washed successively (MeOH, hot H_2O). It was recrystallized from DMF–EtOH; yield 3.5 g (70%) as orange-red needles, mp 193–194°. *Anal.* ($C_{34}H_{25}N_5O$) C, H, N.

1-Thiocarbamoyl-3,5-diphenyl-4-phenylazopyrazole.—Thiosemicarbazide hydrochloride (2.5 g, 0.02 mole) was dissolved in H_2O (30 ml) and mixed with 1,3-diphenyl-2-phenylhydrazono-1,2,3-propanetrione (6.5 g, 0.02 mole) which is in turn prepared by coupling of 1,3-diphenyl-1,3-propanedione (4.5 g, 0.02 mole) with diazotized $PhNH_2$ (2.0 g, 0.02 mole) in absolute EtOH (20 ml). The mixture was allowed to condense at moderate temperature on a steam bath for 1 hr, and then kept for 2 hr at room temperature. It separated and was recrystallized (EtOH); yield 6.3 g (85%) as pale yellow needles, mp 187–188°. *Anal.* ($C_{29}H_{19}N_6OS$) N, S.

Similarly several 1-thiocarbamoyl-3,5-diphenyl-4-arylazopyrazoles were obtained; see Table II. Yields of the products depend upon the pH of the reaction medium. Best results were obtained at pH 4–5.

Acknowledgment. We wish to thank Professor W. U. Malik, Head of the Chemistry Department, for providing the necessary facilities for carrying out the work and the C.S.I.R., New Delhi (India), for a Junior Research Fellowship (held by R. A. S.).

Some Iodine Derivatives of Dibenamine

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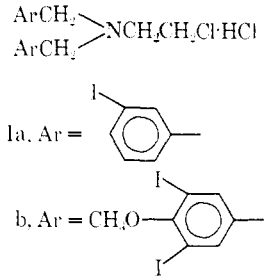
Though many derivatives of Dibenamine have been synthesized and evaluated biologically as adrenergic blocking agents, very few containing iodine have been prepared. We report here the preparation of two such compounds of potential interest. It is expected that the iodine atoms will confer sufficient electron density on the compounds to allow their localization in tissue by means of electron microscopy.



Experimental Section[1]

N,N-Bis(3-iodobenzyl)-2-chloroethylamine Hydrochloride (Ia).—*m*-Iodobenzyl bromide[2] (16.5 g, 0.056 mole) and 2-aminoethanol (3.4 g, 0.056 mole) were combined and heated on a steam bath for 12.5 hr. The product was dissolved in $CHCl_3$ and the solution was extracted with aqueous NaOH (pH 9) followed by dilute sodium thiosulfate. The $CHCl_3$ layer was dried ($MgSO_4$), the solvent was evaporated to 25 ml, and $SOCl_2$ (4.0 ml) was added. After stirring overnight at room temperature the solvent was removed under reduced pressure. The residue was dissolved in MeOH which was then evaporated *in vacuo*. Upon standing for a few days the mixture became crystalline. The crystals were triturated with C_6H_6 containing a slight amount of $CHCl_3$, yield 6.5 g. The compound was recrystallized from a minimum amount of $CHCl_3$ to which C_6H_6 was added until the turbidity point when hot; yield 5.1 g (33%). The melting point of the compound was indefinite and could not be used for characterization purposes. *Anal.* ($C_{16}H_{15}Cl_2I_2N$) C, H, N.

2-[N,N-Bis(3,5-diiodo-4-methoxybenzyl)]ethanolamine (IIa). 3,5-Diiodo-4-methoxybenzyl chloride[3] (4.4 g, 0.01 mole) and 2-aminoethanol (0.61 g, 0.01 mole) were allowed to react at 40°. The reaction proceeded over 3 hr during which time the temperature was gradually raised to 120°. The product was partitioned between C_6H_6 and 25% NaOH. The C_6H_6 layer was extracted with aqueous sodium thiosulfate and dried ($MgSO_4$). Removal of the C_6H_6 under reduced pressure left a brown residue which was triturated with EtOAc to yield 1.3 g (16%) of colorless crystals, mp 151–152°. *Anal.* ($C_{18}H_{19}I_4NO_3$) C, H, N.

N,N-Bis(3,5-diiodo-4-methoxybenzyl)-2-chloroethylamine Hydrochloride (Ib). Compound II (1.3 g, 1.6 mmoles) was dissolved in 15 ml of $SOCl_2$ and the solution was refluxed for 4 hr. Excess solvent was evaporated under reduced pressure. The residue was dissolved in a minimum of $CHCl_3$ and was chromatographed on silica gel with $CHCl_3$. The material separated into a slow-moving brown band and a rapidly moving broad yellow band. The eluent containing the latter band was collected and the solvent was evaporated. The compound was recrystallized from ether to yield 0.60 g (43%) of colorless crystals, mp 120–121°. *Anal.* Calcd for $C_{18}H_{19}Cl_2I_4NO_2 \cdot 0.25C_4H_{10}O$: C, 25.98; H, 2.47; N, 1.59. Found: C, 26.31; H, 2.21; N, 1.68.

Acknowledgment.—The authors are grateful to the School of Medicine for help from a general Research Support Grant.

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1-Methyl-4-[5(3)-methyl-3(5)-pyrazolyl]-quinolinium Iodide. An Analog of the Hypoglycemic Pyrazolylpyridinium Salts

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A number of 4-[3(5)-pyrazolyl]pyridinium salts (**1**), for instance, have been found to display interesting hypoglycemic activity in laboratory animals.[1] To determine whether this activity extends to the related quinolinium salt series, 1-methyl-4-[5(3)-methyl-3(5)-pyrazolyl]quinolinium iodide (**2**) was synthesized in two steps from the known[2] 4-acetoacetylquinoline. Compound **2**, when administered orally to male mice (Carworth Farms, 25–30 g) in saline solution at a dose of 1.5–3.0 mmoles/kg failed to depress blood sugar levels significantly below untreated controls when estimated by the method of Hoffman[3] as adapted to the Technicon Auto-Analyzer.[4]

(1) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc. Knoxville, Tenn. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

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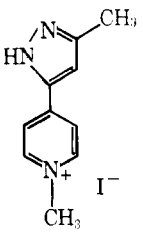
(4) Testing results were supplied by Drs. D. A. Blickens and S. J. Riggi of the Metabolic Chemotherapy Department of these laboratories.



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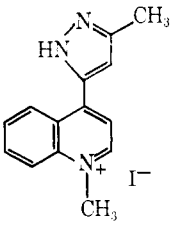

2

Experimental Section[5]

4-[5(3)-Methyl-3(5)-pyrazolyl]quinoline.—A mixture of 2.9 g (0.014 mole) of 4-acetoacetylquinoline[2] and 5.8 ml (0.12 mole) of 100% NH_2NH_2 was stirred at room temperature for 15 min, heated on a steam bath for 15 min, and diluted with H_2O. Filtration gave 2.1 g (66%) of tan crystals, mp 122–125°. Sublimation gave yellow crystals, mp 123–126°. *Anal.* ($C_{13}H_{11}N_3 \cdot H_2O$) C, H, N.

1-Methyl-4-[5(3)-methyl-3(5)-pyrazolyl]quinolinium Iodide.—A solution of 1.9 g (0.008 mole) of 4-[5(3)-methyl-3(5)-pyrazolyl]-quinoline, 10 ml of MeI, and 100 ml of EtOH was heated under reflux with stirring for 2 hr. The solvent was distilled, and the residue was triturated with Et_2O to leave 2.1 g of yellow crystals, mp 180–185°. Two recrystallizations (EtOH) gave 1.6 g (55%) of yellow crystals: mp 211–213° [*Anal.* ($C_{14}H_{14}IN_3 \cdot 0.5H_2O$) C, H, I, N]; uv (MeOH) 243 mμ (ε 30,900) and 352 mμ (ε 12,700), uv (0.1 *N* NaOH) 392 mμ (ε 14,100).

(5) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. Uv spectra were determined with a Cary 11 spectrophotometer by Mr. W. Fulmor and staff.

Some 9-(2,3,4-Tri-O-benzyl-D-arabinopyranosyl)purines[1]

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The arabinofuranoside of 6-mercaptopurine (6-MP) has interesting antitumor activity.[2] To compare the effect of a change in ring size, we recently synthesized the α- and β-arabinopyranosides of 6-MP (**1a** and **1b**).[3,4] We have now prepared their O-benzyl-blocked derivatives (**2a** and **2b**), whose greatly altered solubility properties may influence their biological properties. The synthesis of **2a** and **2b** became feasible when a practical separation of their precursors **3a** and **3b**[5] was found. The conversion of **3** by nitrous acid to **4** and the thiation of **4** to **2** proceeded in good yields by standard procedures. Compounds **2a**, **2b**, **4a**, and **4b** were inactive against leukemia L1210 in mice.[6]

(1) This work was carried out under the auspices of Chemotherapy, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the sponsoring agency.

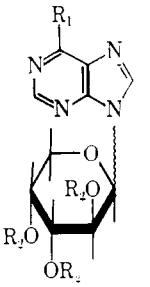
(2) A. P. Kimball, G. A. LePage, and B. Bowman, *Can. J. Biochem.*, **42**, 1753 (1964).

(3) A. P. Martinez and W. W. Lee, *J. Org. Chem.*, **34**, 416 (1969).

(4) The formulas are written in the completely aromatic form for convenience, although the 6-hydroxy and 6-thiol derivatives exist as the keto tautomers.

(5) A. P. Martinez, W. W. Lee, and L. Goodman, *ibid.*, **34**, 92 (1969).

(6) These compounds were screened for antitumor activity by Chemotherapy, National Cancer Institute, according to its protocol described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).



1. $R_1 = SH$; $R_2 = H$
2. $R_1 = SH$; $R_2 = CH_2C_6H_5$
3. $R_1 = NH_2$; $R_2 = CH_2C_6H_5$
4. $R_1 = OH$; $R_2 = CH_2C_6H_5$

a = α anomer

b = β anomer

Experimental Section[7]

Separation of 3a and 3b.—Column chromatography experiments with silica gel and alumina did not give good separation of these anomers. However, Florisil[8] was satisfactory. A synthetic mixture of 1.30 g of **3a** and 1.43 g of **3b** in 10 ml of warm toluene was placed on a 60-g column (2.2 × 47 cm) of 100–200 mesh Florisil[8] and eluted with Et_2O. The first fraction of 500 ml of eluent was discarded. The next two fractions of 1.1 l. of Et_2O and 250 ml of EtOAc–Et_2O (1:4) contained 1.32 g of **3b** (92.5% recovery). The fourth fraction, 100 ml of EtOAc–Et_2O (1:4), contained 0.09 g of **3a** and **3b**. The final two fractions of 500 ml of EtOAc–Et_2O (1:4) and 500 ml of EtOAc contained 1.21 g (93%) of **3a**. The separation was followed by tlc in solvent A with R_f 0.50 and 0.22 for **3b** and **3a**, respectively.

This procedure was applied to the crude reaction mixtures of **3a** and **3b**[5] from which about 10–15% of the less soluble **3a** had been first removed by fractional crystallization from toluene and ether.

9-(2,3,4-Tri-O-benzyl-D-arabinopyranosyl)hypoxanthine (4a and 4b).—Stirring 1.0 g (1.9 mmoles) of 9-(2,3,4-tri-O-benzyl-α-D-arabinopyranosyl)adenine (**3a**) with $NaNO_2$ (3.5 g, 40 mmoles) in 59 ml of AcOH, 50 ml of H_2O, and 2.5 ml of 1 *N* HCl for 24 hr afforded 60–70% of **4a**: mp 150–151° after recrystallization from toluene and trituration with Et_2O; $\lambda_{max}^{pH\ 1}$ 250 mμ (ε 11,200), $\lambda_{max}^{pH\ 7}$ 249 (11,800), $\lambda_{max}^{pH\ 13}$ 253 (13,600); $[\alpha]^{23}D$ −13.6° (*c* 1.38, CH_2Cl_2); R_f 0.10 in solvent A. *Anal.* ($C_{31}H_{30}N_4O_5$) C, H, N.

Compound **4b**, similarly prepared in 66% yield had mp 162–163° (triturated with Et_2O); $\lambda_{max}^{pH\ 1}$ 251 mμ (ε 11,200), $\lambda_{max}^{pH\ 7}$ 249 (12,000), $\lambda_{max}^{pH\ 13}$ 253 (13,800); $[\alpha]^{23}D$ +34.5° (*c* 1.50, CH_2Cl_2); R_f 0.34 in solvent A. *Anal.* ($C_{31}H_{30}N_4O_5$) C, H, N.

9-(2,3,4-Tri-O-benzyl-D-arabinopyranosyl)-9H-purine-6-thiol (2a and 2b).—A solution of 0.50 g (0.93 mmole) of **4b** and 1.7 g of P_2S_5 in 30 ml of dry C_5H_5N was heated at reflux for 3.5 hr under N_2 and then worked up to afford 0.48 g (93%) of **2b**, mp 177.5–179.0°. Recrystallization from EtOAc afforded 0.35 g (68%) of the β anomer **2b**: mp 199–200°; the solubility of **2b** was too low for determining λ_{max} at pH 1; λ_{max}^{MeOH} 322 mμ (ε 23,100), $\lambda_{max}^{pH\ 13}$ 313 (23,400); $[\alpha]^{21}D$ −21° (*c* 0.50, DMF); R_f 1.00 in solvent B. *Anal.* ($C_{31}H_{30}N_4O_4S$) C, H, N.

The preparation of the α anomer **2a** was similar except that a larger amount of P_2S_5 (3.0 g) for 0.50 g of **4a** was required for complete reaction. The yield was 0.37 g (72%) of the α anomer **2a**: mp 226–230°; $\lambda_{max}^{pH\ 1}$ 323 mμ (ε 20,300), $\lambda_{max}^{pH\ 7}$ 321 (19,300), $\lambda_{max}^{pH\ 13}$ 312 (21,600); $[\alpha]^{22}D$ +23° (*c* 0.50 DMF); R_f 0.81 in solvent B (R_f 0.31 for **4a**). *Anal.* ($C_{31}H_3PN_4O_4S$) C, H, N.

Acknowledgment.—The authors are indebted to Mr. O. P. Crews, Jr., and staff for the preparation of intermediates and to Dr. Peter Lim and staff for the spectra.

(7) Melting points were determined in a Fisher-Johns apparatus and are uncorrected. Tlc was run on silica gel HF (E. Merck AG Darmstadt) in the following solvents: A, EtOAc; B, MeOH–EtOAc (1:9). The spots were detected by uv light. For the uv spectra, the samples were dissolved in MeOH or 2-methoxyethanol and diluted either five- or tenfold with 0.1 *N* HCl pH 7 buffer or 0.1 *N* NaOH, as required. Where analyses are indicated only by symbol of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(8) Trade name for the magnesium silicate product of the Floridin Co.