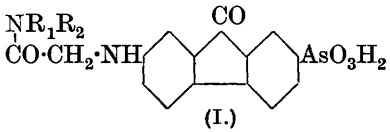
219. *Arsonic Acids of the Fluorenone Series. Derivatives of Aminofluorenone-2-arsonic Acid.*

By GILBERT T. MORGAN AND JESSIE STEWART.

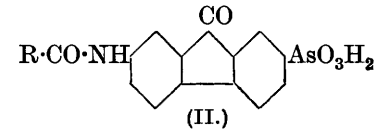
IN continuation of our examination of the therapeutic effect of introducing arsenic into the fluorenone molecule (J., 1931, 620) we have made fluorenone-7-glycineamide-2-arsonic acid (I; $R_1 = R_2 =$ H) and 7-acetamidofluorenone-2-arsonic acid (II; $R = CH_3$) the basis of further investigation. On being tested for trypanocidal potency, the former of these derivatives of aminofluorenone-2-arsonic acid has been found to possess some therapeutic activity when administered in maximum doses, while the latter—the most efficacious member of our first series of compounds—is capable of curative action in doses which do not exceed two-thirds of the minimum lethal dose of the drug.

We have prepared compounds of the general formula (I) by Jacobs and Heidelberger's method (*J. Amer. Chem. Soc.*, 1919, **41**,

1587) for the isolation of similar derivatives of *p*-arsanilic acid, inasmuch as the replacement of chloroacetamide by chloroacetomethylamide, chloroacetanilide, and *p*-chloroacetamidoacetophenone has led to the direct formation from aminofluorenone-2-arsonic acid of *fluorenone-7-glycinemethylamide-2-arsonic acid* ($R_1 = H$, $R_2 = CH_3$), *fluorenone-7-glycineanilide-2-arsonic acid* ($R_1 = H$, $R_2 = C_6H_5$), and *fluorenone-7-glycine-p-acetophenonylamide-2-arsonic acid* ($R_1 = H$, $R_2 = C_6H_4{\cdot}CO{\cdot}CH_3$), respectively. Each of these alterations in the fluorenoneglycineamide-2-arsonic acid molecule, however, is accompanied by a diminution in therapeutic activity, until in the last-named instance it has disappeared completely.



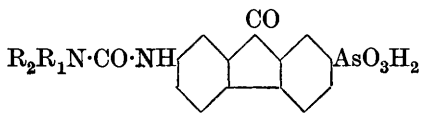
(I.)



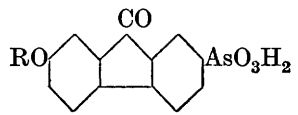
(II.)

Since the most potent member of our first series (*v. supra*) was an acyl derivative of the general formula (II) in which $R = CH_3$, it seemed advisable to ascertain the effect on the therapeutic properties of the molecule, of variations in the size of R. Accordingly we have prepared the *formyl* ($R = H$), *propionyl* ($R = C_2H_5$), n-*butyryl* ($R = C_3H_7$), and *benzoyl* ($R = C_6H_5$) derivatives of 7-aminofluorenone-2-arsonic acid. Curative power is manifested when $R = H$, attains a maximum when $R = CH_3$, but decreases rapidly when R is still further increased, being very slight when $R = C_3H_7$. It has again disappeared when $R = C_6H_5$.

The general formula (III; $R_1 = H$, $R_2 =$ alkyl or aryl) indicates the third type of compound which we have investigated. Such derivatives combine the R_2R_1N group present in type (I) with the CO·NH linkage of type (II). The simplest of these—7-*carbamido-*



(III.)



(IV.)

fluorenone-2-arsonic acid ($R_1 = R_2 = H$)—exercises a curative action, the *methyl* homologue ($R_1 = H$, $R_2 = CH_3$) has slight curative power, while 7-*phenylcarbamidofluorenone-2-arsonic acid* ($R_1 = H$, $R_2 = C_6H_5$) is quite inactive.

7-*Hydroxyfluorenone-2-arsonic acid* (IV; $R = H$), which is derived from the corresponding amino-arsonic acid, is curative in its action. Acetylation of the free hydroxy-group to form the *acetoxy*-derivative (IV; $R = CO{\cdot}CH_3$) results in an enhanced potency, which is comparable in degree with that of the acetamido-compound (II; $R = CH_3$).

7-*Oxalylaminofluorenone*-2-*arsonic acid* and the two diarsonic acids, *oxamido*-pp′-*fluorenone*-2-*arsonic acid* and the simple s-*carbamide* of aminofluorenone-2-arsonic acid complete the derivatives which are included in this paper.

The chemotherapeutic reports from Professor Warrington Yorke of the Liverpool School of Tropical Medicine on the *sodium* salts of those compounds which exert a curative action are summarised in the following table—acetamidofluorenone-2-arsonic acid being again cited for purposes of comparison.

Sodium salt.	*Tr. Equi-perdum.*	M.L.D.*	M.C.D.†
Formamido (II; R = H)	1—20	20	20
Acetamido (II; R = CH_3)	20—1	15	10
	1—3	15	5
Propionylamido (II; R = C_2H_5)	5—1	5	5
Carbamido (III; $R_1 = R_2 = H$)	1—2	30	15
Methylcarbamido (III; $R_1 = H$, $R_2 = CH_3$)	5—1	10—20	20
Hydroxy (IV; R = H)	1—1	10—20	5
Acetoxy (IV; R = CO·CH_3)	10—1	6	3

* M.L.D. = Minimum lethal dose in mg. per 20 g. mouse.

† M.C.D. = Minimum curative dose in mg. per 20 g. mouse.

Experimental.

Fluorenone-7-*glycinemethylamide*-2-*arsonic Acid* (I; $R_1 = H$, $R_2 = CH_3$).—A solution of aminofluorenone-2-arsonic acid (6·4 g.) in *N*-sodium hydroxide (40 c.c.) and water (10 c.c.) was boiled under reflux for 1½ hours with chloroacetomethylamide (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1919, **41**, 472; *J. Biol. Chem.*, 1915, **21**, 147). The purple crystalline precipitate (3·6 g.) was purified by conversion into its sodium salt and reprecipitation with 2*N*-acetic acid (Found: As, 19·4. $C_{16}H_{15}O_5N_2As$ requires As, 19·2%).

The *sodium* salt was precipitated by adding alcohol to a solution of the acid in 2*N*-sodium hydroxide diluted with twice its volume of water; it was purified by reprecipitation with alcohol from its deep red aqueous solution, crystallising in clusters of red needles ($2H_2O$) (Found: As, 17·0. $C_{16}H_{14}O_5N_2AsNa,2H_2O$ requires As, 16·75%). M.L.D., 20 mg. Therapeutic action, slight.

Fluorenone-7-*glycineanilide*-2-*arsonic Acid* (I; $R_1 = H$, $R_2 = C_6H_5$). —A solution of aminofluorenone-2-arsonic acid (4·8 g.) in *N*-sodium hydroxide (15 c.c.) and water (35 c.c.) was boiled for 5 hours with chloroacetanilide (2·6 g.) (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 1441), sodium iodide (3 g.), and absolute alcohol (50 c.c.); the product (4·8 g.) was washed with 50% alcohol, dissolved in 2*N*-sodium hydroxide (1 mol.), diluted considerably with water to prevent separation of sodium salt as a gel, warmed gently, and

reprecipitated with 2*N*-acetic acid as a red, glistening, filamentous mass (Found : As, 16·85. $C_{21}H_{17}O_5N_2As$ requires As, 16·6%).

The red-purple *sodium* salt ($1H_2O$) separated slowly on addition of several volumes of absolute alcohol to a neutral solution of the acid in warm dilute sodium hydroxide. All efforts to recrystallise it from water resulted in the formation of a deep red gel (Found after dehydration : As, 15·9. $C_{21}H_{16}O_5N_2AsNa$ requires As, 15·8%). M.L.D., 5 mg. Therapeutic action, slight.

Fluorenone-7-glycine-p-acetophenonylamide-2-arsonic acid (I; R_1 = H, $R_2 = C_6H_4{\cdot}CO{\cdot}CH_3$) was isolated as minute glistening needles when chloroacetanilide was replaced by *p*-chloroacetamidoacetophenone (Jacobs, Heidelberger, and Rolf, *J. Amer. Chem. Soc.*, 1919, **41**, 469) in the foregoing condensation. It was extremely difficult to purify through its sodium salt in consequence of the still greater tendency of solutions of the latter derivative towards gel formation (Found after dehydration : As, 15·0. $C_{23}H_{19}O_6N_2As$ requires As, 15·2%). The sparingly soluble, purple *sodium* salt separated slowly from its solution in 50% alcohol (Found after dehydration : As, 14·3. $C_{23}H_{18}O_6N_2AsNa$ requires As, 14·5%). M.L.D., >50 mg. The relative insolubility does not allow of the administration of larger doses of the drug. Therapeutic action, nil.

7-Formamidofluorenone-2-arsonic Acid (II; R = H).—Finely powdered aminofluorenone-2-arsonic acid (3 g.) was boiled for 1 hour with formic acid (20 c.c.; *d* 1·2). The reaction mixture was poured into ice-cooled water, and the bright yellow precipitate purified by solution in 2*N*-sodium carbonate at room temperature and reprecipitation with 2*N*-hydrochloric acid, giving a product (3·1 g.) entirely free from unchanged aminofluorenone-2-arsonic acid (Found : As, 21·8. $C_{14}H_{10}O_5NAs$ requires As, 21·6%).

The *sodium* salt was sparingly soluble in cold water but dissolved readily on gentle warming; it separated from alcohol–water in clusters of orange-yellow needles ($3H_2O$) (Found : As, 17·7. $C_{14}H_9O_5NAsNa,3H_2O$ requires As, 17·7%).

7-Propionylamidofluorenone-2-arsonic acid (II; R = C_2H_5), prepared from aminofluorenone-2-arsonic acid (3·5 g.) and propionic anhydride (15 c.c.), was purified in a similar manner and separated as a deep orange, crystalline solid (3·5 g.), very slightly soluble in boiling water (Found : As, 20·0. $C_{16}H_{14}O_5NAs$ requires As, 20·0%).

The *sodium* salt was much less soluble in water than was the corresponding formyl derivative; it separated from hot aqueous solutions in glistening golden-plates ($1H_2O$) (Found : As, 17·9. $C_{16}H_{13}O_5NAsNa,H_2O$ requires As, 18·07%).

7-n-Butyrylamidofluorenone-2-arsonic acid (II; R = C_3H_7), prepared from aminofluorenone-2-arsonic acid and *n*-butyric anhydride,

was a deep orange, glistening, crystalline solid (Found: As, 19·0. $C_{17}H_{16}O_5NAs$ requires As, 19·3%).

The *sodium* salt separated from hot aqueous solutions in golden plates ($2H_2O$) (Found: As, 16·9. $C_{17}H_{15}O_5NAsNa,2H_2O$ requires As, 16·8%). M.L.D., 1 mg. Therapeutic action, very slight.

Disodium 7-benzamidofluorenone-2-arsonate (as II; R = C_6H_5) was gradually precipitated when a solution in which aminofluorenone-2-arsonic acid had been condensed with benzoyl chloride at 35—40° in the presence of excess of 60% sodium hydroxide, was left overnight at 0°. Unchanged amino-arsonic acid remained in solution. The crude product was washed with alcohol. It crystallised slowly from water in minute, deep yellow needles ($1H_2O$) (Found: As, 15·4. $C_{20}H_{12}O_5NAsNa_2,H_2O$ requires As, 15·5%). M.L.D., 20 mg. Therapeutic action, nil.

The more sparingly soluble *sodium* salt separated from hot water as a glistening, orange-yellow, filamentous mass (Found: As, 16·7. $C_{20}H_{13}O_5NAsNa$ requires As, 16·9%).

7-Benzamidofluorenone-2-arsonic acid (II; R = C_6H_5) separated as a bright yellow, gelatinous solid on addition of dilute hydrochloric acid to an aqueous solution of the disodium salt (1·25 g.) in water (30 c.c.) at 20° (Found: As, 17·5. $C_{20}H_{14}O_5NAs$ requires As, 17·7%).

7-Carbamidofluorenone-2-arsonic Acid (III; R_1 = H, R_2 = H).—Solutions of potassium cyanate (1·2 g.) in water (10 c.c.) and of aminofluorenone-2-arsonic acid (1·6 g.) in 2*N*-sodium hydroxide (2·5 c.c.) and water (15 c.c.) were mixed and glacial acetic acid (1·2 c.c.) was added, causing immediate precipitation. The mixture was left for several days and stirred at frequent intervals. The precipitate was dissolved in warm water (50 c.c.) and filtered into 2*N*-hydrochloric acid (slightly more than 1 equiv.) diluted to 10 c.c. The deep orange *carbamido*-compound (1 g.), washed free from hydrochloric acid, was further purified through its sodium salt (Found: As, 20·8. $C_{14}H_{11}O_5N_2As$ requires As, 20·7%).

The orange-brown *sodium* salt ($2H_2O$) was isolated by adding absolute alcohol to a cooled solution of the free acid in the requisite amount of dilute aqueous sodium hydroxide and was recrystallised from water–alcohol (Found: As, 17·6. $C_{14}H_{10}O_5N_2AsNa,2H_2O$ requires As, 17·9%).

7-Methylcarbamidofluorenone-2-arsonic Acid (III; R_1 = H, R_2 = CH_3).—Aminofluorenone-2-arsonic acid (4 g.), dissolved in 2*N*-sodium hydroxide (6·2 c.c.) and water (25 c.c.), was cooled to 5°, methylcarbimide (1·4 g.) added, and the mixture left overnight at 0°. The yellow crystalline precipitate proved to be largely, if not entirely, unchanged sodium aminofluorenone-2-arsonate. It was

therefore redissolved in water (50 c.c.) and added to the main filtrate. The latter was kept at 0° for 10—12 days; the precipitate was then still largely unchanged material, but a second fraction—a crude *methylcarbamido*-derivative (2 g.) obtained from the filtrate—contained a relatively small amount of unchanged amino-acid, which was removed by diazotisation with sodium nitrite and dilute hydrochloric acid. There remained ultimately a red-brown product (1 g.) (Found: As, 19·9. $C_{15}H_{13}O_5N_2As$ requires As, 19·95%).

The *sodium* salt separated as minute plates from a 50% water–alcohol mixture (Found: As, 17·9. $C_{15}H_{12}O_5N_2AsNa,H_2O$ requires As, 18·0%).

Sodium 7-Phenylcarbamidofluorenone-2-arsonate (III; $R_1 = H$, $R_2 = C_6H_5$).—Sodium aminofluorenone-2-arsonate (3·9 g.), dissolved in warm water (100 c.c.), was cooled to 10°, phenylcarbimide (1·8 g.) added gradually, and the whole well cooled and stirred. A heavy gelatinous precipitate soon formed; the reaction mixture was cooled at 0° over-night, and the pink precipitate collected, the red filtrate still containing some unchanged amino-arsonic acid. This finely powdered product (3·5 g.) was digested with boiling water (100 c.c.), whereupon it no longer contained any free amino-group. It was dissolved in boiling 2*N*-sodium carbonate (100 c.c.), filtered from traces of undissolved yellow solid, and was deposited almost immediately in the alkaline filtrate; it separated from boiling water (1000 c.c.), in which it was very sparingly soluble, as glistening pink filaments (1·85 g.) (Found: As, 14·9. $C_{20}H_{14}O_5N_2AsNa,2H_2O$ requires As, 15·1%).

The much more soluble *disodium* salt ($2H_2O$), a brick-red solid, dissolved sparingly in water to a red-yellow solution which was alkaline to litmus (Found: As, 14·6. $C_{20}H_{13}O_5N_2AsNa_2,2H_2O$ requires As, 14·5%). M.L.D., >20 mg. Therapeutic action, nil.

7-Ureidoaminofluorenone-2-arsonic Acid.—A slow stream of carbonyl chloride was passed through a solution of aminofluorenone-2-arsonic acid (3 g.) in 2*N*-sodium carbonate (30 c.c.; 3 equivs.) and water (50 c.c.). 2*N*-Sodium carbonate (85 c.c. in all) was added at intervals to maintain the alkalinity of the solution. After 6 hours the mixture was strongly acid and free from primary base. The *s-carbamide*, a deep orange precipitate (2·85 g.), was purified by conversion into a solution of its disodium salt and reprecipitation with dilute hydrochloric acid (Found after dehydration: As, 22·6. $C_{27}H_{18}O_9N_2As_2$ requires As, 22·6%).

The *disodium* salt, which separated in needles from water–alcohol, dissolved in water to a red solution (Found after dehydration: As, 20·9. $C_{27}H_{16}O_9N_2As_2Na_2$ requires As, 21·2%). M.L.D., 10—20 mg. Therapeutic action in maximum doses.

7-*Oxalylaminofluorenone*-2-*arsonic Acid*.—An intimate mixture of sodium aminofluorenone-2-arsonate (3·9 g.) and oxalic acid (7·6 g.; 6 mols.) was heated at 180—190° for 2 hours. The cooled mass was then free from unchanged amino-acid. Attempts to purify it by reprecipitation from a solution of its sodium salt were unsuccessful, for it separated as a gel. It was digested repeatedly with hot water to remove soluble products, the deep yellow *oxalyl* compound (3·2 g.) remaining undissolved (Found: As, 19·7. $C_{15}H_{10}O_7NAs$ requires As, 19·2%). This somewhat high arsenic content suggested the presence of a trace of oxamido-*pp'*-fluorenone-2-arsonic acid, a diarsonic acid which would result from the condensation of two molecular proportions of the original amino-arsonic acid with one of oxalic acid. When the latter were heated together in the same molecular proportion (1 : 6), but at 125° for 6 hours, the resulting oxalyl derivative was free from this impurity; the yield, however, was small (1 g.) and the crude product consisted largely of unchanged amino-arsonic acid. This was removed in the manner described subsequently for the purification of the diarsonic acid (Found: As, 19·1. $C_{15}H_{10}O_7NAs$ requires As, 19·2%).

The *disodium* salt ($1H_2O$), a light yellow solid readily soluble in water, was purified by recrystallisation from 50% alcohol (Found after dehydration: As, 17·1. $C_{15}H_8O_7NAsNa_2$ requires As, 17·2%). M.L.D., 10 mg. Therapeutic action, nil.

7-*Oxamido*-pp'-*fluorenone*-2-*arsonic Acid*.—Sodium aminofluorenone-2-arsonate (3·9 g.) and oxalic acid (3·8 g.; 3 mols.) were heated together at 180—190° for 2 hours. The small amount of unchanged amino-acid was removed from the crude product by diazotisation of its suspension in water with sodium nitrite and dilute hydrochloric acid. The undissolved product (2·6 g.) was digested repeatedly with boiling water. The combined aqueous filtrates were acidified and a small amount of the oxalyl derivative (0·2 g.) was precipitated. The light brown *diarsonic acid* (2·4 g.) remained undissolved (Found: As, 21·4. $C_{28}H_{18}O_{10}N_2As_2$ requires As, 21·7%).

The *disodium* salt crystallised from 50% alcohol in clusters of small brown needles ($4H_2O$) (Found after dehydration: As, 20·4. $C_{28}H_{16}O_{10}N_2As_2Na_2$ requires As, 20·4%). M.L.D., 40 mg. Therapeutic action, nil.

7-*Hydroxyfluorenone*-2-*arsonic Acid* (IV; R = H).—Aminofluorenone-2-arsonic acid, suspended in water containing 2*N*-hydrochloric acid (2½ mols.), was diazotised with aqueous sodium nitrite; the filtered solution was heated gently until evolution of nitrogen had ceased; a small amount of tarry matter was removed, and the deep

yellow *hydroxy*-compound which gradually separated was dissolved in dilute sodium carbonate and reprecipitated with hydrochloric acid (Found : As, 23·2. $C_{13}H_9O_5As$ requires As, 23·4%).

The orange-yellow *sodium* salt ($1H_2O$), which was crystallised from 50% alcohol, was readily soluble in water (Found after dehydration : As, 22·0. $C_{13}H_8O_5AsNa$ requires As, 21·9%).

7-Acetoxyfluorenone-2-arsonic acid (IV; R = $CO{\cdot}CH_3$), a pale yellow product (4·3 g.) prepared from hydroxyfluorenone-2-arsonic acid (4 g.) and acetic anhydride (20 c.c.), was purified through its sodium salt (Found : As, 20·8. $C_{15}H_{11}O_6As$ requires As, 20·7%). This *sodium* salt ($1H_2O$) was crystallised from its bright yellow solution in water–alcohol (Found : As, 18·5. $C_{15}H_{10}O_6AsNa,H_2O$ requires As, 18·7%).

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NOTE.

A Synthesis of Diphenyl. By IAN RUSSEL SHERWOOD and WALLACE FRANK SHORT.

WHEN 1-phenyl*cyclo*hexanol (Sabatier and Mailhe, *Compt. rend.*, 1904, **138**, 1321) or 1-phenyl-Δ^1-*cyclo*hexene is heated with sulphur (2 atoms) at 200—240° for 4 hours, diphenyl (m. p. 70°; 4-nitrodiphenyl, m. p. 114°) is obtained in 70% yield. A methoxyl group, when present, is unaffected by this process.

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