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

Carbinolamines Derived from 6-ω-Bromoacetyl-*N*-acetyl *asym*-Octahydroacridine[1]

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The ω-bromoacylation of 1,2,3,4,4a,9,9a,10-*N*-acetyloctahydroacridine (under Friedel-Crafts conditions) was shown to occur at C-6 of the heterocycle. Three carbinolamines of the type R—CHOH—CH_2NR_2', derived from the bromoketone were synthesized and found to be devoid of both plasmodicidal and antiviral activity.

The introduction of diverse carbinolamine groups at various positions of the acridine system with the view to evaluating their plasmodicidal activity was the subject of recent investigations in this laboratory.[2] The present communication deals with an extension of this idea in that 1,2,3,4,4a,9,-9a,10-*N*-acetyloctahydroacridine serves as the heterocyclic moiety in order to study the influence, on activity, of gross saturation of the acridine nucleus. A further consideration that prompted this study was the possibility that the pharmacological properties of these substances would parallel the recently observed antiviral activity (in tissue cultures of influenza types A and B, as well as mumps virus) of certain carbinolamines derived from 2,3-dimethoxy-6-nitroacridine.[3]

The route to the octahydroacridine carbinolamines was patterned after methods developed earlier in this laboratory.[2a] Thus acridine was selectively hydrogenated to *asym*-octahydroacridine,[4] whose *N*-acetyl derivative was bromacylated (Friedel-Crafts) and the bromoketone (I) transformed to the respective carbinolamines by way of the intermediate aminoketones. Because this approach incidentally afforded the first example of a successful *C*-acylation of an octahydroacridine, it was necessary to determine the position of the bromoacetyl function. This was accomplished in a manner analogous to that worked out earlier with dihydroacridine (see chart) whereby I was degraded to an ethylacridine of known constitution.[5] The palladium-charcoal catalyzed hydrogenolysis of I occurred so rapidly that it was necessary to interrupt the reduction after the adsorption of 1 mole of hydrogen. Failure to do so led to considerably lower yields of the desired IV. *N*-Acyl hydrolysis of the latter gave V which was reduced (Wolff-Kishner) to VI and this upon palladium-charcoal dehydrogenation afforded VII, identical in all respects with synthetic 3-ethylacridine. Since it recently was shown that alkyl group migration does not occur under the dehydrogenation conditions employed,[2c,6] and because the 3 and 6 positions in acridine are equivalent, it follows that bromoacylation of *asym*-octahydroacridine had occurred at C-6.

The octahydroacridine carbinolamines described below were ineffective toward *Plasmodium gallinaceum* (chick infection),[7] as well as in influenza virus and MM(neurotropic) virus infected mice.[8]

EXPERIMENTAL[9]

N-Benzoyl asym-octahydroacridine. The high pressure hydrogenation of acridine was carried out according to Adkins,[4] and the *asym*-octahydroacridine isolated in the form of its *N*-benzoyl derivative. In a typical run, 39 g. of purified acridine and 8 g. of copper chromite in 200 ml. of rectified dioxane were shaken at 190° under hydrogen at an initial pressure of 125 atmospheres. The crude reduction product (78 g. from 3 runs) was fractionated at 184–189° (25 mm.) to give 55 g. of mixed, isomeric octahydroacridines which upon benzoylation afforded 38.2 g. (20% yield based on acridine) of twice crystallized (ethanol) *N*-benzoyl *asym*-octahydroacridine, m.p. 184–185° (lit.[4] m.p. 186–187°).

N-Acetyl asym-octahydroacridine. A mixture of 26 g. of the *N*-benzoyl derivative with 1 liter of 20% ethanolic potassium hydroxide was heated for 4.5 hr. (steam bath). With cooling, the solution was nearly neutralized by cautious addition of 180 ml. of glacial acetic acid and the system concentrated (vacuum) to *ca.* 300 ml. This was poured into 2.5 liters of 10% sodium chloride solution and the octahydroacridine collected, 16.4 g., m.p. 79–81° (lit.[4] m.p. 82°). Acetylation was effected by heating the latter 2 hr. with 50 ml. of acetic anhydride. The crude product (19 g.) was recrystallized from petroleum ether (30–60°) and obtained as thick, colorless prisms (16.5 g.), m.p. 85–87°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.6; H, 8.35. Found: C, 78.3; H, 8.13.

6-ω-Bromoacetyl-N-acetyl asym-octahydroacridine (I). Utilizing the customary Friedel-Crafts conditions, 36.5 g.

(1) Studies in the Acridine Series XI.

(2) (a) L. J. Sargent and L. F. Small, *J. Org. Chem.*, **13**, 447 (1948); (b) T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 583 (1949); (c) L. J. Sargent and L. F. Small, *J. Org. Chem.*, **19**, 1400 (1954); (d) L. J. Sargent, *J. Org. Chem.*, **21**, 1286 (1956).

(3) M. D. Eaton, F. S. Cheever, and C. G. Levenson, *J. Immunol.*, **66**, 463 (1951).

(4) H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

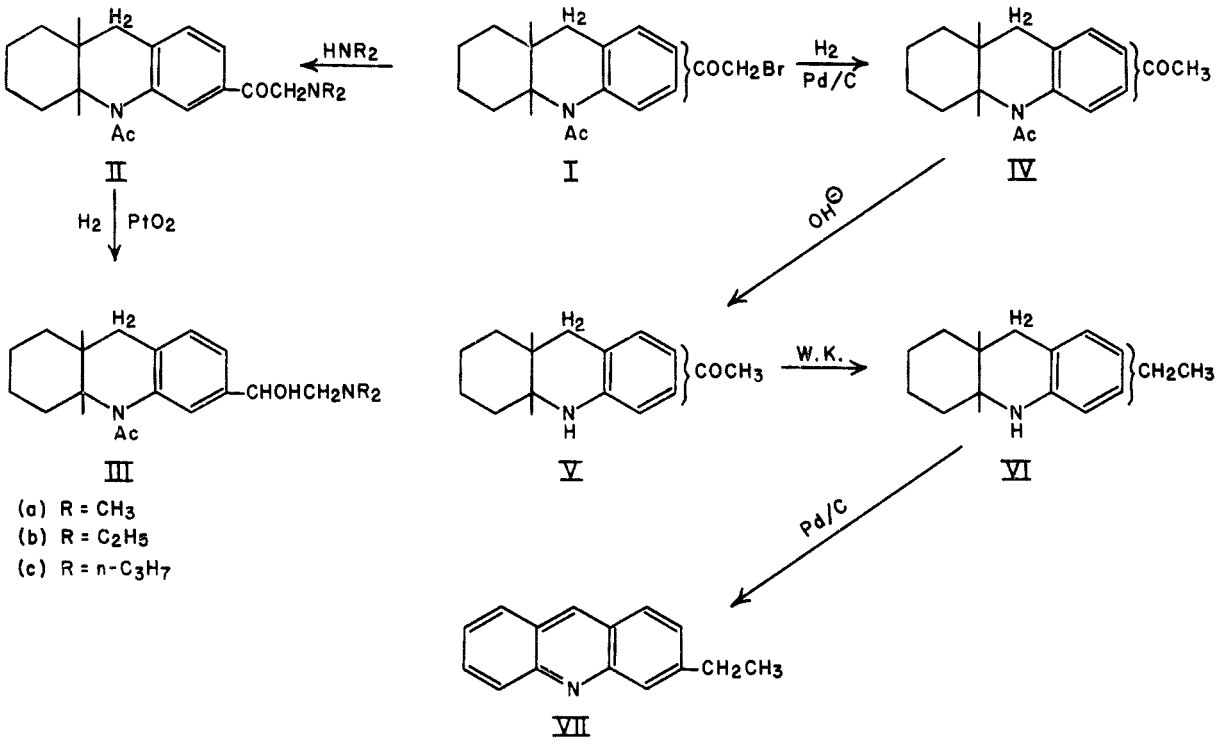
(5) L. J. Sargent, *J. Org. Chem.*, **19**, 599 (1954).

(6) W. Cocker, *et al.*, *J. Chem. Soc.*, 72 (1952).

(7) G. R. Coatney, National Institutes of Health, private communication.

(8) We are indebted to Drs. W. S. Boneice and A. Pohland, of the Lilly Research Laboratories, Indianapolis, Ind., for the virus screening tests.

(9) Analyses by the Analytical Services Unit of this Laboratory under the supervision of Dr. W. C. Alford. Melting points and boiling points are uncorrected.



(0.275 mole) of powdered anhydrous aluminum chloride was gradually added (during 45 min.) to a stirred mixture of 20.9 g. (0.091 mole) of powdered *N*-acetyloctahydroacridine and 20.3 g. (0.10 mole) of bromoacetyl bromide in 150 ml. of carbon disulfide. Ten minutes after the initial aluminum chloride addition, the temperature of the system was brought to and maintained at 50–60°. The reaction appeared to get under way when *ca.* one half of the catalyst had been added (as evidenced by the evolution of hydrogen bromide and the separation of a yellow gum). Stirring and heating were maintained for 1 hr. after the final aluminum chloride addition, and stirring continued for 0.75 hr. longer at 25°. After decanting the solvent, the residue was decomposed by adding it, portionwise, to a stirred slurry of ice and 2*N* hydrochloric acid. The precipitate was collected, washed with water, triturated twice with small portions of cold methanol, and air-dried, to give 26.6 g. of a nearly colorless powder, m.p. 118–135°. Recrystallization from acetone (Norit) afforded 12.3 g. (39%) of bromoketone (prisms), m.p. 168–172°. A sample was recrystallized again from acetone, m.p. 172–174°.

Anal. Calcd. for $C_{17}H_{20}BrNO_2$: C, 58.3; H, 5.76. Found: C, 58.2; H, 6.07.

6-Acetyl-N-acetyl asym-octahydroacridine (IV) *semicarbazone.* A suspension of 2 g. of powdered I in 100 ml. of 95% ethanol was shaken under hydrogen with 0.5 g. of 5% palladium-charcoal and 0.85 g. of powdered fused sodium acetate. The reduction was interrupted after the absorption of 1 mole of hydrogen (5 mins.). Concentration (vacuum) yielded a sirup which was taken up in 15 ml. of 90% ethanol and heated 2.5 hr. with 0.8 g. of semicarbazide hydrochloride and 0.6 g. of fused sodium acetate. The product obtained upon addition of water was collected and dried; yield 1.15 g. Recrystallization (methanol) gave 0.95 g. of prisms, m.p. 228–229°. After a second recrystallization, m.p. 235–237°.

Anal. Calcd. for $C_{18}H_{24}N_4O_2$: C, 65.8; H, 7.37. Found: C, 65.9; H, 7.34.

Regeneration of the ketone (IV). A mixture of 0.9 g. of the above semicarbazone with 15 ml. of glacial acetic acid, 0.85 ml. of 50% pyruvic acid[10] and 4.5 ml. of water was boiled (reflux) for 15 min. With ice-cooling, 15 ml. of water and a few drops of ether were added followed by the dropwise addition of 20 ml. (excess) of concd. ammonium hydroxide. The washed and dried precipitate (0.7 g., m.p. 110–112°) was evaporatively distilled at 120°/0.05 mm. to yield a colorless glass that crystallized when moistened and rubbed with a little absolute ethanol. A sample, dried at 70°/0.1 mm., showed m.p. 112–113.5°.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.2; H, 7.80. Found: C, 75.7; H, 8.00.

6-Acetyl asym-octahydroacridine (V). *N*-acyl hydrolysis was effected by heating 0.55 g. of IV in 12 ml. of 95% ethanol with 8 ml. of 10% ethanolic potassium hydroxide for 1 hr. (N_2 atm.). Dropwise addition of water precipitated a magma of tacky yellow needles which was collected and dried; 0.32 g. Recrystallization (methanol) gave 0.25 g. of pale yellow needles, m.p. 118.5–120°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.6; H, 8.35. Found: C, 78.9; H, 8.30.

6-Ethyl asym-octahydroacridine (VI). A mixture of V (0.13 g.), potassium hydroxide (0.15 g.) and 0.15 ml. of 85% hydrazine hydrate in 4 ml. of diethylene glycol was heated 4 hr. according to Huang-Minlon.[11] The addition of water precipitated a crystalline powder which was collected and dried; 0.11 g., m.p. 58–60°. A sample was sublimed at 60–70°/0.2 mm., m.p. 62–63°.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.7; H, 9.83. Found: C, 83.5; H, 9.86.

6-(or 3-) Ethylacridine (VII). A mixture of 0.2 g. of VI, 0.45 g. of 5% palladium-charcoal and 4 g. of diphenyl was heated at 250–260° (metal bath) for 2.5 hr. The cooled mass was taken up in 50 ml. of ether, filtered, and extracted with 5 × 10 ml. portions of 0.2*N* hydrochloric acid. After washing the combined extracts with ether, the basic material was recovered (ammonium hydroxide-ether) as a sirup (0.075 g.) that crystallized spontaneously. This was chromatographed on 3 g. of alumina, using benzene-ether (9:1) for elution. The slightly tacky crystals were triturated with a few drops of petroleum-ether (b.p. 30–60°) and then recrystallized from the same solvent to yield 0.05 g. of slender colorless prisms, m.p. 89–90°; undepressed when mixed with

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

(11) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

authentic 3-ethylacridine, m.p. 90–91°;[5] the respective infrared spectra were identical.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.9; H, 6.32. Found: C, 87.1; H, 6.45.

Similarly, the *perchlorate* of the dehydrogenation product (m.p. 181–182°) was indistinguishable from that of synthetic 3-ethylacridine perchlorate of m.p. 184–185°.[5]

6-(2-Dimethylamino-1-hydroxyethyl)-N-acetyl asym-octahydroacridine hydrochloride (IIIa). To an ice-cooled solution of 4 g. (*ca.* 6 moles) of dimethylamine in 125 ml. of dry ether (containing 3 ml. of 95% ethanol), 4 g. of powdered I was added and the system mechanically shaken for 15 hr. After removing dimethylamine hydrobromide (1.7 g. or 90%) the washed and dried ether solution afforded 3.5 g. of sirupy aminoketone. A solution of this in 15 ml. of acetone was acidified with 4 ml. of 2.2*N* ethanolic hydrogen chloride and strongly diluted with dry ether. Scratching induced the separation of the powdery hydrochloride. The salt was triturated twice with dry ether and the amino ketone regenerated (ammonium hydroxide-ether); yield 2.7 g. The latter, in 25 ml. of methanol with 0.15 g. of platinum oxide, absorbed 1.0 mole of hydrogen during 24 hr. and gave rise to 2.2 g. of sirupy aminoalcohol which, in 17 ml. of acetone, was acidified with 4 ml. of 2.2*N* ethanolic hydrogen chloride. Dropwise addition of dry ether (*ca.* 2 vols.) precipitated the crystalline hydrochloride; yield 1.5 g. Recrystallization from acetone gave 1.2 g. of colorless plates, m.p. 200–202°. Another recrystallization elevated the melting point to 204–206°.

Anal. Calcd. for $C_{19}H_{29}ClN_2O_2$: C, 64.7; H, 8.28. Found: C, 64.5; H, 8.17.

6-(2-Diethylamino-1-hydroxyethyl)-N-acetyl asym-octahydroacridine hydrochloride (IIIb). Employing the above procedure, the condensation of 5 g. of powdered I with 2.3 g. (2.2 moles) of diethylamine in 75 ml. of U.S.P. ether gave in the order named: 5.4 g. of crude amino ketone base (sirup); 5.5 g. of amino ketone hydrochloride and 4.9 g. of regenerated base. Reduction of the latter in 25 ml. of methanol with 0.2 g. of platinum oxide (0.88 mole of hydrogen absorbed in 40 hr.) yielded 3.8 g. of a sirup which, in 20 ml. of acetone, was acidified with 2.5 ml. of 5.4*N* ethanolic hydrogen chloride. Dilution with dry ether yielded a yellow gum that crystallized when scratched. Recrystallization (acetone-ether) gave 2.9 g. of colorless plates, m.p. 194–196°. After a second recrystallization the m.p. 200–201° was noted.

Anal. Calcd. for $C_{21}H_{33}ClN_2O_2$: C, 66.2; H, 8.73. Found: C, 65.8; H, 9.07.

6-(2-Di-n-propylamino-1-hydroxyethyl)-N-acetyl asym-octahydroacridine hydrochloride (IIIc). Five and one-half grams of powdered I was shaken with 3.45 g. (2.2 moles) of di-*n*-propylamine in 125 ml. of U.S.P. ether and, after the usual work-up, yielded in turn, 4.4 g. of crude amino ketone hydrochloride and 3.9 g. of regenerated amino ketone base which, in 25 ml. of methanol with 0.25 g. of platinum oxide, absorbed 0.9 mole of hydrogen (45 hr.) to give 3 g. of sirupy amino alcohol. The latter in acetone, gave an amorphous (gum) salt when treated with ethanolic hydrogen chloride and dry ether. Recrystallization (acetone-ether) yielded 2 g. of colorless prisms, m.p. 160–162°. Another recrystallization raised the m.p. to 166–168°.

Anal. Calcd. for $C_{23}H_{37}ClN_2O_2$: C, 67.5; H, 9.11. Found: C, 67.3; H, 9.08.

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[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

8-Selenapurines[1,2]

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Selenium-containing purine type compounds as possible antimetabolites for cancer therapy were prepared by reaction of 6-substituted 4,5-diaminopyrimidines with selenous acid. The compounds prepared were 6-amino-, 6-hydroxy-, and 6-morpholyl-8-selenapurine.

The carcinostatic activity resulting from the substitution of a nitrogen atom for the 8-carbon of guanine[5] made it of interest to introduce a more radical change in such compounds by substituting in this position an element less closely related to carbon and nitrogen. The element chosen was selenium.

The toxicity of selenium has been known for many years.[6] This was only of academic interest until it was realized that selenium is present in high concentrations in plants grown on soils rich in this element and that animals feeding on such plants become affected. The first report of the essential role of selenium in the animal body has recently been made.[7]

The approach used here has been the incorporation of the element selenium into heterocyclic systems which are related to known purine antimetabolites. These compounds are derivatives of 8-selenapurine, I. This ring system is shown as an ortho quinone since it is formed in a reaction analogous to the preparation of the known ortho quinone,2,1,3-benzoselenadiazole, II,[8-10] by the

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(5) R. W. Miner, (Editor), *Ann. N. Y. Acad. Sci.*, **60**, No. 2, 183 (1954).

(6) K. W. Frank, *J. Nutrition*, **8**, 597 (1934).

(7) K. Schwarz and C. M. Foltz, *J. Am. Chem. Soc.*, **79**, 3292 (1957).

(8) V. Luzzati, *Acta Cryst.*, **4**, 193 (1951).

(9) V. Luzzati, *Compt. rend.*, **226**, 738 (1948).

(10) V. Luzzati, *Compt. rend.*, **227**, 210 (1948).