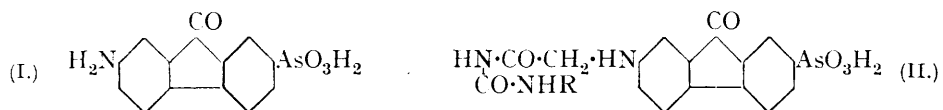


342. Arsonic Acids of the Fluorenone and the Fluorenol Series.

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THE most promising of those derivatives which we have already recorded as having been prepared from 7-aminofluorenone-2-arsonic acid (I) during our investigation of the therapeutic effect of introducing arsenic into the fluorenone molecule (J., 1932, 1634) are the 7-acetamido-, 7-carbamido-, 7-hydroxy-, and 7-acetoxy-fluorenone-2-arsonic acids.



In continuation of this work we have increased the length of the side chain of the carbamido-compound to give ureides of the general formula (II), but this alteration in

structure has been accompanied by very rapid decrease in trypanocidal activity. On the other hand, 7-carbamylmethoxyfluorenone-2-arsonic acid (III; R = CH₂·CO·NH₂) is more potent than is the 7-acetoxy-member (III; R = CO·CH₃) of this series of 7-oxy-derivatives.



In accordance with our intention (J., 1931, 621) to use 2-aminofluoreno! as a starting material in the production of substances likely to be of interest in chemotherapy we introduced arsenic into position 2 of the fluoreno! molecule, but in consequence of the instability of the 9-hydroxy-group towards oxidising agents we abandoned the attempt to prepare 7-aminofluoreno!-2-arsonic acid by substitution at position 7 of 9-fluoreno!-2-arsonic acid on finding that we could pass readily from the fluorenone to the fluoreno! series by catalytic reduction of the keto-group of 7-aminofluorenone-2-arsonic acid.

Simple derivatives of 7-aminofluoreno!-2-arsonic acid of the type (IV), selected by analogy with those members of the fluorenone series (*loc. cit.*) which do exert a curative action when tested on experimental trypanosomiasis in mice, exhibit, with two exceptions, only a very slight degree of activity. 7-Acetamidofluoreno!-2-arsonic acid, like the corresponding acetamidofluorenone-2-arsonic acid, is curative in doses which do not exceed one-half of the minimum lethal dose of the drug. 9-Fluoreno!-7-glycineamide-2-arsonic acid is more efficacious than is the analogous fluorenone derivative.

The chemotherapeutic reports from Professor Warrington Yorke of the Liverpool School of Tropical Medicine on the sodium salts of these compounds are summarised in the following table.

Sodium Salt.	Tr. Equi- perdum.	M.L.D.*	Trypanocidal Potency.
<i>Fluorenone Series.</i>			
7-Glycineureide (II; R = H)	2—1	10	M.C.D.* = 6
7-Glycinemethylureide (II; R = Me)	—	10	Inactive
7-Glycinephenylureide (II; R = Ph)	—	10	Slight activity in maximum doses
7-Carbamylmethoxy (III; R = CH ₂ ·CO·NH ₂)	15—1	30	M.C.D. = 10
<i>Fluoreno! Series.</i>			
7-Amino (IV; R = H)	10—1	9	Curative in maximum doses
7-Acetamido (IV; R = COMe)	5—1	30	M.C.D. = 15
7-Glycineamide (IV; R = CH ₂ ·CO·NH ₂)	1—1	30—50	M.C.D. = 12·5
7-Carbamido (IV; R = CO·NH ₂)	20—1	15—30	Some in maximum doses
7-Methylcarbamido (IV; R = CO·NHMe) ...	3—1	12·5	Slight in maximum doses
7-Phenylcarbamido (IV; R = CO·NHPh) ...	10—1	12·5—20	Some in maximum doses

* M.L.D. and M.C.D. = Minimum lethal dose and minimum curative dose, respectively, in mg. per 20 g. mouse.

EXPERIMENTAL.

Fluorenone-7-glycineureide-2-arsonic Acid (II; R = H).—A solution of sodium amino-fluorenone-2-arsonate (7·8 g.) in hot water (150 c.c.) was boiled for 4 hours with chloroacetyl-carbamide (3·6 g.), sodium iodide (3·6 g.), 2*N*-sodium hydroxide (2·5 c.c.), and absolute alcohol (50 c.c.). A preliminary purification of the red-purple glistening precipitate (6·5 g.) was effected by regenerating it with *N*-acetic acid from its solution in *N*-ammonium hydroxide, and heating gently to coagulate the product (4·9 g.). For analysis it was precipitated from a hot aqueous solution of its sodium salt by 2*N*-acetic acid and coagulated by the addition of absolute alcohol, forming red-purple filaments (Found: As, 18·2; N, 10·4. C₁₆H₁₄O₆N₃As requires As, 17·9; N, 10·0%).

The sodium salt crystallised from hot water in minute purple needles (Found after dehydration: As, 16·9; N, 9·5. C₁₆H₁₃O₆N₃AsNa requires As, 17·0; N, 9·5%).

Fluorenone-7-glycinemethylureide-2-arsonic acid (II; R = Me) was isolated as red needles when chloroacetylcarbamide was replaced by α -chloroacetyl- β -methylcarbamide (Jacobs, Heidelberger, and Rolf, *J. Amer. Chem. Soc.*, 1919, 41, 473) and the condensation was carried out in 50% alcohol.

The sparingly soluble sodium salt (1H₂O) separated from hot alcohol-water in red filaments. Its aqueous solutions showed great tendency towards gel formation (Found after dehydration: As, 16·6; N, 9·2. C₁₇H₁₅O₆N₃AsNa requires As, 16·5; N, 9·2%).

Fluorenone-7-glycinephenylureide-2-arsonic acid (II; R = Ph) was isolated as bright red filaments when α -chloroacetyl- β -phenylcarbamide was used in the foregoing condensation (Found: As, 15.2. $C_{22}H_{18}O_6N_3As$ requires As, 15.2%).

The sparingly soluble *sodium* salt separated from water-alcohol in bulky orange-pink filaments (Found after dehydration: As, 14.6; N, 8.3. $C_{22}H_{17}O_6N_3AsNa$ requires As, 14.5; N, 8.1%). The *disodium* salt ($6H_2O$) was slightly more soluble in water to a deeper purple solution (Found: As, 11.6. $C_{22}H_{16}O_6N_3AsNa_2, 6H_2O$ requires As, 11.6%).

Sodium 7-Carbamylmethoxyfluorenone-2-arsonate (III; R = $CH_2 \cdot CO \cdot NH_2$).—A solution of 7-hydroxyfluorenone-2-arsonic acid (3.2 g.) in 2*N*-sodium hydroxide (12.5 c.c.) and water (40 c.c.) was boiled for 5½ hours with chloroacetamide (1.4 g.). On cooling the solution at 0° for 24 hours, a yellow solid was slowly precipitated; it was washed with alcohol and recrystallised from hot water, separating in minute yellow plates. Only the first fraction (0.8 g.), however, was free from unchanged hydroxyfluorenonearsonic acid (Found after dehydration: As, 18.7. $C_{15}H_{11}O_6NAsNa$ requires As, 18.8%).

2-Amino-9-fluorenone was prepared in quantity by the reduction of an alcoholic suspension of 2-nitrofluorenone at 50° with hydrogen under a pressure of 60 atmospheres in the presence of 5–6% of platinic oxide. It was separated from the catalyst and purified by conversion into its readily soluble hydrochloride.

9-Fluorenone-2-arsonic Acid.—A solution of 2-amino-9-fluorenone (8 g.) in water (90 c.c.) and 10*N*-hydrochloric acid (10 c.c.) was diazotised at 0° with sodium nitrite (3.2 g.) dissolved in water (20 c.c.). The resulting solution of the diazonium chloride was converted by the Bart reaction into the corresponding *arsonic acid*, which separated from hot alcohol in minute needles (Found: As, 24.5. $C_{13}H_{11}O_4As$ requires As, 24.5%).

The *sodium* salt crystallised from water-alcohol in yellow needles (Found after dehydration: As, 22.65. $C_{13}H_{10}O_4AsNa$ requires As, 22.9%).

Sodium 7-Amino-9-fluorenone-2-arsonate.—A solution of sodium 7-amino-9-fluorenone-2-arsonate (20 g.) in 50% alcohol (400 c.c.) was reduced at 50° with hydrogen under a pressure of 60 atmospheres. After removal of platinum catalyst and of any unreduced material which had separated, the filtrate was concentrated to small bulk and the required fluorenone derivative was precipitated, by the addition of absolute alcohol, as an almost colourless solid, which tended, however, to develop a pink colour on exposure (Found after dehydration: As, 21.7. $C_{13}H_{11}O_4NAsNa$ requires As, 21.9%). The corresponding *acid* was liberated from an aqueous solution of the sodium salt by the careful addition of dilute acid (Found: As, 23.2. $C_{13}H_{12}O_4NAs$ requires As, 23.4%). It was appreciably amphoteric and dissolved readily in excess of mineral acid.

7-Acetamido-9-fluorenone-2-arsonic Acid (IV; R = COMe).—When sodium aminofluorenone-2-arsonate (8 g.) was shaken with acetic anhydride (16 c.c.), complete solution took place almost immediately and the temperature rose rapidly. The mixture was straightway cooled, poured into water (100 c.c.), thoroughly agitated to induce precipitation of the yellow *acetyl* compound, and the colloidal product (6.7 g.) was coagulated by vigorous stirring. Repeated digestion with hot alcohol separated the crude material into two portions, the one (4.4 g.) undissolved in alcohol, the other (1.8 g.) separating from its alcoholic solution on concentration to very small bulk (Found in the soluble portion: As, 20.4. $C_{15}H_{14}O_5NAs$ requires As, 20.7%).

The pale yellow *sodium* salt prepared from the latter was readily soluble in water to a red-yellow solution (Found after dehydration: As, 19.1. $C_{15}H_{13}O_5NAsNa$ requires As, 19.5%).

The major portion of the acetyl derivative (Found: As, 20.0%) was converted into its sodium salt by warming it with the requisite amount of dilute aqueous sodium hydroxide, and reprecipitated from this solution with 2*N*-hydrochloric acid. The product (3.9 g.) was digested with alcohol: a small quantity (0.5 g.) remained undissolved and its analysis indicated that it was the diacetyl compound *7-acetamido-9-acetoxyfluorenone-2-arsonic acid* (Found: As, 18.9. $C_{17}H_{16}O_6NAs$ requires As, 18.5%); but the remaining portion now separated in a pure condition from the alcoholic concentrate (Found: As, 20.5%).

More drastic treatment with acetic anhydride increased the proportion of 7-acetamido-9-acetoxyfluorenone-2-arsonic acid. Sodium aminofluorenone-2-arsonate (4 g.) was boiled under reflux for 1 hour with acetic anhydride (15 c.c.). The deep yellow product (3.5 g.) was recrystallised from alcohol (50 c.c.) and thereby separated into the sparingly soluble diacetyl derivative (0.75 g.) (Found: As, 18.8%) and the more readily soluble *N*-acetyl compound (2 g.) (Found: As, 21.0%).

9-Fluorenone-7-glycineamide-2-arsonic Acid (IV; R = $CH_2 \cdot CO \cdot NH_2$).—A solution of sodium aminofluorenone-2-arsonate (7.6 g.) in water (40 c.c.) was boiled for 2 hours with chloroacetamide

(3.6 g.), sodium iodide (3.6 g.), and absolute alcohol (40 c.c.). Pale pink, minute needles of the *glycineamide* (3.7 g.) which separated were filtered off from the hot reaction mixture and purified by conversion into sodium salt and decomposition of the latter in aqueous solution with 2*N*-acetic acid (Found : As, 19.8. $C_{15}H_{15}O_5N_2As$ requires As, 19.85%).

The *sodium* salt separated from water-alcohol in very pale pink filaments, which dissolved readily in water to a red solution (Found after dehydration : As, 18.5. $C_{15}H_{14}O_5N_2AsNa$ requires As, 18.75%).

9-O-Carbamylmethylfluoreno-7-glycineamide-2-arsonic Acid.—When the alcohol of the filtrate from the deposition of 9-fluoreno-7-glycineamide-2-arsonic acid in the foregoing preparation was distilled off, there remained a concentrate which deposited a dull pink-buff powder (3.4 g.) (Found : As, 16.8. $C_{17}H_{18}O_6N_3As$ requires As, 17.2%). Its conversion into sodium salt, followed by precipitation from an aqueous solution of the latter with 2*N*-acetic acid, yielded a practically colourless product (Found : As, 16.8%). Recrystallisation from alcohol-water proved both wasteful and destructive as an alternative method of purification. A sample of the crude material (7.4 g.) was digested several times with 50% alcohol until practically no more solid would dissolve. The now colourless residue (1.7 g.) was pure *9-O-carbamylmethylfluoreno-7-glycineamide-2-arsonic acid* (Found : As, 17.2. $C_{17}H_{18}O_6N_3As$ requires As, 17.2%). The concentrate from the alcohol-water extracts deposited a small amount of the simple glycineamide in a state of purity (Found : As, 19.7%), followed by a less pure main fraction (Found : As, 18.9%).

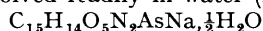
The *disodium* salt separated from water-alcohol as almost colourless filaments (Found after dehydration : As, 15.6. $C_{17}H_{16}O_6N_3AsNa_2$ requires As, 15.6%). M.L.D. 20 mg. Therapeutic action—nil.

7-Carbamido-9-fluoreno-2-arsonic Acid (IV; $R = CO \cdot NH_2$).—Solutions of potassium cyanate (2.4 g.) in water (10 c.c.) and of sodium aminofluoreno-2-arsonate (3.8 g.) in water (25 c.c.) were mixed and glacial acetic acid (2.4 c.c.) was added slowly with repeated shaking of the mixture. The product which separated almost immediately was washed with 2*N*-hydrochloric acid to dissolve any trace of the original amino-acid, freed from hydrochloric acid, and further purified through its sodium salt. The pale yellow *carbamido*-compound (3 g.) was recrystallised from boiling water, in which it was very sparingly soluble (Found : As, 20.4. $C_{14}H_{13}O_5N_2As$ requires As, 20.6%).

The yellow *sodium* salt ($2H_2O$) was recrystallised from water-alcohol (Found : As, 17.8. $C_{14}H_{12}O_5N_2AsNa, 2H_2O$ requires As, 17.8%).

7-Methylcarbamido-9-fluoreno-2-arsonic Acid (IV; $R = CO \cdot NHMe$).—A dilute aqueous solution of sodium aminofluoreno-2-arsonate was allowed to react for 24 hours with methylcarbimide at 0–3°. Traces of unchanged amino-acid were removed from the crude product by treatment with 2*N*-hydrochloric acid and the remaining *methylcarbamido*-derivative was finally purified through its sodium salt (Found : As, 19.9. $C_{15}H_{15}O_5N_2As$ requires As, 19.85%).

The colourless *sodium* salt dissolved readily in water (Found : As, 18.4.



requires As, 18.34%).

7-Phenylcarbamido-9-fluoreno-2-arsonic Acid (IV; $R = CO \cdot NHPh$).—Sodium aminofluoreno-2-arsonate (2.5 g.), dissolved in water (25 c.c.), was cooled to 10°. The gradual addition of phenylcarbimide (1.4 g.) to the clear solution—the temperature not being allowed to exceed 10°—caused almost immediate formation of a yellow precipitate. The reaction mixture was cooled at 0° over-night. The resulting *phenylcarbamido*-derivative was recrystallised from 50% alcohol, the main fraction separating as yellow filaments (1.4 g.); the small second fraction was contaminated with a pale pink solid. Further purification was effected by solution of the main fraction in dilute sodium carbonate solution to the sparingly soluble sodium salt (Found : As, 17.0. $C_{20}H_{17}O_5N_2As$ requires As, 17.05%).

The more soluble *disodium* salt separated from water-alcohol in pale yellow needles (Found : As, 14.1. $C_{20}H_{15}O_5N_2AsNa_2, 3H_2O$ requires As, 13.9%).