added and the reflux was cut off so that over the next 20 hr. the temperature rose to 185°. The cooled reaction mixture was diluted with 100 ml. of ether and placed in the icebox overnight. The heavy amorphous precipitate was rejected. After ether evaporation the residual oil was pumped out to remove starting materials (2 hr., bath temperature 110–115° at 1–2 mm.). The residual oil, weighing 10.5 g., was carried through the usual guanidine condensation. From the chloroform and 2*N* hydrochloric acid soluble fraction of reaction product 3.2 g. of pyrimidine was obtained. Recrystallization from methanol gave crystals, m.p. 240–242°.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Structure of *x*-Bromoacetyl-*N*-acetyl-9,10-dihydroacridine*[1]

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The elucidation of the position occupied by the bromoacetyl group in the title compound has been achieved. This, incidentally, represents the first example of a successful Friedel-Crafts acylation in acridine chemistry.

Some years ago in a study of the plasmodicidal properties of diverse acridine derivatives, a series of amino alcohols derived from *x*-bromoacetyl-*N*-acetyl-9,10-dihydroacridine (I) was synthesized.[2]

It was pointed out at the time that the proof of the structure of this key substance depended upon the availability of certain acridine derivatives then unknown. This deficiency was rectified shortly thereafter by the synthesis of the four requisite ethylacridines by unambiguous routes,[3] and the present communication reports the final phase in arriving at the constitution of I.

The reactions involved in degrading I to an ethylacridine of known constitution are shown in the chart. In the presence of sodium acetate the palladium-charcoal catalyzed debromination step occurred smoothly with hydrogen absorption coming to a virtual halt after the uptake of one mole. On the other hand, when sodium acetate was omitted, the hydrogen bromide formed *in situ* not only induced *N*-acyl cleavage–as evidenced by the isolation of a small amount of *x*-acetyl-9,10-dihydroacridine (III) in one instance–but apparently catalyzed reduction at other sites in the molecule as well. The product isolated from the buffered reduction system, *x*-acetyl-*N*-acetyl-9,10-dihydroacridine (II) was a colorless glass that resisted crystallization even after passage through its well-defined semicarbazone. *N*-acyl hydrolysis of II gave *x*-acetyl-9,10-dihydroacridine (III) which was reduced (Wolff-Kishner) to *x*-ethyl-9,10-dihydroacridine (IV). The latter substance proved to be exceedingly air sensitive, more so than the parent 9,10-dihydroacridine. For example, while a pure sample of the latter showed virtually no change in melting point even after one year's keeping in a closed vial, a sublimed specimen of IV exhibited a marked melting point drop after only two days storage in a vial. Potassium dichromate oxidation[4,5] of IV yielded a substance which was identical in all respects with synthetic 3-ethylacridine.[3]

In another approach, *x*-acetyl-9,10-dihydroacridine (III) was oxidized with potassium dichromate to *x*-acetylacridine (VI) which, upon Wolff-Kishner reduction, gave 3-ethylacridine thereby establishing VI as the presently unknown 3-acetylacridine.

After demonstrating that I could be debrominated to *x*-acetyl-*N*-acetyl-9,10-dihydroacridine (II), several attempts (five in all) were made to prepare II through Friedel-Crafts acylation of *N*-acetyl-9,10-dihydroacridine by acetyl chloride or acetyl bromide under the conditions utilized in the synthesis of I.[2] Two experiments with acetyl chloride failed to yield any of the desired product; only starting material was recovered. In one of the two acetyl bromide runs (where the reaction mixture was allowed to stand overnight at 25° before workup) it was possible to isolate *ca.* 1.5% of the desired II (as its semicarbazone) from the mother liquors of recovered (85%) starting material. The infrared spectrum of this semicarbazone was identical with that of the corresponding derivative of II obtained *via* the bromoketone. A final acylation with acetyl bromide in nitrobenzene yielded the following three products: (*a*) starting material, 40%, (*b*) acridine, 20%, and (*c*) dihydroacridine, 10%, along with some tarry material. It is of interest that the latter two substances should turn up in this reaction, and

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Studies in the Acridine Series X.

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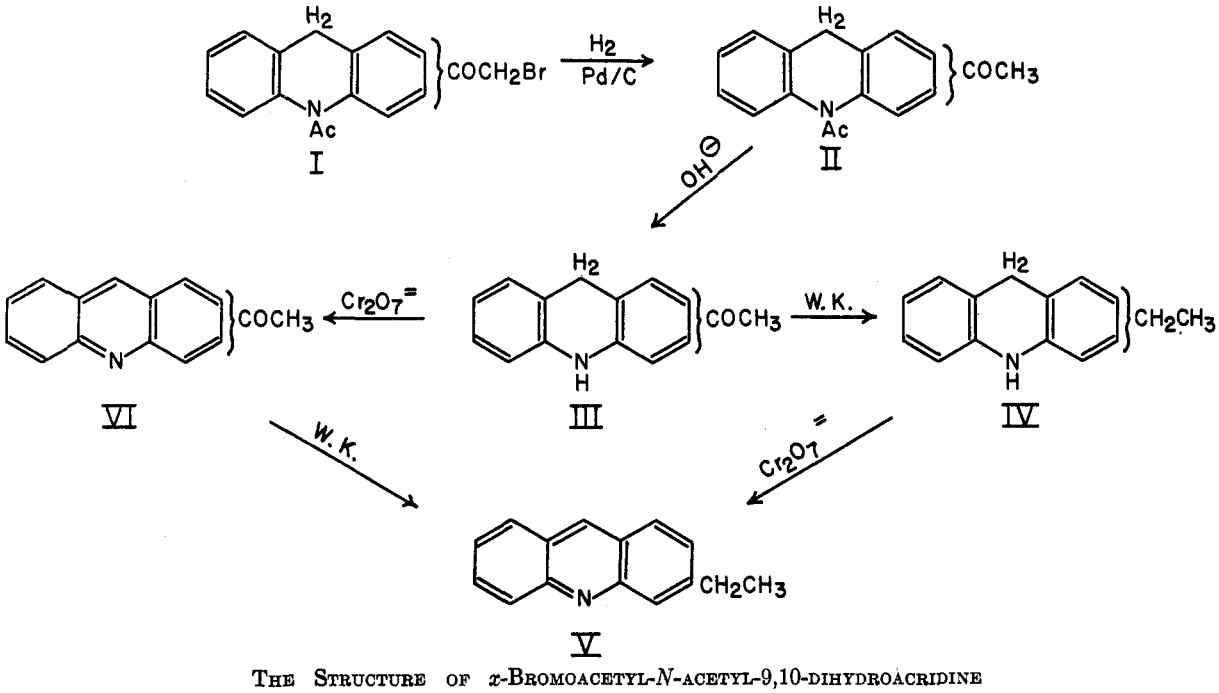

THE STRUCTURE OF x-BROMOACETYL-N-ACETYL-9,10-DIHYDROACRIDINE

it is very likely that they were formed during the steam removal of the nitrobenzene by a combination of effects, *viz.* (*a*) hydrolysis of the *N*-acyl group by the hot acid solution and (*b*) oxidation of the sensitive dihydroacridine to acridine by the nitrobenzene.

EXPERIMENTAL[6]

X-Acetyl-N-acetyl-9,10-dihydroacridine (II) *semicarbazone.* A suspension of 1.9 g. of finely powdered I in 90 ml. of 95% ethanol was shaken under hydrogen with 0.63 g. of 5% palladium-on-charcoal and 0.8 g. of powdered, fused sodium acetate. Initial hydrogen uptake was rapid (30 ml./min.) but, after the absorption of 1.15 moles, slowed markedly (*ca.* 0.8 ml./min.). After removal of the catalyst, the colorless filtrate was concentrated (*in vacuo*) and the sirupy residue taken up in 15 ml. of 90% ethanol and heated for 2.5 hr. (reflux) with 0.81 g. of semicarbazide hydrochloride and 0.6 g. of fused sodium acetate. The addition of water precipitated a colorless solid which was collected and recrystallized from methanol to yield colorless prisms (1.25 g.), m.p. 134–136° (foams; apparently solvated). A sample was recrystallized twice again from methanol and dried at 98°/0.1 mm. for 4 hr., m.p. 150–153°.

Anal. Calcd. for $C_{15}H_{18}N_4O_2$: C, 67.1; H, 5.63. Found: C, 66.8; H, 5.95.

Regeneration of the ketone (II). A suspension of 1.12 g. of the above semicarbazone in a solution of 18 ml. of glacial acetic acid, 0.95 ml. of 50% pyruvic acid[7] and 5 ml. of water was boiled under reflux for 15 min. With ice-cooling, 15 ml. of water was added followed by dropwise addition of concd. ammonium hydroxide (in slight excess). The curdy suspension was taken up in ether, the solution washed with saturated sodium bicarbonate and dried. Concentration gave 0.75 g. of a colorless glass.

X-Acetyl-9,10-dihydroacridine (III). A solution of 0.75 g. of II in 15 ml. of 95% ethanol and 9 ml. of 10% ethanolic potassium hydroxide was heated on the steam bath (reflux) for 1 hr. The reaction mixture was diluted with water and the bright-yellow precipitate collected and air-dried—0.63 g. The product was suspended in 50 ml. of methanol at 25°, filtered from a small amount of insoluble material (0.1 g.) and concentrated to a small volume (*in vacuo*) to yield 0.5 g. of pale-yellow leaves, m.p. 169–171°. After sublimation at 165–170°/0.25 mm., the sample melted at 174.5–176°.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.7; H, 5.87; N, 6.28. Found: C, 80.3; H, 5.81; N, 6.42.

X-Ethyl-9,10-dihydroacridine (IV). A mixture of III (0.65 g.), potassium hydroxide (0.65 g.) and 0.8 ml. of 85% hydrazine hydrate in 12 ml. of diethylene glycol was heated for 4.5 hr. according to Huang-Minlon.[8] Dilution with cold water precipitated 0.6 g. of a pale-yellow solid which was collected, washed with water and dried under N_2. Although the substance crystallizes in colorless plates from methanol, and may be sublimed at 105°/0.1 mm. in small prisms, m.p. 127–129°, it appears to be even more air-sensitive than 9,10-dihydroacridine and is largely oxidized in a matter of *ca.* 48 hr. (new m.p. 95–105°).

3-Ethylacridine (V). A suspension of 0.6 g. of IV in a hot mixture of 4.5 ml. of 2*N* sulfuric acid and 45 ml. of water was oxidized with 0.3 g. of potassium dichromate in 4 ml. of water, and the product was converted to the dichromate salt with 0.73 g. of potassium dichromate in 8 ml. of water.[4,5] Regeneration of the free base (concd. ammonium hydroxide–ether) gave 0.4 g. of a pale-yellow oil which crystallized when rubbed with petroleum ether. An ice-cooled solution of the base in 2 ml. of absolute ethanol was treated with 0.25 ml. (excess) of 60% perchloric acid; the yellow salt which was collected and washed with a few ml. of absolute ethanol–ether (2:1) weighed 0.49 g. Recrystallization from absolute ethanol (Norit) gave 0.32 g. of slender, yellow prisms, m.p. 179–181° (not depressed when mixed with authentic 3-ethylacridine perchlorate of m.p. 184–185°[3]). A benzene solution of the regenerated base was chromatographed on 6 g. of aluminum oxide, collecting 125 ml. of eluate. Concentration (*in vacuo*) yielded 0.15 g. of a pale-yellow oil which crystallized spontaneously, m.p. 83–85°. After sublimation at 100°/0.1 mm., the m.p. was 87–88.5°, unde-

(6) Analyses are by the Analytical Service Laboratory of this Institute, under the supervision of Dr. W. C. Alford. Melting points are uncorrected.

(7) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(8) Huang-Minlon, *J. Am. Chem. Soc.*, **64**, 2653 (1942).

pressed when mixed with synthetic 3-ethylacridine.[3] Moreover, the infrared spectra were identical.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.8; H, 6.32. Found: C, 85.8; H, 6.43.

3-Acetylacridine (VI). A hot suspension of 0.33 g. of III in 22 ml. of water (containing 20 drops of acetone) and 2.5 ml. of 2*N* sulfuric acid was oxidized with 0.18 g. of potassium dichromate in 4 ml. of water. The filtered solution was treated with 0.4 g. of potassium dichromate in 4 ml. of water and the precipitated salt converted to the free base (concd. ammonium hydroxide–ether). Concentration of the dried solution gave 0.24 g. of a light-yellow solid which was sublimed at 125–130°/0.1 mm., lemon yellow prisms, m.p. 135–136.5°. The compound possessed a strong carbonyl band at 5.95 μ.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.01. Found: C, 81.2; H, 5.04.

A Wolff-Kishner reduction of 60 mg. of VI in 4 ml. of diethylene glycol with 60 mg. of potassium hydroxide and 0.1 ml. of 85% hydrazine hydrate gave, after the usual work-up, 40 mg. of a tacky yellow solid which was chromatographed on 3 g. of aluminum oxide (benzene). The resulting base was converted to the *perchlorate*, m.p. 176–178° (undepressed when mixed with 3-ethylacridine perchlorate). Regeneration of the base gave a pale yellow oil which crystallized rapidly (scratching), m.p. 75–77°; not depressed when mixed with synthetic 3-ethylacridine. The infrared spectra of the regenerated base and 3-ethylacridine were the same.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Some Reactions of Solasodine*[1]

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The degradation of the steroidal alkaloid solasodine has led to 5,16-pregnadien-3β-ol-20-one. Solasodine has also been converted into a new isomeric solanidanone and into the diacetate and monoacetate of a "pseudosolasodine." Some reactions of the latter are discussed.

Solasodine (I),[2,3] the aglycone of solasonine[4] obtained from certain solanum species, can be converted to a pregnane derivative by treatment with acetic anhydride and oxidation of the resulting amorphous mass. Thus solasodine (I) yielded the acetate of 5,16-pregnadien-3β-ol-20-one (IV) and 16α-methoxy-5-pregnen-3β-ol-20-one. The latter presumably arose from the addition to the 15,16-double bond of the methanol used in the alkaline hydrolysis[5] of the side chain moiety.

The crude oil obtained from the acetic anhydride treatment of solasodine failed to crystallize, but yielded upon chromatography on alumina a crystalline compound. The analytical values of the latter indicated the structure of the unsaturated *O,N*-diacetyl derivative III. Its principal infrared absorption bands ($\lambda_{max}^{chlf.}$ 2.91 and 3.00 μ, NH; 5.98, 6.61 μ, HN—C—CH_3) agreed well with those of the unsaturated *O,N*-diacetyl tomatidine[6] obtained by a similar chromatography on alumina of the so-called unsaturated triacetyltomatidine.[7]

The principal bands of III were also in agreement with those of *N*-acetyldihydrotomatidine and *N*-acetyltetrahydrosolasodine whose structures have been established.[8] The course of the oxidation of compound II, and the analogy of the latter with the unsaturated triacetyl derivative[7,9] of tomatidine obtained in the acetic anhydride treatment indicate strongly structures II and III, tentatively designated as derivatives of pseudosolasodine A. The amorphous material obtained from the acetic anhydride treatment of solasodine, unlike that from tomatidine,[7] was a mixture (indicated by infrared spectra and the isolation of another component as yet unidentified) and the yield of the pregnadienolone acetate (IV) was low (10–20%), while tomatidine had yielded about 60% of 16-allopregnenolone.[7] When 5,6-dihydrosolasodine was employed in this degradation the yield of 16-allopregnenolone again was quite poor showing that it is not the 5,6-double bond that is responsible for the difference in yields.

The exhaustive reduction of solasodine leads to the formation of tetrahydrosolasodine,[10] VIIa, with the uptake of 2 moles of hydrogen. When VIIa was

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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