The hydrochloride may be precipitated by adding anhydrous alcoholic hydrogen chloride to the base dissolved in acetone.

Anal. Subs., 0.5715. Calcd. for $C_6OH_{13}N.HCl$: Cl, 23.40. Found: 23.48.

The quartz spectroscope and sector photometer used in this work form part of the equipment of the New York State Institute for the Study of Malignant Diseases, at Buffalo; permission to use the instruments was secured through the courtesy of the physicist of the Institute, Dr. K. Wilhelm Stenström, to whom we are also indebted for valuable advice.

Summary

1. The absorptions in the near ultraviolet region (to 2100 Å.) of γ-pyridone, N-methyl-γ-pyridone, γ-pyrone (Group A), chelidamic acid, N-methyl-chelidamic acid, chelidonic acid (Group B), γ-hydroxy-piperidine, N-methyl-γ-hydroxy-piperidine (Group C), have been studied and recorded.

2. Curves have been plotted by means of the molecular extinction coefficient as abscissa, the wave length as ordinate; from these curves the persistence is obtained.

3. Group A and Group B show selective absorption; the persistence for Group A is three times as great as that for Group B. Group C has only very slight selective absorption.

4. The curves for Group B are shifted toward the red, when compared to Group A; this shift is due to the introduction of two carboxyl groups into the uncarboxylated molecule, and is in agreement with the rule of Hartley. For two members, the shift is considerable; for one, it is slight.

BUFFALO, NEW YORK

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

TRIPHENYLMETHYL. XXXV. HALOGEN-SUBSTITUTED ACRIDYLS. THE REACTIVITY OF THE HALOGEN IN THEM

BY M. GOMBERG AND D. L. TABERN[1]

RECEIVED JANUARY 14, 1926 PUBLISHED MAY 5, 1926

In previous papers the theory has been advanced that triarylmethyls possess their property of selective absorption in the visible spectrum not merely because of the trivalent carbon atom in them, but rather in virtue of the quinoidation of the free radical. In support of this view we have: (1) the depth of color is not directly proportional to the amount of the monomolecular free radical in solution; (2) the triarylmethyls contain a benzene nucleus which evidences a degree of reactivity wholly unusual in an ordinary benzene ring. Thus, *p*-bromotriphenylmethyl, in complete

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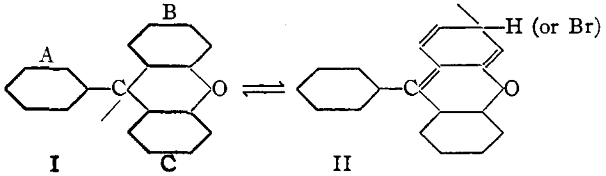
[1] The material here presented is from the dissertation submitted by D. L. Tabern to the Faculty of the University of Michigan in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1924.

contrast to the corresponding methane, carbinol, etc., gives up bromine to metallic silver even at room temperature. The free radical behaves as if its bromine linking is nearer aliphatic (III) than aromatic (V) in nature, or as if there exists a shifting equilibrium between these.

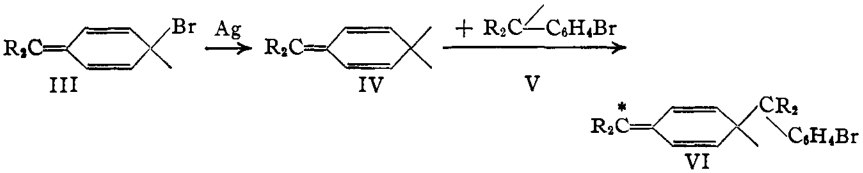
Obviously, any one of the three aryl groups may assume the quinonoid state, and in such triarylmethyls wherein the three groups are different from one another, undoubtedly all three possible tautomeric quinonoid isomers exist in equilibrium with the benzenoid isomer. Not so is the case with the free radicals, the aryl-xanthenyls and the aryl-thio-xanthenyls. Here, it has been found, there exists a strict differentiation between benzene ring (A) on the one hand and, on the other hand, the two rings (B) and (C) which constitute the xanthone complex proper.



I II

Tested by the reactivity of the halogen when placed in each of the three possible positions *para* to the central carbon atom in I, it has been found that quinonoidation is limited to Rings B and C alone, as indicated in II.

The puzzling fact that in all cases never more than one-half atom of halogen is removed from a mono-*p*-halogen substituted free radical, may be explained plausibly on the following assumption: as the halogen is being progressively taken out, the new dehalogenated molecule (IV), very unsaturated, combines at once with a benzenoid molecule of the still undehalogenated triarylmethyl (V).

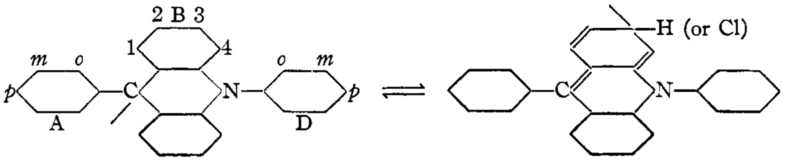


In this new radical (VI), which is dimolecular in comparison with the original triarylmethyl, but which, however, still contains one trivalent carbon atom, tautomerization to the quinonoid state is obviously limited exclusively to those three aryl groups which are linked directly to the carbon atom $\overset{*}{C}$. Consequently, the ring in VI, which contains the halogen, maintains now its benzenoid, non-reactive state. Thus, from two R_3C only one atom of ring halogen has been removed, and VI, which may be designated as a "radical of second order," should be able to absorb for the formation of its peroxide only one-half the quantity of oxygen as compared with III or V, which is a radical of "first order."[2]

Whatever be the explanation, the fact is, nevertheless, well established experimentally that only one-half atom of halogen can be taken from a triarylmethyl, xanthenyl or thio-xanthenyl which contains a halogen in the *para* position to the central carbon atom, and that the new radical which results in consequence thereof absorbs only half the amount of oxygen as compared with the original R_3C.

Discussion of the Results

We have now extended the study of this phenomenon to the more complex free radicals, the acridyls. These (VII) contain three different types of benzene rings: (1) a C-phenyl ring (A) with the possibility of *o*-, *m*- and *p*- monohalogen isomers; (2) an N-phenyl ring (D), also with the possibility of *o*-, *m*- and *p*- monohalogen isomers; and (3) the acridine rings (B) and (C), with possible substitution of halogen in Positions 1, 2, 3 or 4.



VII VIII

We have prepared acridols which contain chlorine in each of the ten possible different positions (Form VII, but with the free valence of the central carbon atom linked to the OH group), and we have tested the reactivity of the ring halogen in each of the corresponding acridyls. The results show decisively that the chlorine atom in Position 3 in Ring B or C is even more labile than that in the corresponding positions in the triarylmethyls, xanthenyls and thio-xanthenyls, while in no other of the ten possible positions could the halogen be removed without complete decomposition of the acridyl molecule. The inference, therefore, is justified that tautomerization of the acridyls into the quinonoid form occurs only with rings B and C, as indicated above by VIII, and not with rings A or D. Thus once more we encounter the same general phenomenon: aryl-acridanes, aryl-acridols, etc., are colorless, and all the benzene nuclei in them are stable; the corresponding acridyls, on the other hand, are colored, and contain a very reactive benzene nucleus. The ensuing of such striking reactivity is best expressed by the change of the benzene ring into a quinonoid nucleus. Color and quinonoidation in the free radicals here also appear to be concomitant phenomena.

The synthesis of the acridine derivatives in which chlorine atoms occupy definite positions has been made possible through the application of the

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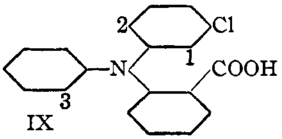
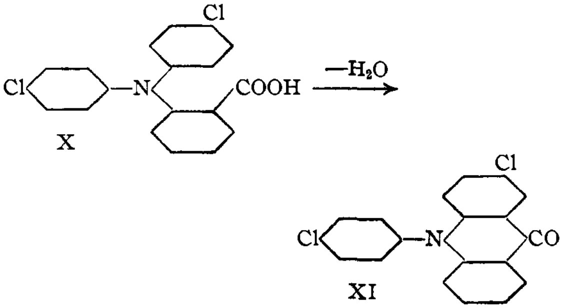
[2] The explanation here given differs slightly from that proposed in previous papers. See Gomberg and Blicke, THIS JOURNAL, 45, 1765 (1923).

Ullmann reaction[3] for building up triaryl-amine-carboxylic acids and from these, the acridones. It is obvious that from compound (IX) three different acridones may result upon ring closure, the reaction involving, respectively, one or the other of the three hydrogen atoms indicated in the formula. In order to obviate the possible formation of a mixture of isomers, it was decided in such instances to place one or more chlorine atoms in those rings of the triphenylamine acid which do not carry the carboxyl group. For instance, the condensation of X could result in the formation of but one acridone (XI) (see pp. 1355–1356).



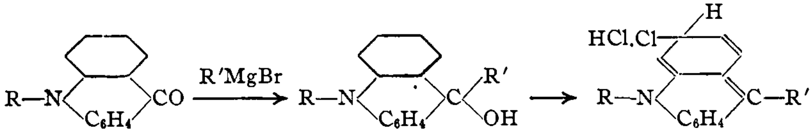
IX



X

XI

The C-phenyl nucleus was in each case introduced into the acridone by means of the Grignard reaction in order to make the acridols XII. The acridols were converted into the corresponding chloride hydrochlorides (XIII) and these changed to the normal chlorides, both of quinocarbonium constitution.[4] Solutions of the acridyl sulfates were also prepared by the method suggested by Cone. The acridyl radicals were prepared in the standard triphenylmethyl apparatus by the action of zinc dust upon an aqueous solution of the requisite chloride or sulfate, in the presence of a solvent immiscible with water. Carbon disulfide and bromobenzene were found particularly suitable for this purpose. As soon as the zinc was introduced into the aqueous solution of the acridyl salt, reduction of the latter ensued, and the free radical, insoluble in water, deposited upon the metal. The immiscible solvent, however, dissolved the free radical when the mixture was shaken, and by thus removing it from immediate contact with zinc it served to delay further reduction of the colored free radical to the corresponding colorless acridane (XIV). The non-aqueous layer



XII XIII

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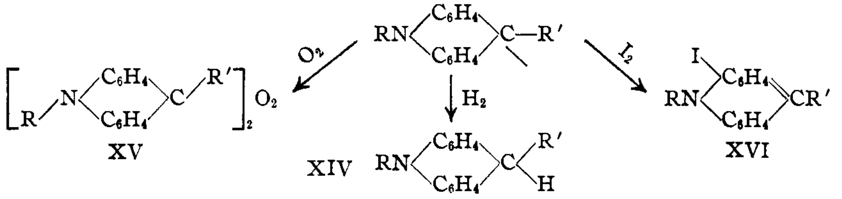
[3] Ullmann, *Ann.*, **355**, 312 (1907).

[4] Gomberg and Cone, *Ann.*, **370**, 203 (1909). Cone, This Journal, **36**, 2105 (1914).

was then rapidly separated from the emulsion, filtered in an atmosphere of carbon dioxide into a second free-radical apparatus while the aqueous layer was reserved to be tested to determine whether any nucleus halogen had been removed by the metal. By employing known amounts of reagents, the concentration of the radical in the carbon disulfide could be calculated; definite amounts of this solution were employed for the quantitative experiments.

Two reactions were employed for the characterization of the acridyls: (1) the formation of colorless peroxides (XV) on exposure of solutions of the radicals to air, and (2) the quantitative formation of red insoluble iodides (XVI) on the addition of iodine to solutions of the acridyls.



Experimental Part

p-Chloro-C-phenyl-N-phenylacridyl Derivatives

***p*-Chloro-C-phenyl-N-phenylacridol.**—Attempts to prepare this and other chloro-acridols from the requisite chloro-phenylmagnesium iodides and N-phenylacridone invariably resulted in the formation of red, insoluble acridyl iodides which could not be decomposed by means of alkali; when the chloro-phenylmagnesium bromides were employed, the desired acridols were readily secured.

A mixture of 0.9 g. of magnesium, 7.5 g. of *p*-bromo-chlorobenzene and 300 cc. of ether was refluxed until all of the metal had dissolved. Six g. of dry, finely powdered N-phenylacridone was then added in small portions during the course of an hour, while the Grignard reagent was being vigorously agitated. After several hours' refluxing, most of the ether was evaporated, whereupon the Grignard addition compound separated as a gray powder. The solid was filtered off and dissolved in dil. acetic acid; the acridol was precipitated by ammonium hydroxide in the presence of ammonium chloride, and the nearly pure product was once more dissolved in acid and reprecipitated by sodium hydroxide. The dry acridol was recrystallized from benzene and petroleum ether. If this procedure did not yield a colorless product—as was sometimes the case—conversion of the acridol into the chloride hydrochloride and subsequent regeneration of the base by an excess of alkali obviated the difficulty. The acridol is soluble in ether, acetone, benzene, slightly soluble in alcohol and insoluble in petroleum ether; m. p., 178–179°.

Anal. Calcd. for $C_{25}H_{18}ONCl$: Cl, 9.25. Found: 9.20.

When boiled with methyl or ethyl alcohol the acridol gave the corresponding ethers melting at 169° and 157°, respectively.

THE CHLORIDE HYDROCHLORIDE AND THE NORMAL CHLORIDE.—With acetyl chloride and hydrogen chloride, the acridol in a mixture of benzene and chloroform gave a yellow chloride hydrochloride which, after being dried for three hours over soda lime, contained 14% instead of 16% of hydrolyzable chlorine. This decreased stability as compared with acridyl halides, which are devoid of nucleus halogen, is quite what would be expected from the less basic nature of the acridol. Short refluxing of the acid salt in chloroform with dry calcium carbonate removed quantitatively the hydrochloric acid. Upon the gradual addition of dry petroleum ether to the concentrated solution, there resulted a bulky precipitate of the normal chloride. The yellow solid was filtered off rapidly in the absence of moisture, and dried at 100° in a vacuum.

Anal. Calcd. for $C_{25}H_{17}NCl_2$: hydrolyzable Cl, 8.85. Found: Cl, 8.80.

The normal chloride does not dissolve extensively in water, as hydrolysis of the salt takes place and the acridol soon settles to the bottom of the vessel.

THE ACRIDYL RADICAL, THE CORRESPONDING PEROXIDE AND THE IODIDE.—The solid chloride was mixed intimately with dry zinc dust and after the addition of bromobenzene and water, the mixture was shaken vigorously to insure immediate reaction. The bromobenzene immediately became colored a deep brownish-red. It was removed at once from the aqueous layer and after filtration through a capsule containing anhydrous calcium chloride it was exposed to air, when complete decolorization took place with the formation of the peroxide. Upon spontaneous evaporation of the solvent, and extraction of the residue with ether, there remained the peroxide, slightly yellow, and melting with decomposition at 183°.

A solution of the acridyl equivalent to 0.54 g. of the acridol consumed 12 cc. of 0.1 *N* iodine dissolved in carbon disulfide, that is, 63% of that required by the formula for the formation of the corresponding iodide. The latter precipitated at once as a brick-red powder, and this was recrystallized from chloroform by the addition of benzene.

Anal. Calcd. for $C_{25}H_{17}NClI$: I, 25.8. Found: 26.4.

Stability of Ring Halogen. Reduction of the Radical to the Acridane.—A solution of 1 g. of acridol in 30 cc. of glacial acetic acid was heated with a little zinc dust at 80° for four hours, stirring being employed to prevent caking of the metal. As an additional precaution, a slow stream of pure carbon dioxide was passed through the apparatus and then through a trap filled with cold acetic acid. The initial red color, due to the intermediate formation of the acridyl radical, rapidly faded. At the end of the stated period the contents of the flask were filtered into a large volume of water. The insoluble acridane separated at once as a solid, and was removed by filtration. No trace of chloride ion could be detected either in the trap or in the aqueous filtrate. After recrystallization from petroleum ether, in which it is only fairly soluble, the pure acridane melted at 147–148° and gave no color with sulfuric acid.

Exactly the same compound was secured when a solution of the free radical in benzene was allowed to stand for some hours in contact with water and zinc dust. Duplicate experiments in which 0.5 g. of the acridyl chloride and 5 g. of zinc were sealed with water and benzene and shaken for several days indicated, respectively, only 8.35% and 8.25% of removable halogen, that is, only one atom of chlorine. Thus, in neither case was even a trace of ring halogen taken out, but only the carbinol halogen, and the radical was completely reduced to the corresponding acridane.

m-Chloro-C-phenyl-N-phenylacridyl Derivatives

The Acridol.—This was prepared from 20 g. of *m*-chlorobromobenzene, 2.6 g. of magnesium and 15 g. of the N-phenyl acridone. The ether was evaporated and replaced by benzene in order to precipitate as completely as possible the Grignard addition compound. The acridol was isolated as previously described for the *p*-chloro isomer. The acridol melts at 177°.

The Chloride Hydrochloride and the Normal Chloride.—The acridol, dissolved in warm chloroform, was treated, drop by drop, with acetyl chloride. By the addition of benzene to the concentrated solution the hydrochloride was obtained quantitatively in the form of yellow crystals soluble in acetone, alcohol, chloroform and nitrobenzene. The hydrochloride was converted into the normal chloride as described for the *p*-chloro isomer.

Anal. Calcd. for $C_{25}H_{18}NCl_3$: hydrolyzable Cl, 16.3. Found: Cl, 16.2.

Calcd. for $C_{25}H_{17}NCl_2$: hydrolyzable Cl, 8.85. Found: Cl, 8.55.

The Acridyl, the Peroxide and the Iodide.—The radical was prepared from a neutral solution of the acridyl sulfate in water by means of zinc dust, bromobenzene being used as the extracting solvent. A quantitative determination of the oxygen absorption showed the presence in the solution of free radical equivalent to 63% of the calculated amount. From the decolorized solution the peroxide was secured in the usual manner; m. p., with gas evolution, 192–193°.

The iodide was prepared in carbon disulfide solution of the free radical; 83% of the calculated amount of iodine was required for complete combination. The weight of the precipitated iodide also indicated that the solution had contained 80% of the calculated amount of radical.

Stability of the Ring Halogen. The Acridane.—One g. of *m*-chloro acridyl sulfate in 20 cc. of water was shaken overnight in a sealed tube with 5 g. of zinc dust, 15 cc. of water and 30 cc. of benzene. The water solution, upon treatment with silver nitrate, gave no precipitate of silver halide, and the benzene layer yielded the acridane pure; m. p., 147°. The same acridane can be prepared by boiling an acetic acid solution of the carbinol with zinc dust. Here again no halogen is removed.

o-Chloro-C-phenyl-N-phenylacridyl Derivatives

The Acridol and the Acridyl Chloride.—This was prepared from 2.6 g. of magnesium, 20 g. of *o*-chlorobromobenzene and 10 g. of N-phenyl acridone; 1.5 g. of the acridol was thus obtained; m. p., 178°. The chloride hydrochloride was prepared in the usual manner. It was converted directly to the chloride.

Anal. Calcd. for $C_{25}H_{17}NCl_2$: hydrolyzable Cl, 8.85. Found: Cl, 8.90.

The Acridyl, the Peroxide and the Iodide.—The free radical was directly converted into the peroxide and the iodide. The peroxide, slightly yellowish, melts with decomposition at 186–187°. The radical combined with iodine to the extent of 70% of that theoretically necessary, and the dark red iodide precipitated out quantitatively.

Stability of the Ring Halogen. The Acridane.—A small sample of acridol in acetic acid was boiled gently with zinc dust for one hour. The acridane, after several recrystallizations from petroleum ether, was found to melt at 183–184°, and to give no color with sulfuric acid. No halogen was found in the extracted aqueous layer. In another experiment, the acridyl chloride was shaken with water, benzene and zinc until the free radical initially formed was completely reduced to the acridane. Here again no nucleus halogen was taken out.

C-Phenyl-N-phenyl-2-chloro-acridyl Derivatives

4-Chlorotriphenylamine-2-carboxylic Acid.—*p*-Dichlorobenzene was nitrated[5] and the resulting compound reduced by means of tin and strong hydrochloric acid. The amine was converted into the nitrile, and this to the acid. From the latter, 4-chloro-

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[5] Jungfleisch, *Jahresber.*, **1868**, 345.

diphenylamine-2-carboxylic acid was next synthesized as described by Ullmann and Wagner;[6] m. p., 208°.

Five g. of the diphenylamine-carboxylic acid, 3.5 g. of potassium carbonate, 8 cc. of iodobenzene and a trace of copper bronze were added to 30 cc. of warm nitrobenzene and the whole was heated to boiling for two hours. The solvent was distilled by means of steam, and the triphenylamine acid was precipitated from the cold filtered alkaline solution by dil. acetic acid. Unchanged starting product was removed by solution of the triphenylamine acid in carbon disulfide and precipitation with petroleum ether. The acid is soluble in chloroform, benzene, alcohol and carbon disulfide; m. p., 157–158°.

Anal. Calcd. for $C_{19}H_{14}O_2NCl$: Cl, 11.00. Found: 11.6%.

N-Phenyl-2-chloro-acridone.—Two and one-half g. of the acid described above and 2 g. of phosphorus pentachloride were refluxed in dry benzene until solution was complete, and the solution was slowly treated with 1.5 g. of aluminum chloride. After removal of the benzene by steam, the acridone remained as a yellow, granular powder, and this was recrystallized from glacial acetic acid. The melting point of the acridone, 229–230°, is unexpectedly low. Presumably slight chlorination of the product by the phosphorus pentachloride had occurred.

Anal. Calcd. for $C_{19}H_{12}ONCl$: Cl, 11.62. Found: 12.15.

C-Phenyl-N-phenyl-2-chloro-acridol.—This acridol was obtained from phenylmagnesium bromide and the acridone described above, in the usual manner. The recrystallized, pure white substance melted somewhat unsharply near 202°. It is soluble in acetone, ether and benzene, and insoluble in petroleum ether.

Anal. Calcd. for $C_{25}H_{18}ONCl$: Cl, 9.25. Found: 9.26.

THE CHLORIDE HYDROCHLORIDE AND THE NORMAL CHLORIDE.—These were prepared as described above for similar compounds.

Anal. Calcd. for $C_{25}H_{18}NCl_3$: hydrolyzable Cl, 16.3. Found: Cl, 15.9. Calcd. for $C_{25}H_{17}NCl_2$: hydrolyzable Cl, 8.85. Found: Cl, 8.85.

THE ACRIDYL, THE PEROXIDE AND THE IODIDE.—An aqueous solution of the acridyl sulfate was shaken with zinc dust and carbon disulfide for two or three minutes, and very shortly thereafter all traces of the original yellow had vanished from the aqueous portion. The solution of the free radical decolorized to a very light straw color when air was blown through it. The peroxide melts at 218–219° with decomposition.

Anal. Calcd. for $C_{50}H_{34}N_2O_2Cl_2$: Cl, 9.26. Found: 9.28.

A solution of the free radical took up 74% of the calculated amount of iodine. The iodide is quite insoluble in almost all of the usual organic solvents save chloroform.

Stability of the Ring Halogen. The Acridane.—The acridane was prepared from the acridol dissolved in acetic acid by reduction with zinc dust, and also in the cold from the acridyl sulfate, zinc dust and benzene. In neither instance was there any ring halogen removed, and in each instance the beautifully crystalline acridane was secured; m. p., 197°.

C-Phenyl-N-phenyl-3-chloro-acridyl Derivatives

5-Chlorotriphenylamine-2-carboxylic Acid.—One g. of 5-chloro-diphenylamine-2-carboxylic acid (m. p., 196–197°), 0.6 g. of potassium carbonate, 4 cc. of iodobenzene, 8 cc. of bromobenzene and a bit of copper bronze were boiled together under a reflux con-

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[6] Ullmann and Wagner, *Ann.*, **355**, 365 (1907); **371**, 388 (1909).

denser for six hours. After removal of the solvent by steam distillation, the triphenylamine acid was precipitated, ice-cold, with hydrochloric acid. Twice again it was redissolved in dil. alkali and reprecipitated by acid. The dry acid is almost completely soluble in a little cold carbon tetrachloride or benzene, and may be separated from the more insoluble impurities by this means. Upon slow removal of the solvent in a vacuum, yellow needles of the acid deposited; m. p., 138°.

Anal. Calcd. for $C_{19}H_{14}O_2NCl$: C, 70.47; H, 4.33; Cl, 11.00. Found: C, 70.01; H, 4.65; Cl, 11.46.

N-Phenyl-3-chloro-acridone.—Seven g. of the acid described above and 4.5 g. of phosphorus pentachloride were warmed in benzene, and then 2.9 g. of aluminum chloride was added during vigorous agitation. After the mixture had been refluxed for a few minutes, the solvent was removed, the solid residue washed with water, then with dil. aqueous ammonia, and the dried acridone was recrystallized from boiling toluene employing a Soxhlet extractor. The desired product separated in yellow needles; m. p., 288–289°. It is insoluble in nearly all the usual organic solvents at ordinary temperatures.

Anal. Calcd. for $C_{19}H_{12}ONCl$: C, 74.63; H, 3.94; Cl, 11.62. Found: C, 74.72; H, 4.14; Cl, 12.39.

C-Phenyl-N-phenyl-3-chloro-acridol.—This was prepared from the chloro-acridone described above and an excess of phenylmagnesium bromide. It was recrystallized from benzene and petroleum ether; m. p., 155°. It is fairly soluble in the usual organic solvents.

Anal. Calcd. for $C_{25}H_{18}ONCl$: Cl, 9.25. Found: 9.21.

THE CHLORIDE HYDROCHLORIDE AND THE NORMAL CHLORIDE.—The acid chloride was precipitated crystalline when hydrogen chloride was passed through a solution of the acridol in a mixture of benzene and chloroform. An excess of gas sometimes caused the formation of a red oil, presumably a higher hydrochloride of the salt, but boiling for a time resulted in complete crystallization. The product was quite hygroscopic, and for purposes of analysis was rapidly filtered, washed with absolute ether and dried for half an hour in a moderate vacuum over soda lime. The normal chloride was prepared in the usual manner from the acid salt. Unlike the latter, the normal salt is not very hygroscopic.

Anal. Calcd. for $C_{25}H_{18}NCl_3$: hydrolyzable Cl, 16.3. Found: Cl, 16.0. Calcd. for $C_{25}H_{17}NCl_2$: hydrolyzable Cl, 8.85. Found: Cl, 8.85.

Lability of the Ring Halogen. Acridyl Radicals of the First and Second Orders.—From the chloride the free radical was prepared by zinc dust and water in the presence of carbon disulfide. The primary product, an analog of triphenylmethyl, resulting from the removal of the carbinol atom of halogen, dissolved in the carbon disulfide forming a solution with an intense iodine-like color. Upon longer shaking, however, there resulted, due to the removal of one-half atom of ring chlorine, a radical of the second order, which seemed to possess almost the same color as its predecessor. When exposed to air the carbon disulfide layer decolorized almost completely. Upon evaporation of the solvent there remained a cream-colored gum; this was dissolved in a very little dry ether and reprecipitated by low-boiling petroleum ether, and it then became granular. The product, peroxide of the second order radical, probably was not quite pure, for in the length of time required for the removal of the nuclear portion of the chlorine, reduction of a part of the original monomolecular radical to the corresponding acridane must have ensued. The chlorine content (4.64%) and the decomposition point, approximately 200°, distinguish the peroxide, however, from the acridane. The latter melts at 146° as given below.

The rapidity with which the half atom of ring halogen is removed is surprising, and the quantitative exactness of this reaction, in that only one-half atom of ring halogen is removed, is illustrated in the following table.

Starting product	3-Chloro-acridyl sulfate			3-Chloro-acridyl chloride	
Reaction time	3 min.	30 min.	Overnight	Overnight	Overnight
Atoms of Cl removed	0.22	0.41	0.44	1.48	1.50

Attempts were made to arrest the reaction at that stage when only the carbinol chlorine had been removed, that is, when the primary radical had been formed. For this purpose the chloride and zinc, with water and carbon disulfide, were shaken in the presence of air, in the hope that in this way the peroxide of the true acridyl would be produced. In spite of all precautions, the reaction with zinc proceeded further than was desired, ring halogen being removed by the metal even under these conditions. The amount of oxygen absorbed by the resulting complex radical was only about one-half that theoretically necessary for a primary, and almost exactly that required for the corresponding secondary acridyl.[7]

C-Phenyl-N-phenyl-3-anilino-acridyl Chloride.—The lability of the nucleus chlorine atom is further evidenced in the ease with which it is replaced by the phenylamino group, when the normal chloride is warmed with an excess of aniline for a few minutes. The chloride of this salt is brick-red and is soluble in water, alcohol and acetone, but insoluble in benzene and ether.

Anal. Calcd. for $C_{31}H_{23}N_2Cl$: hydrolyzable Cl, 7.75. Found: Cl, 7.60.

C-Phenyl-N-phenyl-3-chloro-acridane.—Since zinc dust and acetic acid were found to remove a large portion of the ring halogen from the acridol, preparation of the leuco body could not be carried out by this method. Employing anhydrous formic acid,[8] however, the desired compound was obtained in good yield. One-half g. of the acridol was dissolved in 25 cc. of anhydrous formic acid containing 5 g. of sodium formate and the whole heated to boiling for five hours. On dilution with water, the acridane precipitated; it was recrystallized from alcohol; yield, 0.43 g.; m. p., 146–147°. Unlike the acridol, it gave no color with cold concd. sulfuric acid.

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[7] Ref. 2, p. 1775.

[8] Guyot and Kovache, *Compt. rend.*, **154**, 121 (1912).

C-Phenyl-N-*p*-chlorophenyl-2-chloro-acridyl Derivatives

4′-4″-Dichloro-triphenylamine-2-carboxylic Acid.—Five g. of 4′-chloro-diphenylamine-2-carboxylic acid,[9] 3 g. of potassium carbonate, 7.5 g. of *p*-chloro-iodobenzene and 0.1 g. of copper bronze were boiled in 50 cc. of nitrobenzene for six hours; the solvent was then removed by steam distillation and the triphenylamine acid precipitated by acetic acid. Recrystallized from slightly diluted acetic acid, it formed yellowish crystals; m. p., 220–221°.

Anal. Calcd. for $C_{19}H_{13}NO_2Cl_2$: Cl, 19.85. Found: 19.40.

N-*p*-Chlorophenyl-2-chloro-acridone.—This substance was prepared in the manner described for N-phenyl-2-chloro-acridone, and was recrystallized from boiling xylene. It did not melt even at 270°.

Anal. Calcd. for $C_{19}H_{11}ONCl_2$: Cl, 20.3. Found: 20.39.

C-Phenyl-N-*p*-chlorophenyl-2-chloro-acridol.—When this acridol was prepared from phenylmagnesium bromide and the above acridone, there resulted on decomposition of the reaction mixture with ice and hydrochloric acid, the acridol bromide, deep red in color, insoluble in water, in acids, and which is affected but slightly by alkalies. The method of decomposition finally adopted consisted in dissolving the bromide in hot glacial acetic acid, and then adding the solution to cold sodium hydroxide. When thus purified, it still tended to retain a slightly yellow color. The melting point was found to be 169–170°.

Anal. Calcd. for $C_{25}H_{17}ONCl_2$: Cl, 16.98. Found: 16.80.

THE CHLORIDE HYDROCHLORIDE AND THE NORMAL CHLORIDE.—The chloride hydrochloride is most advantageously prepared by passing dry hydrogen chloride over the solid acridol contained in a porcelain boat. A quantitative experiment in which the acridol was exposed in an atmosphere of the gas, first at room temperature, then at 80°, and finally at room temperature again, showed a gain in weight corresponding to 103% of that equivalent to the formation of the chloride hydrochloride. An analysis at this point indicated approximately the halogen content calculated for the acid salt. After this sample had been dried to constant weight in a vacuum at 90°, the loss was found to correspond almost exactly with that calculated for one molecular equivalent of hydrogen chloride. Analysis, too, indicated the presence of the normal chloride.

Anal. Calcd. for $C_{25}H_{16}NCl_3$: hydrolyzable Cl, 8.14. Found: Cl, 8.21.

This acridyl chloride, because of the two chlorine atoms in the phenyl rings, is a salt of a feeble base, and consequently unites only loosely with more hydrogen chloride.

The Acridyl Radical, the Peroxide and the Iodide.—Two g. of the chloride was suspended in water and shaken with zinc dust and carbon disulfide. After a few minutes the emulsion was filtered from the zinc, and air blown into the mixed liquids until the deep red color of the free radical had vanished. Ether extracted from the crude peroxide a small amount of black tar, leaving 1 g. of pure, very white, peroxide. This melts sharply with decomposition at 223–224°.

Anal. Calcd. for $C_{50}H_{30}O_2N_2Cl_4$: Cl, 16.99. Found: 16.91.

A solution of the acridyl radical was titrated with iodine, and 85% of that required by the formula was taken up.

Stability of the Ring Halogen. The Acridane.—The corresponding acridane was prepared by reduction of the pure acridol with zinc dust and acetic acid and also by

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[9] Ref. 3, p. 339.

shaking the acridyl chloride with zinc dust, water and benzene during 60 hours. No nucleus halogen was removed. The acridane melts at 163°.

Anal. Calcd. for $C_{25}H_{17}NCl_2$: Cl, 17.6. Found: 17.2.

C-Phenyl-N-*o*-chlorophenyl-4-chloro-acridyl Derivatives

2′-2″-Dichlorotriphenylamine-2-carboxylic Acid.—The required starting product, *o*-chloro-phenylanthranilic acid has been described by Ullmann.[10] From this, the *o*-*o*′-dichloro-diphenylanthranilic acid was synthesized, employing essentially the procedure suggested on p. 1355 for the di-*para* isomer. It forms yellowish crystals which melt at 212–213°, and it is only fairly soluble in benzene, alcohol and ethyl acetate.

Anal. Calcd. for $C_{10}H_{13}O_2NCl_2$: Cl, 19.85. Found: 19.56.

N-*o*-Chlorophenyl-4-chloro-acridone.—Five g. of *o*,*o*′-dichloro-diphenylanthranilic acid was converted to the acridone by treatment in benzene solution successively with 3.5 g. of phosphorus pentachloride and 2.5 g. of aluminum chloride. Even with this excess of reagents, conversion was found to be incomplete after half an hour of boiling, 3.5 g. of the acridone being the maximum yield obtained. The acridone is best recrystallized from toluene, from which it separates in golden-yellow leaflets.

Anal. Calcd. for $C_{19}H_{11}ONCl_2$: Cl, 20.3. Found: 19.95.

C-Phenyl-N-*o*-chlorophenyl-4-chloro-acridol.—This was prepared from phenylmagnesium bromide and the acridone. The acridol proved to be soluble in dil. hydrochloric acid (1–500). Extraction was carried out repeatedly with this reagent, and the cooled extracts were made decidedly alkaline in order to precipitate the acridol. This, on recrystallization from benzene and petroleum ether, gave white to slightly yellow crystals; m. p., 158–159°.

Anal. Calcd. for $C_{25}H_{17}ONCl_2$: Cl, 16.98. Found: 16.80.

THE CHLORIDE HYDROCHLORIDE AND THE NORMAL CHLORIDE.—These were prepared in the customary manner.

Anal. Calcd. for $C_{25}H_{16}NCl_3$: hydrolyzable Cl, 8.14. Found: 8.20.

The Acridyl Radical, the Peroxide and the Iodide.—This acridyl was obtained in the same manner as were the radicals described above. On evaporation of the solvent, there remained a semi-solid oil; from this, ether took away a considerable quantity of black gum, and left the peroxide, slightly gray. It decomposes sharply at 197–198°.

Anal. Calcd. for $C_{50}H_{30}O_2N_2Cl_4$: Cl, 16.99. Found: 16.7.

A freshly prepared solution of the radical took up 71% of the iodine required by the formula for complete reaction, and the iodide was secured in crystalline form.

Stability of the Ring Halogen. The Acridane.—The acridane was made from the acridol in acetic acid by reduction with zinc dust. It melts at 135°. No halogen was removed during the course of the reduction. Even on prolonged shaking of the acridyl chloride with zinc dust in the presence of benzene and water no ring halogen was removed, and the benzene layer was found to contain very pure acridane.

Anal. Calcd. for $C_{25}H_{17}NCl_2$: Cl, 17.60. Found: 17.75.

C-Phenyl-N-*o*-*m*-dichlorophenyl-1,4-dichloro-acridyl Derivatives

2′,5′-Dichlorodiphenylamine-2-carboxylic Acid (2-5-Dichlorophenyl-anthranilic Acid).—Five g. of the potassium salt of *o*-chlorobenzoic acid, 7.5 g. of 2,5-dichloro-

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[10] Ref. 3, p. 336.

aniline, 12 cc. of amyl alcohol and 0.1 g. of copper bronze were gently boiled together in an oil-bath for six hours, and from the reaction mixture 3.5 g. of the desired acid was isolated. It may be recrystallized from acetic acid and benzene or xylene, and obtained in pearly-white crystals. These melt at 235° to form a colorless liquid. The acid is soluble in acetone and warm ethyl acetate; it is insoluble in chloroform and carbon disulfide.

Anal. Calcd. for $C_{13}H_9O_2NCl_2$: Cl, 25.2. Found: 25.4.

2′,5′,2″,5″-Tetrachloro-triphenylamine-2-carboxylic Acid.—A mixture of 5 g. of 2-5-dichloro-phenylanthranilic acid in 10 cc. of nitrobenzene, 9 g. of 2,5-dichloro-iodobenzene, 3 g. of potassium carbonate and 0.1 g. of copper bronze was heated to boiling during six or seven hours. The acid, recrystallized successively from acetic acid, xylene and bromobenzene, melted unsharply at 223–227°. Analysis of the purest material obtained in the work described above indicated the presence of some of the unchanged starting product.

Anal. Calcd. for $C_{19}H_{11}O_2N_2Cl_4$: Cl, 33.2. Found: 31.4.

Ullmann had previously found in other cases that the more negative the original molecule, the less readily did further phenylation take place.

N-*o,m*-Dichloro-phenyl-1,4-dichloro-acridone and the Corresponding C-Phenylacridol.—The acid described above, purified as well as possible, was converted to the acridone by means of phosphorus pentachloride and aluminum chloride. From this, after recrystallization, the acridol was prepared by means of phenylmagnesium bromide.

Stability of the Ring Halogen.—Upon subjecting 1 g. of this acridol to reduction by zinc in acetic acid during several hours, a fairly crystalline acridane was secured, and from the diluted acid not more than a few milligrams of silver chloride precipitated on treatment with silver nitrate.

Although the experimental proof presented in this last section is unfortunately not as complete as could be desired, nevertheless the results demonstrate the relatively very great stability of halogen in the *meta* position of the N-phenyl group and in the 1-position as compared with that in the 3-position of the acridyl complex.

Summary

1. A series of eight chlorine-substituted C-phenyl-N-phenylacridols have been synthesized: five monochloro compounds, two dichloro and one tetrachloro. From the salts of all these acridols, except one, the corresponding acridyls, with a trivalent carbon atom, have been obtained and characterized by the isolation of their peroxides and iodides.

2. The eight chloro-acridols mentioned above contain each a chlorine atom in some one of the ten possible different positions, respectively, (Formula VII). With the transition of the acridols into the acridyls, the chlorine atom in nine of the ten possible positions retains fully its benzenoid and non-reactive character. When, however, the halogen is in Position 3 in Rings B or C, then, in the acridyl, it becomes surprisingly labile, and is removable to the same extent as in the *para*-halogenated triarylmethyls and xanthenyls.

3. The facts that the halogen becomes affected in this manner only when it is in Rings B or C, and therein only when in Position 3, are interpreted as indicating that of the four rings in the acridyls only these two are capable of undergoing a tautomeric change from benzenoid (VII) to the more reactive quinonoid state (VIII). The conclusion is drawn that in the acridyls, in common with other free radicals, the acquisition of the property of selective absorption on the one hand, and on the other, their capacity to exist tautomerically in the quinonoid state, are concomitant phenomena.

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[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL]

SOME DERIVATIVES OF GALLIC ACID AND PYROGALLOL

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RECEIVED JANUARY 15, 1926 PUBLISHED MAY 5, 1926

Studies which are being made in this Laboratory necessitated the preparation of a number of polyhydric phenols of the gallic acid and pyrogallol series. Some of these compounds are new and are reported in this paper together with a few general observations.

Esterification of gallic acid by the alcohol-hydrogen chloride process proceeds very smoothly when methyl[1] and *n*-butyl alcohols are employed; excellent yields are obtained and unchanged gallic acid is not recovered. However, in the case of the *iso*propyl compound 40% of the gallic acid remains unesterified.

Gallic acid reacts with chloro-acetic acid in aqueous solution containing three molecular equivalents of sodium hydroxide to form a dihydroxycarboxyphenoxyacetic acid. That the condensation involves one of the hydroxyl groups and not the carboxyl group of the gallic acid molecule is evinced by the facts that the reaction product is not hydrolyzed by boiling sodium hydroxide and does yield a dimethyl ester when treated with absolute methyl alcohol and hydrogen chloride. If the product were a trihydroxybenzoyl-glycolic acid, gallic acid would be obtained by alkaline hydrolysis, and the only ester obtainable would be a monomethyl ester.

In an attempt to determine whether one of the hydroxyl groups in the *meta* positions to the carboxyl group of gallic acid or the one in the *para* position takes part in this reaction, the preparation of 2,6-dihydroxy-4-carboxyphenoxyacetic acid was undertaken by the process represented by the following reactions.

[1] Methyl gallate was prepared according to the directions of Will, *Ber.*, **21,** 2022 (1888).