LXXXIV.—*Arsonic Acids of the Fluorene Series.*

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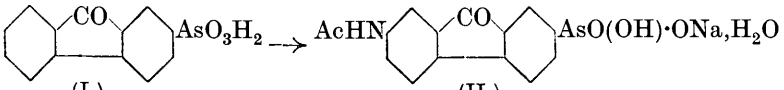
THE work described below was undertaken with the object of preparing derivatives of fluorene and fluorenone which might prove to be of value in the treatment of trypanosomiasis. As outlined in earlier publications (*Chem. and Ind.*, 1930, **49**, 800; British Association Report, 1930, 48), we have hitherto undertaken the two following series of researches : (1) preparation of symmetrical ureas of Bayer 205 or Fourneau 309 type, with fluorene and fluorenone groups replacing the naphthalene residues of these drugs; (2) an examination of the therapeutic effect of introducing arsenic into the fluorene and fluorenone molecules.

The former series having failed to yield trypanocidally active compounds of the symmetrical urea type, we decided to concentrate on the second series, in which we were able to show that trypanocidal potency is manifested when an arsonic acid radical is introduced into the fluorenone molecule in conjunction with an amino-group. In the discussion on Chemotherapy (*Chem. and Ind., loc. cit.*), reference was made to *fluorene-2-arsonic acid* and to *fluorenone-2-arsonic acid* (I), which had already served as starting materials in the production of fluorene and fluorenone derivatives of pharmacological interest.

We had intended to defer publication until a more complete series of such compounds had been prepared and tested, but the recent appearance of a paper by F. E. Cislak and C. S. Hamilton (*J. Amer. Chem. Soc.*, 1931, **53**, 746) on " Some Arsonic Acids of Fluorene and its Derivatives," suggesting the use of the same starting materials, leads us to record our experiments, which have carried the chemotherapeutic aspect of the matter further than is described by the American authors.

Since our first preliminary note (*v. supra*) we have prepared the *acetyl*, *glycine*, and *glycinamide* derivatives of *aminofluorenone-2-arsonic acid*. These compounds, which have been tested for trypanocidal activity by Professor Warrington Yorke, show a distinct improvement in this respect on aminofluorenone-2-arsonic acid itself.

Sodium 7-acetamidofluorenone-2-arsonate (II) has so far proved to be the most efficacious member of this series.



(I.) (II.)

EXPERIMENTAL.

2-Nitrofluorene and 2-nitrofluorenone were prepared by Diels's method (*Ber.*, 1901, **34**, 1758), but the necessity for obtaining larger quantities of the corresponding amines for conversion into arsonic acids led us to abandon the reduction methods of this author in favour of the catalytic reduction process employed by Bennett and Noyes (*J. Amer. Chem. Soc.*, 1930, **52**, 3438; compare Voorhees and Adams, *ibid.*, 1922, **44**, 1397).

A development of this reduction under pressure has enabled us to prepare not only 2-aminofluorenone and 2-aminofluorene but also 2-aminofluorenol, the intermediate reduction product of 2-nitrofluorenone. We propose to use this amino-alcohol as a starting point in the production of substances likely to be of interest in chemotherapy.

Fluorene-2-arsonic Acid.—2-Aminofluorene was diazotised in the manner described by Diels (*Ber.*, 1901, **34**, 1758) and by Cislak and Hamilton (*loc. cit.*); the resulting diazonium chloride was converted into the corresponding *arsonic acid* by the Bart reaction as applied by Burton and Gibson (J., 1927, 2386) in the preparation of 9-methylcarbazole-3-arsonic acid. The acid crystallised from hot alcohol in sparingly soluble, white needles (Found: As, 25·8. $C_{13}H_{11}O_3As$ requires As, 25·9%). It formed only a *monosodium* salt, crystallising from hot water in colourless plates containing $1H_2O$ (Found after dehydration: As, 24·0. $C_{13}H_{10}O_3NaAs$ requires As, 24·0%). M.L.D. approximately 0·25 mg. Therapeutic action nil.

2-Dichloroarsinofluorene separated in colourless needles, m. p. 109°, from petroleum (b. p. 60—80°) (Found: As, 23·6. $C_{13}H_9Cl_2As$ requires As, 24·1%). Dissolved in acetone, this chloroarsine is converted by ammonia into the corresponding oxide.

Fluorenone-2-arsonic acid (I) separated in yellow needles from alcohol (Found: As, 24·4. $C_{13}H_9O_4As$ requires As, 24·67%). It yielded a *monosodium* salt which crystallised in pale yellow needles readily soluble in water (Found: As, 22·8. $C_{13}H_8O_4AsNa$ requires As, 23·0%).

M.L.D. approximately 1 mg.* Therapeutic action practically nil. The *disodium* salt formed deeper yellow crystals containing water ($6H_2O$) (Found after dehydration: As, 21·4. $C_{13}H_7O_4Na_2As$ requires As, 21·6%).

2-Dichloroarsinofluorenone crystallised from benzene in bright yellow plates, m. p. 142° (Found: As, 22·4. $C_{13}H_7OCl_2As$ requires As, 23·0%). It was readily converted by ammonia into the

* Mg. per 20 g. of mouse weight.

corresponding bright yellow oxide. The *semicarbazone* of fluorenone-2-arsonic acid, an orange-yellow substance, was purified by recrystallisation from absolute alcohol, in which it was very sparingly soluble (Found: As, 21·25; N, 11·6. $C_{14}H_{12}O_4N_3As$ requires As, 20·8; N, 11·63%).

7-*Nitrofluorenone*-2-*arsonic Acid*.—Fluorenone-2-arsonic acid (12 g.) was added gradually, with thorough shaking, to a mixture of concentrated sulphuric acid (26 c.c.) and fuming nitric acid (26 c.c.), initially at 20° and not allowed to exceed 30° after any one addition of the arsinic acid. After the whole had been left for ½ hour at room temperature, the clear solution was poured into ice-cooled water and the resulting cream-coloured *nitro*-derivative was crystallised from absolute alcohol (Found: As, 21·4; N, 4·2. $C_{13}H_8O_6NAs$ requires As, 21·5; N, 4·0%).

Sodium 7-*nitrofluorenone*-2-*arsonate*, a bright yellow, crystalline derivative ($1H_2O$), was readily soluble in water (Found after dehydration: As, 19·7. $C_{13}H_7O_6NAsNa$ requires As, 20·2%).

7-*Aminofluorenone*-2-*arsonic Acid*.—A boiling solution of nitrofluorenone-2-arsonic acid (7 g.) in 2*N*-sodium hydroxide (10 c.c.), diluted with water (90 c.c.), was added to a well-stirred suspension of ferrous hydroxide, prepared by addition of 6*N*-sodium hydroxide (60 c.c.) to a rapidly stirred solution of ferrous chloride (28 g.) in cold water (90 c.c.). The mixture was gradually warmed in a water-bath; reduction was rapid but to ensure its completion stirring was continued for 1 hour. The cold, deep red filtrate was treated with charcoal and made just acid to Congo-red. The pale buff *amino-arsonic acid* was purified through its sodium salt (Found: As, 23·35; N, 4·4. $C_{13}H_{10}O_4NAs$ requires As, 23·5; N, 4·4%).

Sodium 7-*aminofluorenone*-2-*arsonate*, glistening reddish-gold plates ($3H_2O$), dissolved readily in water to a deep red solution (Found after dehydration: As, 21·9; N, 4·4. $C_{13}H_9O_4NAsNa$ requires As, 22·0; N, 4·1%).

M.L.D. approximately 25 mg. Therapeutic activity is shown only in maximum doses.

7-*Acetamidofluorenone*-2-*arsonic Acid*.—Finely powdered aminofluorenone-2-arsonic acid (5 g.) was boiled under reflux with acetic anhydride (25 c.c.). There was marked change in colour after about 10 minutes, the suspended solid appearing bright yellow. To ensure complete acetylation, heating was continued for ½ hour; the reaction mixture was then poured into ice-cooled water and the deep yellow *acetyl* derivative was collected (5·2 g.) (Found: As, 20·4; N, 3·95. $C_{15}H_{12}O_5NAs$ requires As, 20·8; N, 3·9%).

The *sodium* salt was precipitated in bright yellow needles from its yellow aqueous solution by addition of alcohol (Found:

As, 18·5; N, 3·6. $C_{15}H_{11}O_5NAsNa,H_2O$ requires As, 18·7; N, 3·49%).

M.L.D. 15 mg. Therapeutic activity: 10 mg., curative; 5 mg., some action.

Fluorenone-7-glycine-2-arsonic Acid.—Aminofluorenone-2-arsonic acid (3·19 g.) was ground into a paste with 2*N*-sodium hydroxide (5 c.c.; 1 equiv.) and diluted with water (70 c.c.) to give a clear red solution on gentle warming. The addition of an aqueous solution of chloroacetic acid (1·6 g.) caused reprecipitation of part of the amino-arsonic acid. 2*N*-Sodium hydroxide (8·4 c.c.) was added to restore neutrality and on gentle boiling under reflux a clear red solution was obtained. After an hour, some unchanged amino-arsonic acid separated and was removed by filtration. Heating was continued for 3 hours and the reaction mixture was then filtered from a trace of the original arsonic acid and acidified with 2*N*-hydrochloric acid. A bright red, crystalline solid (1·7 g.) separated, which was purified through its sodium salt. The free acid appeared to be somewhat unstable; it was therefore kept and analysed as its *monosodium* salt ($2H_2O$) (Found after dehydration: As, 18·5. $C_{15}H_{11}O_6NAsNa$ requires As, 18·8%). M.L.D. 50 mg. Therapeutic activity, some in maximum doses.

Fluorenone-7-glycinamide-2-arsonic Acid.—Aminofluorenone-2-arsonic acid (4·5 g.) was ground into a thin paste with *N*-sodium hydroxide (14·2 c.c.; 1 equiv.) and diluted with water (10 c.c.) to a clear red solution. Chloroacetamide (2·7 g.; 2 equivs.) was added, and the whole boiled under reflux for 1½ hours. A deep purple, crystalline solid was suddenly precipitated, whereupon the reaction mixture was cooled and the product collected (5 g.). It was purified by conversion into its sodium salt and reprecipitation with 2*N*-acetic acid (Found: As, 19·9; total N, 7·25; hydrolysable N, 3·6. $C_{15}H_{13}O_5N_2As$ requires As, 19·95; total N, 7·45; hydrolysable N, 3·7%).

The *sodium* salt dissolved readily in water to a deep red solution (Found: As, 16·5; hydrolysable N, 2·9. $C_{15}H_{12}O_5N_2AsNa,3H_2O$ requires As, 16·6; hydrolysable N, 3·1%. Found after dehydration: total N, 6·6. $C_{15}H_{12}O_5N_2AsNa$ requires total N, 7·0%). M.L.D. about 30 mg. Some therapeutic action in maximum doses.

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