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# AMINO CARBINOLS DERIVED FROM 2-ACETYLFLUORENE[1]

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The marked plasmodicidal activity exhibited by amino carbinols of the type $>CHOHCH_2NR_2$ prepared from various acetylphenanthrenes (1) and 1-acetylnaphthalene (2) prompted this investigation, the objective of which was to synthesize and examine pharmacologically, analogous compounds derived from 2-acetylfluorene.

The proposed scheme called for the conversion of the ketone to the ω-bromo ketone, condensation of the latter with various secondary amines, followed by reduction of the resulting amino ketones to the amino carbinols, either catalytically ($PtO_2$) or with aluminum isopropoxide. In the initial bromination experiments, treatment of 2-acetylfluorene (3) in dry $CHCl_3$ (at 0°) afforded 2-ω-bromoacetylfluorene in 42% yield. In addition, some halogen-containing by-product was isolated which probably consisted of nuclear brominated material. It is known that bromination of fluorene in $CHCl_3$ solution leads to nuclear halogenation (4). Because of the tedious fractional crystallizations involved in the separation of the pure bromo ketone, an attempt was made to circumvent the bromination step through direct bromoacetylation of fluorene. The reaction of fluorene with bromoacetyl bromide in dry $CS_2$ (at −5°) in the presence of anhydrous $AlCl_3$ led to the desired 2-ω-bromoacetylfluorene (50% yield), identical with that obtained by brominating 2-acetylfluorene. The oily by-products of this reaction were not examined. The bromination of 2-acetylfluorene to the ω-bromo ketone, in anhydrous ether, in yields somewhat superior to those reported in this communication, was reported recently by Ray and MacGregor (5).

The bromo ketone-amine condensations were effected at room temperature either in ether, compounds 2, 4, 5, 7, 8 (Table I) or in chloroform, compound 3. In view of the relative instability of the free amino ketones it was found judicious, in all cases, to reduce these substances or their salts to the corresponding amino alcohols without delay. The amino ketones derived from the aliphatic amines were amber syrups, while those formed from the heterocyclic amines were crystalline. Owing, probably, to low basicity, the condensation of 1,2,3,4-tetrahydroquinoline with ω-bromoacetylfluorene could not be effected in solution. Fusion of the components at 100°, however, gave the desired (solid) amino ketone, but the latter could not be reduced to the corresponding amino alcohol. This abnormal behavior, towards hydrogen, of amino ketones derived from

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TABLE I

FLUORENE AMINO CARBINOLS

| S.N. | COMPOUND | APPEARANCE | FORMULA | M.P., C. | ANALYSES | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Calc'd | | Found | |
| | | | | | C | H | C | H |
| — | 2-ω-Bromoacetylfluorene | Prisms[a] | $C_{15}H_{11}BrO$ | 147–149 | 62.7 | 3.86 | 62.5 | 4.00 |
| 1807 | 2-(2-Diethylamino-1-hydroxyethyl)-fluorene HCl | Needles[b] | $C_{19}H_{24}ClNO$ | 172–174 | 71.8 | 7.61 | 71.9 | 7.71 |
| 15,077 | 2-(2-Di-*n*-propylamino-1-hydroxyethyl)-fluorene HCl | Prisms[g] | $C_{21}H_{28}ClNO$ | 175–177 | 72.9 | 8.16 | 72.7 | 8.19 |
| 1808 | 2-(2-Piperidino-1-hydroxyethyl)fluorene HCl | Plates[e] | $C_{20}H_{24}ClNO$ | 256–257d. | 72.8 | 7.33 | 72.5 | 6.88 |
| 1811 | 2-(2-Morpholino-1-hydroxyethyl)fluorene HCl | Long Plates[b] | $C_{19}H_{22}ClNO_2$ | 246–247d. | 68.7 | 6.68 | 68.7 | 6.55 |
| 2695 | 2-(2-Tetrahydroquinolino-1-oxoethyl)-fluorene | Leaves[f] | $C_{24}H_{21}NO$ | 166–168 | 84.9 | 6.24 | 84.5 | 6.63 |
| 1809 | 2-(2-Tetrahydroisoquinolino-1-hydroxy-ethyl)fluorene HCl[2] | Plates[d] | $C_{24}H_{24}ClNO$ | 248–249d. | 76.2 | 6.40 | 75.8 | 6.38 |
| — | 2-(2-*trans*-Decahydroquinolino-1-oxo-ethyl)fluorene[2] | Crusts[c] | $C_{24}H_{27}NO$ | 104–106 | 83.4 | 7.88 | 82.8 | 8.04 |
| 1810 | 2-(2-*trans*-Decahydroquinolino-1-hydroxy-ethyl)fluorene HCl | Needles[b] | $C_{24}H_{30}ClNO$ | 263–264d. | 75.0 | 7.88 | 74.7 | 8.21 |

[a] Acetone. [b] Absol. alcohol plus ether. [c] Methanol. [d] Methanol plus ether. [e] Acetone, methanol plus ether. [f] Absol. alcohol. [g] Acetone.

ω-bromomethyl ketones with tetrahydroquinoline has been observed by others in this Laboratory in the naphthalene (6) as well as in the phenanthrene series (1).

The synthesis of 2-(2-diethylamino-1-hydroxyethyl)fluorene hydrochloride outlined below, is illustrative of the methods used in the preparation of compounds 2, 4, 5, 7, 8 (Table I). With compounds 4 to 8, however, the solid amino ketones were usually mixed with amine hydrobromides. Separation of the two was readily effected by repeated leachings with warm (60°) water in which the amine hydrobromides were soluble. The insoluble amino ketones were then purified either alone or as their hydrochlorides and then reduced. The synthesis of 2-(2-di-*n*-propylamino-1-hydroxyethyl)fluorene hydrochloride, compound 3, describes the aluminum isopropoxide reduction of the amino ketone to the amino carbinol.

Plasmodicidal activity towards *P. gallinaceum* (chick infection) was absent in the amino carbinols described in this work.

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## EXPERIMENTAL

Melting points are uncorrected.

*2-ω-Bromoacetylfluorene by bromination of 2-acetylfluorene.* To a cooled (0°) and stirred solution of 8 g. of 2-acetylfluorene (3) in 75 ml. of C.P. $CHCl_3$, containing a few drops of a solution of HBr in glacial acetic acid, 6.15 g. (1 mole) of bromine was added dropwise during 1 hr. After stirring at 0° and at room temperature respectively for 0.25-hr. periods, a quantity of yellow, crystalline, $CHCl_3$-insoluble material was removed and the filtrate concentrated to a syrup *in vacuo*. On cooling, the latter afforded 5.7 g. of crude, crystalline material which consisted of the bromo ketone mixed with nuclear-halogenated material. Recrystallization from acetone (Norit) gave 2.7 g. of bromo ketone, m.p. 143–145°. The concentrated mother liquor yielded another 0.7 g.

The chloroform-insoluble fraction, probably a perbromide, was dissolved in boiling $CHCl_3$ (attended by copious HBr evolution) and the solvent removed *in vacuo*. The residual, syrupy product was dissolved in acetone (Norit), concentrated, seeded with the above bromo ketone and refrigerated for 24 hrs. This afforded a further quantity (1.3 g.) of bromo ketone of m.p. 140–143°, (total yield 4.7 g. or 42%). 2-ω-Bromoacetylfluorene crystallizes in slender, colorless prisms from acetone, m.p. 147–149° (after 3 recrystallizations).

*2-ω-Bromoacetylfluorene by direct bromoacetylation of fluorene.* A stirred solution of 50 g. of fluorene in 350 ml. of dry $CS_2$ was cooled to −5° and treated all at once with 88 g. (2.2 moles) of powdered, anhydrous $AlCl_3$. The color of the solution darkened to a brownish-purple and the temperature rose slightly. During the course of 0.75 hr., a solution of 65 g. (1.05 moles) of bromoacetyl bromide in 45 ml. of $CS_2$ was added dropwise while the temperature was held at *ca.* −4°. Stirring was continued at −4° to 0° for 3 hrs., then for another 2.5 hrs. at 0° to +5°. The reaction mixture was poured onto a mixture of cracked ice and 2 *N* HCl, a little ether was added to take up a small amount of oily by-product, and the suspension shaken vigorously for several minutes to complete decomposition of the reaction product. The resulting, cream-colored suspension was refrigerated overnight, filtered, washed with water and dried; yield 80 g. Recrystallization from acetone (Norit) afforded 36.5 g. of pure 2-ω-bromoacetylfluorene identical with that obtained above. From the concentrated mother liquor, another 7 g. of bromo ketone was isolated (total yield, 43.5 g. or 50%).

*2-(2-Diethylamino-1-oxoethyl)fluorene hydrochloride.* A mixture of 12 g. of 2-ω-bromoacetylfluorene with 6.75 g. (2.2 moles) of diethylamine in 200 ml. of ether was shaken for 12 hrs. After removing the precipitated diethylamine hydrobromide (6 g., 93%), the ethereal solution of the amino ketone was washed several times with cold water and dried over sodium sulfate. The filtered solution was cooled in ice, treated with one-third of the calculated amount of 6 *N* alcoholic HCl and seeded with crystals obtained in a test tube experiment. After 10 mins., the remaining two-thirds of alcoholic HCl was added and the whole refrigerated for 12 hrs. The amino ketone hydrochloride was a pale-yellow, microcrystalline powder (11.5 g.), which was recrystallized by dissolving it in a mixture of acetone-ethanol (9:1) and diluting with dry ether; yield 8.7 g.

*2-(2-Diethylamino-1-hydroxyethyl)fluorene hydrochloride.* Reduction of the above described amino ketone hydrochloride (8.7 g.) in absolute methanol solution (125 ml.), in the presence of $PtO_2$ (0.2 g.), proceeded smoothly and was complete in 8.5 hrs. The syrup obtained from the filtered and concentrated (*vacuo*) solution was taken up in the minimum of acetone and refrigerated for 36 hrs. During this interval 5.8 g. (65%) of colorless crystals separated. The salt crystallized in rosettes of colorless needles from an absolute ethanol-ether mixture, m.p. 172–174°.

*2-(2-Tetrahydroquinolino-1-oxoethyl)fluorene.* Five grams of 2-ω-bromoacetylfluorene was covered with 4.8 g. (2 moles) of tetrahydroquinoline[2] and the mixture heated at 95–100° (oil-bath) for 10 mins. On cooling, the melt solidified to a hard, yellow-brown cake, which was broken up and digested several times with hot water in order to remove the amine hydrobromide. The pale-yellow, insoluble material was filtered and dried; 6 g. From dilute acetone (Norit), the amino ketone crystallized in pale yellow plates, m.p. 167–169°. This substance could not be hydrogenated to the corresponding carbinol under the conditions employed for the reduction of the other amino ketones in this series.

*2-(2-Di-n-propylamino-1-hydroxyethyl)fluorene hydrochloride.* To a solution of 12 g. of 2-ω-bromoacetylfluorene in 100 ml. of C.P. $CHCl_3$ was added 8.4 g. (2 moles) of di-*n*-propylamine and the mixture kept at 20° overnight. Concentration of the solution at 40–45° (*vacuo*) afforded a syrup which was triturated with 80 ml. of dry ether and cooled in ice, whereupon 6.9 g. (92%) of amine hydrobromide was recovered. The oily amino ketone (13.3 g.) obtained from the concentrated filtrate was reduced by the method of Meerwein, Ponndorf, and Verley employing 48 ml. (1.1 moles) of 3 *N* aluminum isopropoxide solution. The resulting, syrupy amino alcohol solidified to a waxy mass on standing overnight. Preparation of the hydrochloride was effected in absolute ethanol solution using a slight excess of 20% alcoholic HCl; addition of dry ether (to light turbidity) caused the slow separation of a light tan, microcrystalline powder (6.3 g.). Three recrystallizations from a concentrated acetone solution (Norit) afforded minute, colorless prisms, m.p. 173–175°.

SUMMARY

The synthesis of 2-ω-bromoacetylfluorene by (a) bromination of 2-acetylfluorene and (b) bromoacetylation of fluorene is reported.

The preparation of a series of amino carbinols derived from 2-acetylfluorene is described.

Plasmodicidal activity was absent in this group of compounds.

BETHESDA 14, MD.

[2] 1,2,3,4-Tetrahydroquinoline was prepared by high-pressure reduction (copper-chromite) of quinoline. For the preparation of 1,2,3,4-tetrahydroisoquinoline and *trans*-decahydroquinoline, see ref. 7 (a) and (b) respectively.

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