drouracil gave 95–100% growth inhibition of these same organisms at a concentration of 1000 p.p.m. or greater.

The chlorine derivatives appear to be quite stable while the bromine compounds are somewhat less so. One sample of 4-methyl-1,3-dibromohydrouracil decomposed spontaneously after a few days while a companion sample remained undecomposed after some months. It would seem advisable that compounds of this type should be handled with some care.

EXPERIMENTAL[3]

1,3-Dichlorohydrouracil. Hydrouracil[4] (57 g., 0.5 mole) was suspended in one liter of water in a two-liter beaker furnished with a gas dispersion tube, a mechanical stirrer, and an addition funnel. The electrodes of a Beckman model H-2 *p*H meter were so arranged that the *p*H of the contents of the beaker could be followed continuously. Chlorine (75 g., 1.05 mole) was passed in over a 2-hr. period while 6*N* sodium hydroxide was added at such a rate as to maintain the *p*H of the reaction mixture in the range *p*H 1–3. The resulting solid was filtered off, washed with water, and dried. Yield 73 g. (80%). The solid crystallized from a mixture of chloroform and carbon tetrachloride to give white plates, m.p. 128–129°.

Anal. Calcd. for $C_4H_4Cl_2N_2O_2$: C, 26.2; H, 2.2; Cl, 38.8; N, 15.3; avail. Cl, 77.5. Found: C, 26.7; H, 2.4; Cl, 38.6; N, 15.2; avail. Cl., 76.5.

4-Methyl-1,3-dichlorohydrouracil. 4-Methylhydrouracil[5] (64 g., 0.5 mole) was chlorinated in the manner described above. A lower *p*H (1–2) seemed advantageous. The solid, after washing and drying, weighed 77 g. (78%). Crystallization from carbon tetrachloride gave white plates, m.p. 87–87.5°.

Anal. Calcd. for $C_5H_6Cl_2N_2O_2$: C, 30.4; H, 3.1; Cl, 36.0; N, 14.2; avail. Cl, 72. Found: C, 30.7; H, 3.0; Cl, 37.4; N, 14.2; avail. Cl, 71.7.

4-Methyl-1,3-dibromohydrouracil. 4-Methylhydrouracil (12.8 g., 0.1 mole) was suspended in 500 ml. of water in a one-liter beaker furnished as described above except that the gas dispersion tube was replaced with a second addition funnel. Bromine (37 g., 0.23 mole) was added dropwise over a one-hour period while the *p*H of the mixture was maintained in the range *p*H 6.5–8.6 by the addition of 6*N* sodium hydroxide. The pale yellow solid which remained after filtration, washing and drying, weighed 17.5 g. (61%) and melted at 130–131°.

Anal. Calcd. for $C_5H_6Br_2N_2O_2$: C, 21.2; H, 2.1; N, 9.8; avail. Br, 112. Found: C, 21.3; H, 2.0; N, 9.9; avail. Br, 111.

1,3-Dibromohydrouracil. Hydrouracil (11.4 g., 0.1 mole) was treated as above over a 1.8-hr. period. The pale yellow solid obtained after workup weighed 8 g. (30%) and melted 268–270° with decomposition.

Anal. Calcd. for $C_4H_4Br_2N_2O_2$: avail. Br, 118. Found: avail. Br, 117.9.

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(3) All melting points are uncorrected. Elemental analyses by Diamond Alkali Company Research Analytical Laboratory. Available halogen determinations by sodium thiosulfate titration. The percent available halogen is taken as twice the weight percent of halogen attached to nitrogen.

(4) J. S. Mackay and S. Frank, U. S. Patent 2,688,020 (1954).

(5) E. Fischer and G. Roeder, *Ber.* **34B**, 3751 (1901).

Synthesis of 3,8-Endomethylene-3-azabicyclo[3.2.1]octane (Cyclocamphidine)[1]

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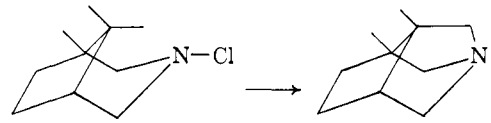
The free-radical chain decomposition of *N*-chloro secondary amines ("Hofmann-Loeffler-Freytag reaction")[2,3] has been used recently to effect the selective introduction of functional groups at the C_{18} (C/D fusion) angular methyl group in steroids.[4,5] We have also applied this useful technique in the camphor series to functionalize one of the "unactivated" π-methyl groups. Irradiation of *N*-chlorocamphidine (I) in sulfuric acid solution gave, after basification, a tertiary amine which was isolated as the crystalline hydrobromide in 67% yield. Chemical and physical evidence clearly show that the cyclocamphidine should be formulated as II. The infrared spectrum of the hydro-



I II

bromide lacks the absorption peak shown by camphidine hydrobromide at 1400 cm.$^{-1}$ which is characteristic of the *gem*-dimethyl grouping. The nuclear magnetic resonance spectrum of the cyclocamphidine hydrobromide (see Experimental) demonstrates the presence of only two methyl groups and is in complete accord with II.

The above synthesis of II, which doubtless can be effected conveniently on large scale from camphor, makes this one of the most readily available bridgehead amines.

EXPERIMENTAL

Camphidine hydrobromide. Camphidine, which has been prepared by the electrolytic reduction of camphoric imide,[6] was made by lithium aluminum hydride-reduction. Camphoric imide (6.2 g., 0.0343 mole) was dissolved in 150 ml. of tetrahydrofuran and added dropwise to a stirred slurry of 2.6 g. of lithium aluminum hydride in 75 ml. of tetrahydrofuran. The resulting mixture was refluxed with stirring for 11 hr., and then treated with water. The precipitate was

(1) This investigation was supported by fellowship AF-7544 to W. R. Hertler from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) (a) A. W. Hofmann, *Ber.*, **18**, 5, 109 (1885); (b) K. Loeffler and C. Freytag, *Ber.*, **42**, 3427 (1909); (c) K. Loeffler, *Ber.*, **43**, 2035 (1910).

(3) For a brief review see R. Lukes and M. Ferles, *Coll. Czech.*, **20**, 1227 (1955).

(4) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **80**, 2903 (1958).

(5) P. Buchschacher, J. Kalvoda, D. Arigoni and O. Jeger, *J. Am. Chem. Soc.*, **80**, 2905 (1958).

(6) J. Tafel and K. Eckstein, *Ber.*, **34**, 3274 (1901).

removed by filtration, and the filtrate was dried over potassium carbonate. Dry hydrogen chloride was bubbled through the dry solution, and the oil which separated was dissolved in 3*N* sodium hydroxide. The basic solution was extracted with ether-pentane. After drying over sodium sulfate, hydrogen bromide was passed into the solution, and the precipitated camphidine hydrobromide weighed 2.231 g. (28%). Crystallization from ethanol-ether gave granules, m.p. 304–307°, $[\alpha]_D^{29}$ +11.1° (50% ethanol, *c*, 3.2). No efforts were made to study the reduction with a view to determining optimal conditions.

Cyclocamphidine hydrobromide. Camphidine hydrobromide (968.3 mg., 4.14 mmol.) was chlorinated in pentane solution by the procedure of Coleman.[7] Removal of the solvent left an oil to which was added 30 ml. of 90% sulfuric acid cooled to 0°. The solution was placed in a quartz flask and irradiated with a mercury arc lamp at 0°. After 16 hr. the solution was poured onto ice and made alkaline with sodium hydroxide. The resulting suspension was heated to boiling, allowed to cool, and extracted twice with ether. Dry hydrogen bromide was passed into the ether solution, and the oily precipitate was stirred with 3*N* sodium hydroxide solution and 3 ml. of benzenesulfonyl chloride overnight. The solution was acidified with hydrochloric acid, and the benzenesulfonamide of secondary amine was removed by washing with ether. The aqueous solution was made alkaline with sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate, and dry hydrogen bromide was passed in. The amine hydrobromide was filtered and dried over phosphorus pentoxide at 0.1 mm. The product weighed 0.6444 g. (67%) and crystallized from ethanol-ether as microcrystals, m.p. 353–357° (dec.), $[\alpha]_D^{29}$ +2.4° (50% ethanol, *c*, 2.5).

Anal. Calcd. for $C_{10}H_{18}NBr$: C, 51.73; H, 7.81; N, 6.03. Found: C, 52.02; H, 7.78; N, 6.00.

Picrate, crystals from ethanol, m.p. 259.5–262° (dec.).

Anal. Calcd. for $C_{16}H_{20}N_4O_7$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.80; H, 5.34; N, 14.63.

The nuclear magnetic resonance spectrum of cyclocamphidine hydrobromide (in D_2O solution with methylene chloride as the external standard) had a split band at 62 cps. (at 40 megacycles), (+N—CH_2—), a split band at 116 cps. (CH_2), and a sharp doublet at 172 cps. (CH_3). The nuclear magnetic resonance spectrum of camphidine hydrobromide had split bands at 55–71 cps. (+N—CH_2—), a band at 111 cps. (CH_2) and a sharp triplet at 143, 149, and 151 cps. (CH_3). The ratio of the area under the peaks corresponding to +N—CH_2— to the area under the peaks corresponding to CH_3 in the product divided by the same ratio found in the starting material is equal to 2.66. The theoretical value based on the change camphidine → cyclocamphidine II is 2.25.

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(7) G. H. Coleman, G. Nichols, and F. F. Martens, *Org. Syntheses*, Coll. Vol. III, 159 (1955).

New Dihydrotriazines of Chemotherapeutic Interest

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From the urine of animals and human volunteers who had received chlorguanide, [1-(*p*-chlorophenyl) - 5 - isopropylbiguanide], Rose[1] and coworkers isolated a metabolite which they characterized as 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (I, free base, R_1 = Cl, R_2, R_3 = CH_3). In addition their studies indicated that this metabolite was ten times as active as the parent drug against infections of *P. gallinaceum* in chicks. Subsequent work by Carrington,[2] Loo,[3] Basu,[4] Modest,[5] and Lux[6] elaborated on the structure, synthesis, and chemotherapeutic activity of the above compound and of a number of its analogs.

Since work done in our laboratories had demonstrated the superior antibacterial properties of racemic *threo*-2-dichloroacetamido-1-(*p*-methylthiophenyl)-1,3-propanediols[7] as compared to the corresponding *p*-chloro analog,[8] it was considered of interest to examine the effect on chemotherapeutic activity of replacing the *p*-chloro atom in the chlorguanide metabolite by groups such as alkylthio as well as other suitable substituents. Accordingly we synthesized a number of compounds which may be represented by the general formula I and which are listed in Table I.

Preliminary testing[9] of the dihydrotriazine hydrochlorides against *P. lophurae* infections in ducks indicated a similar level of activity for the *p*-methylthio-2,2-dimethyl (Ia) and the *p*-chloro analogs.[1] However the latter proved to be considerably more toxic with evidence of toxicity even at the lower effective dose levels. The *p*-sulfamyl analog (Ie) showed slight[10] and the *p*-acetyl analog (Id) moderate antimalarial activity.[11]

It was also found that the *p*-methylthio-2,2-dimethyl compound (Ia) when combined with bithionol [2,2′-thiobis(2,4-dichlorophenol)] gave a synergistic or potentiated mixture having a greater anticoccidial effect in fowl than the sum of the anticoccidial effects of the individual ingredients.

Two of the hydrochlorides, the *p*-methylthio-2,2-dimethyl compound (Ia) and the *p*-methylthio-2-(*n*-propyl) compound (Ic), showed moderate anthelmintic activity against the oxyurid worms

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(3) T. L. Loo, *J. Am. Chem. Soc.*, **76**, 5096 (1954).

(4) U. P. Basu, A. K. Sen, and A. K. Ganguly, *Sci. and Culture (Calcutta)*, **18**, 45 (1952).

(5) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956); E. J. Modest and P. Levine, *J. Org. Chem.*, **21**, 14 (1956).

(6) R. E. Lux, *Antibiotics & Chemotherapy*, **4**, 971 (1954).

(7) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 5475 (1952).

(8) Ng. Ph. Buu-Hoï, Ng. Hoan, P. Jacquignon, and Ng. H. Khoï, *J. Chem. Soc.*, 2766 (1950).

(9) Preliminary testing of these compounds was done by the biology division of these laboratories.

(10) No report of antimalarial activity was given by Basu, *et al.* (ref. 4).

(11) This compound was found by Lux (ref. 6) to be inactive against *E. tenella* infections in chicks, but no report was made of its antimalarial activity.