solid was removed, washed with acetone, dried and recrystallized from 1000 cc. of 95% ethyl alcohol. There was obtained 53.2 g. (78%) of a white crystalline solid which was only slightly soluble in water. See Table I for melting points and analyses.

2′-(3-Piperidino-1-oximidopropyl)-fluorene.—The compound described above (8.6 g.) was refluxed for five hours on a water-bath with 4 g. of hydroxylamine hydrochloride and 7 g. of barium carbonate in 200 cc. of ethyl alcohol. From the hot filtered solution the oxime separated as white crystals melting at 217–218°.

2′-(3-Piperidino-1-aminopropyl)-fluorene Dihydrochloride.—The oxime of the previous experiment was reduced catalytically. Five grams in 250 cc. of ethyl alcohol and 0.1 g. of platinum oxide catalyst and 3 cc. of concentrated hydrochloric acid were shaken together until the theoretical drop in pressure resulted. This required twenty-four hours. The filtered solution was evaporated to half its volume and ether was added to slight cloudiness. It was recrystallized similarly and a yield of 2.2 g. or 37.3% of theory was obtained. The compound could also be purified through its picrate which melted at 237°.

2′-(3-Piperidino-1-hydroxypropyl)-fluorene.—Reduction of the ketones was carried out in the Parr apparatus using 5 g. of substance in 250 cc. of alcohol, 0.1 g. of platinum oxide catalyst and hydrogen under an initial pressure of 55 lb. per sq. in. The reaction was slow, generally requiring twenty-four hours. After filtration the solution was evaporated to one-half its volume or dry ether was added to the warm solution until cloudiness developed. The yield of the substance mentioned above was 62% and the pure compound melted at 217°. The reduced compounds were considerably more soluble than the ketones but had less physiological activity.

Potassium 2′-(3-Piperidino-1-oxopropyl)-fluorene-7′-sulfonate was prepared by adding 10 g. of 2′-(3-piperidino-1′-oxopropyl)-fluorene hydrochloride to 100 g. of concentrated sulfuric acid. The mixture was stirred at room temperature for two hours during which time solution occurred and a green-brown color resulted. On pouring onto ice, the sulfonic acid precipitated in an unfilterable colloidal state. It was warmed to 80° and diluted to 1.5 liter. Potassium hydroxide (25% solution) was added until a clear solution resulted. The addition of potassium chloride caused the potassium salt to separate. It was recrystallized from hot water. An aqueous solution of the potassium salt first gave a precipitate with hydrochloric acid and then dissolved in an excess of acid.

ω-Bromo-2-acetylfluorene.—A suspension of 20.8 g. of 2-acetylfluorene in 1000 cc. of anhydrous ether was cooled to 0° and 5 cc. of bromine in 200 cc. of anhydrous ether was added. The mixture was stirred for two hours at 0° and then allowed to warm up to room temperature. The bromine color had completely disappeared. The gray precipitate was filtered off and a further quantity was obtained by the evaporation of the mother liquor. These were combined and recrystallized from alcohol, yield 17.8 g. (62%). It was slightly soluble in ether, moderately soluble in alcohol and insoluble in water.

ω-Bromo-2-acetylfluorenone was prepared similarly with a yield of 63.1%. It was somewhat less soluble. On oxidation fluorenone-2-carboxylic acid melting at 335–340°[4] and giving no test for halogen was obtained. Substitution must have occurred in the side chain.

ω-Piperidino-2-acetylfluorene Hydrochloride.—This compound was obtained by reacting omega-bromo-2-acetylfluorene with piperidine in absolute ether and treating the solution with an excess of ethereal hydrogen chloride. A yield of 47.4% was obtained. It was slightly soluble in water and fairly soluble in alcohol.

Summary

Side chain amines of fluorene of the following types have been prepared; 2-$C_{13}H_9COCH_2CH_2NR_2$·HCl, 2-$C_{13}H_9CHOHCH_2CH_2NR_2$·HCl and 2-$C_{13}H_9COCH_2NR_2$·HCl. When R_2 was morpholino or piperidino the yields in the Mannich reaction were excellent. The solubility of most of the compounds in water was low. Sulfonation increased the solubility but destroyed the anesthetic property.

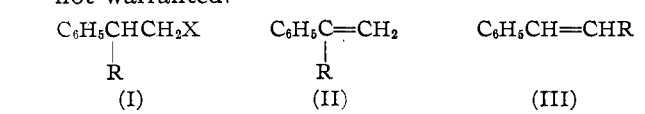
CINCINNATI 21, OHIO RECEIVED NOVEMBER 16, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Removal of Hydrogen Bromide from Certain β-Phenylalkyl Bromides by Means of Potassium Amide in Liquid Ammonia[1,2]

BY CHARLES R. HAUSER, PHILIP S. SKELL,[2a] ROBERT D. BRIGHT AND W. B. RENFROW

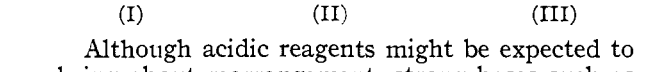
Alcohols or bromides of type (I) exhibit a considerable tendency to undergo rearrangement of the carbon skeleton, especially in the presence of acidic reagents. Thus, on dehydration in the presence of phosphorus pentoxide or infusorial earth, alcohols of this type produce mainly rearranged olefins (III).[3] Amagat[4] has reported that, even in the presence of sodium amide in boiling xylene, bromides of type (I) produce largely rearranged olefins; however, the conclusion that the base effects the rearrangement is not warranted.



(I) (II) (III)

Although acidic reagents might be expected to bring about rearrangement, strong bases such as the amide ion should not.[5] An acidic reagent attacks and removes the X with its bond pair of electrons allowing rearrangement to occur,[6] whereas the amide ion would generally be expected to attack the β-hydrogen effecting β-elimination[7,8] without rearrangement.[9] In the present investigation it has been found that, with potassium amide in liquid ammonia, bromides of type (I) in which R is methyl or ethyl eliminate hydrogen bromide practically without rearrangement of the carbon skeleton to form olefins of type (II). Some substitution product (I, X = NH_2) is also formed but its yield is very low (< 1%).

The bromide in which R is methyl, 2-phenyl-1-bromopropane (IV), was synthesized as represented by the series of reactions



(1) This work was supported in part by a grant from the Duke University Research Council.

(2) Reported at the Boston meeting of the American Chemical Society, September, 1939.

(2a) Present address: University of Chicago, Chicago, Illinois.

(3) Ramart and Amagat, *Ann. chim.*, **8**, 263 (1927).

(4) Amagat, *Bull. soc. chim.*, **49**, 1410 (1931).

(5) Sabetay (*Bull. soc. chim.*, **47**, 614 (1930)) has reported that an alcohol of type (I), 2-phenylpropanol-1, on slow distillation over anhydrous potassium hydroxide forms the unrearranged olefin, α-methylstyrene, but no yield was given.

(6) See especially Whitmore, THIS JOURNAL, **54**, 3274 (1932).

(7) See Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

(8) After the completion of the present work (see ref. 2) evidence was obtained in this Laboratory (from a study of the elimination reaction using alkyl halides containing deuterium) that, even with alkyl halides containing β-hydrogen, the amide ion is capable of removing α-hydrogen effecting α-elimination which may be accompanied by rearrangement (see ref. 9). However, since only a little rearrangement of the carbon skeleton was observed in the present investigation, α-elimination either did not occur to an appreciable extent or was accompanied by the shift of the β-hydrogen to the α-carbon.

(9) See Hauser, THIS JOURNAL, **62**, 933 (1940).