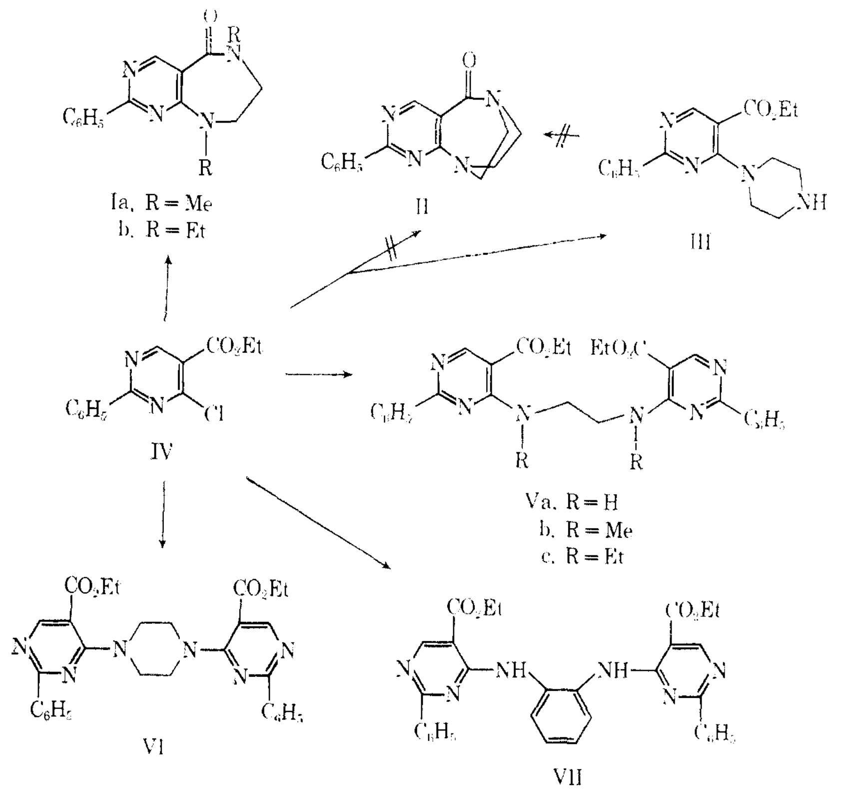
Scheme I



by Et_2O. Recrystallization of the product from cyclohexane afforded an analytical sample, mp 116–118°. *Anal.* ($C_{17}H_{20}N_4O$) C, H, N.

4-(1-Piperazinyl)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (III) was prepared as described for Ia in 75% yield, mp 101–104° (cyclohexane). *Anal.* ($C_{17}H_{20}N_4O_2$) C, H, N.

4,4′-(N,N′-Dialkylethylenediamino)bis(2-phenylpyrimidine-5-carboxylic acid) diethyl ester (Va–c, VI, and VII) were all made as exemplified by the preparation of **4,4′-(1,4-piperazinediyl)bis-(2-phenyl-5-pyrimidinecarboxylic acid) diethyl ester (VI)**. A mixture of IV (5.24 g), piperazine (0.86 g), and Na_2CO_3 (2.65 g) in 30 ml of DMF was heated at reflux for 1 hr. The reaction mixture was then poured into *ca.* 700 ml of cold water, and the precipitate which deposited was collected on a filter. Recrystallization of this material from EtOH afforded 2.1 g of product (see Table I).

Table I

4,4′-(N,N′-Dialkylethylenediamino)bis-(2-phenylpyrimidine-5-carboxylic acid) Diethyl Esters

Compd	Mp, °C	Recrystn solvent	Formula[a]
Va	169–172	EtOH	$C_{28}H_{28}N_6O_4$
Vb	157.5–159.5	EtOH–H_2O	$C_{30}H_{32}N_6O_4$
Vc	155.5–158	Cyclohexane	$C_{32}H_{36}N_6O_4$
VI	163.5–166	EtOH	$C_{30}H_{30}N_6O_4$
VII	178–179.5	EtOH	$C_{32}H_{28}N_6O_4$

[a] All compounds were analyzed for C, H, and N.

CNS Screening Procedure.—The compound is administered orally to three mice and watched for signs of general stimulation, general depression, and autonomic activity for at least 2 hr.

Acknowledgment.—The authors are indebted to Mr. B. Hofmann and associates for the elemental analyses, Mr. R. A. Fieber for his technical assistance, and Dr. M. I. Gluckman and staff for the pharmacological screening.

Potential Antineoplastics. I. 2-Amino-4,6-dimethyl-5-arylazopyrimidines and 1-Thiocarbamoyl-3,5-diphenyl-4-arylazopyrazoles

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It has been reported that an arylazo grouping is of interest in promoting antineoplastic activity.[1,2] This note lists the synthesis of arylazo derivatives of pyrimidine and 1-thiocarbamoylpyrazole ring systems.[3]

Experimental Section[4]

2,3,4-Pentanetrione 3-(2-Methoxyphenyl)hydrazone.—2-Methoxyaniline (2.5 ml, 0.02 mole) was dissolved in 3 *N* HCl (2.5 ml) and cooled to 0°. $NaNO_2$ (1.4 g, 0.02 mole) in H_2O (20 ml) was added gradually. The diazonium salt solution was filtered into a well-cooled, stirred mixture of NaOAc (5.0 g) and 1,3-dimethyl-1,3-propanedione (2.0 ml, 0.02 mole) containing EtOH (50 ml). The product precipitated almost immediately. After keeping for 2 hr, it was filtered, washed (H_2O), and recrystallized (EtOH); yield 4.0 g (86%) as yellow needles, mp 136°. *Anal.* ($C_{12}H_{14}N_2O_3$) C, H, N.

(1) E. J. Modest, H. N. Schlein, and G. E. Foley, *J. Pharm. Pharmacol.*, **9**, 68 (1957).

(2) R. E. Harmon, F. E. Dutton, and H. D. Warren, *J. Med. Chem.*, **11**, 627 (1968).

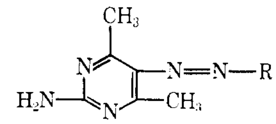
(3) P. N. Gordon, U. S. Patent 3,169,091 (Feb 9, 1965).

(4) All melting points are uncorrected and were determined using a Kofler hot stage type apparatus.

TABLE I

2,3,4-PENTANETRIONE 3-ARYLHYDRAZONES — 2-AMINO-4,6-DIMETHYL-5-ARYLAZOPYRIMIDINES

$RNHN{=}C(COCH_3)_2$

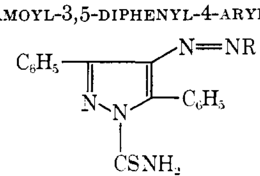


R	Mp, °C	Color[d]	Formula	Mp, °C	Yield, %	Color[d]	Formula
Phenyl	85	YN	$C_{11}H_{12}N_2O_2$[a]	230	70	OP	$C_{12}H_{13}N_5$[a]
2-MePh	110	YN	$C_{12}H_{14}N_2O_2$[a]	211	74	ON	$C_{13}H_{15}N_5$[a]
4-MePh	90	YN	$C_{12}H_{14}N_2O_2$[a]	247	75	ON	$C_{13}H_{15}N_5$[a]
2-ClPh	86	OYN	$C_{11}H_{11}ClN_2O_2$[b]	244	68	ORN	$C_{12}H_{12}ClN_5$[b]
3-ClPh	78	RYP	$C_{11}H_{11}ClN_2O_2$[b]	206	69	ORP	$C_{12}H_{12}ClN_5$[b]
4-ClPh	130	YN	$C_{11}H_{11}ClN_2O_2$[b]	213	70	YON	$C_{12}H_{12}ClN_5$[b]
2-BrPh	135	GYP	$C_{11}H_{11}BrN_2O_2$[b]	239	72	ORF	$C_{12}H_{12}BrN_5$[b]
4-BrPh	137	YN	$C_{11}H_{11}BrN_2O_2$[b]	217	65	ORN	$C_{12}H_{12}BrN_5$[b]
2-NO₂Ph	172	YP	$C_{11}H_{11}N_3O_4$[a]	257	60	ON	$C_{12}H_{12}N_6O_2$[a]
3-NO₂Ph	131	YP	$C_{11}H_{11}N_3O_4$[a]	260	65	OP	$C_{12}H_{12}N_6O_2$[a]
3-MeOPh	76	OYN	$C_{12}H_{14}N_2O_3$[a]	182	70	ORN	$C_{13}H_{15}N_5O$[a]
4-MeOPh	95	YN	$C_{12}H_{14}N_2O_3$[a]	213	72	YOP	$C_{13}H_{15}N_5O$[a]
4-EtOPh	118	BRN	$C_{13}H_{16}N_2O_3$[a]	209	70	ON	$C_{14}H_{17}N_5O$[a]
4-SO₂NH₂Ph	204	YP	$C_{11}H_{13}N_3O_4S$[c]	>280	65	ORN	$C_{12}H_{14}N_6O_2S$[c]
2,3-Me₂Ph	92	YN	$C_{13}H_{16}N_2O_2$[a]	224	65	ORP	$C_{14}H_{17}N_5$[a]
2,4-Me₂Ph	113	ON	$C_{13}H_{16}N_2O_2$[a]	228	68	RN	$C_{14}H_{17}N_5$[a]
2,5-Me₂Ph	103	YN	$C_{13}H_{16}N_2O_2$[a]	222	66	ORP	$C_{14}H_{17}N_5$[a]
2,6-Me₂Ph	98	YP	$C_{13}H_{16}N_2O_2$[a]	197	65	ORF	$C_{14}H_{17}N_5$[a]
2-Cl-6-MePh	72	YP	$C_{12}H_{13}ClN_2O_2$[b]	214	60	RBnN	$C_{13}H_{14}ClN_5$[b]
2-Cl-4-NO₂Ph	103	YP	$C_{11}H_{10}ClN_3O_4$[b]	266 dec	60	OYF	$C_{12}H_{11}ClN_6O_2$[b]
2,3-Cl₂Ph	104	YN	$C_{11}H_{10}Cl_2N_2O_2$[b]	230 dec	65	YOP	$C_{12}H_{11}Cl_2N_5$[b]
2,4-Cl₂Ph	135	ON	$C_{11}H_{10}Cl_2N_2O_2$[b]	274	70	OF	$C_{12}H_{11}Cl_2N_5$[b]
2,5-Cl₂Ph	121	PeYN	$C_{11}H_{10}Cl_2N_2O_2$[b]	245	72	ORF	$C_{12}H_{11}Cl_2N_5$[b]
3,5-Cl₂Ph	148	YN	$C_{11}H_{10}Cl_2N_2O_2$[b]	260 dec	68	ORN	$C_{12}H_{11}Cl_2N_5$[b]
2,4-Br₂Ph	162	ON	$C_{11}H_{10}Br_2N_2O_2$[b]	242	66	OP	$C_{12}H_{11}Br_2N_5$[b]
2,5-Br₂Ph	155	OYN	$C_{11}H_{10}Br_2N_2O_2$[b]	246	65	ORN	$C_{12}H_{11}Br_2N_5$[b]
2,4-MeO₂Ph	150	ON	$C_{13}H_{16}N_2O_4$[a]	182	60	YN	$C_{14}H_{17}N_5O_2$[a]
2,5-MeO₂Ph	129	GYN	$C_{13}H_{16}N_2O_4$[a]	190	65	OP	$C_{14}H_{17}N_5O_2$[a]
4-Cl-2,5-MeO₂Ph	170	OF	$C_{13}H_{15}ClN_2O_4$[b]	273 dec	56	OP	$C_{14}H_{16}ClN_5O_2$[b]

[a] Compounds were analyzed for C, H, N. Results were within 0.4% of calculated values. [b] *Anal.* N, Hal. [c] *Anal.* N, S. [d] B = bright, Bn = brown, F = fiber, G = golden, N = needles, E = orange, P = plates, Pe = pale, R = red, Y = yellow.

TABLE II

1-THIOCARBAMOYL-3,5-DIPHENYL-4-ARYLAZOPYRAZOLES — 1,3-DIPHENYL-2-ARYLHYDRAZONO-1,2,3-PROPANETRIONES



$RNHN{=}C(COC_6H_5)_2$

R	Yield, %	Mp, °C	Color[d]	Formula	Mp, °C	Color[d]	Formula
2-MePH	82	188	ORN	$C_{23}H_{19}N_5S$[a]	130	YN	$C_{22}H_{18}N_2O_2$[b]
4-MePh	80	214	GYN	$C_{23}H_{19}N_5S$[a]	121	BYN	$C_{22}H_{18}N_2O_2$[b]
3-ClPh	76	265	OYN	$C_{22}H_{16}ClN_5S$[c]	149	YN	$C_{21}H_{15}ClN_2O_2$[c]
4-ClPh	78	235	OYN	$C_{22}H_{16}ClN_5S$[c]	136	PeYF	$C_{21}H_{15}ClN_2O_2$[c]
4-BrPh	70	147	OYF	$C_{22}H_{16}BrN_5S$[c]	139	OYN	$C_{21}H_{15}BrN_2O_2$[c]
2-MeOPH	80	155	YN	$C_{23}H_{19}N_5OS$[a]	138	OYN	$C_{22}H_{18}N_2O_3$[b]
3-MeOPh	81	166	BnN	$C_{23}H_{19}N_5OS$[a]	156	YRN	$C_{22}H_{18}N_2O_3$[b]
4-MeOPh	80	151	YN	$C_{23}H_{19}N_5OS$[a]	137	BnYP	$C_{22}H_{18}N_2O_3$[b]
4-EtOPh	72	192	PeYP	$C_{24}H_{21}N_5OS$[a]	74	YN	$C_{23}H_{20}N_2O_3$[b]
3-NO₂Ph	65	139	ORN	$C_{22}H_{16}N_6O_2S$[a]	184	GYN	$C_{21}H_{15}N_3O_4$[b]
4-SO₂NH₂Ph	70	241	OP	$C_{22}H_{18}N_6O_2S_2$[a]	187	PeYN	$C_{21}H_{17}N_3O_4S$[a]
2,4-Me₂Ph	74	222	OYN	$C_{24}H_{21}N_5S$[a]	145	BnYN	$C_{23}H_{20}N_2O_2$[b]
2,5-Me₂Ph	75	154	ON	$C_{24}H_{21}N_5S$[a]	142	YN	$C_{23}H_{20}N_2O_2$[b]
2,6-Me₂Ph	80	138	YOF	$C_{24}H_{21}N_5S$[a]	125	PeYN	$C_{23}H_{20}N_2O_2$[b]
2-Cl-6-MePh	62	155	OYP	$C_{23}H_{18}ClN_5S$[c]	140	YN	$C_{22}H_{17}ClN_2O_2$[c]

[a] See footnote *c* of Table I. [b] See footnote *a* of Table I. [c] See footnote *b* of Table I. [d] See footnote *d* of Table I.

Similarly several 2,3,4-pentanetrione 3-arylhydrazones were prepared; see Table I.

2-Amino-4,6-dimethyl-5-(2-methoxyphenylazo)pyrimidine.— Guanidine nitrate (2.5 g, 0.02 mole) was added to 2,3,4-pentanetrione 3-(2-methoxyphenyl)hydrazone (4.68 g, 0.02 mole) containing 10 *N* NaOH (10 ml) and MeOH (15 ml). The mixture was stirred for 6 hr at 60–70°, and left for another 4 hr at room temperature. The product thus precipitated was collected and 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.* ($C_{19}H_{15}N_5O$) 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.* ($C_{22}H_{19}N_5OS$) 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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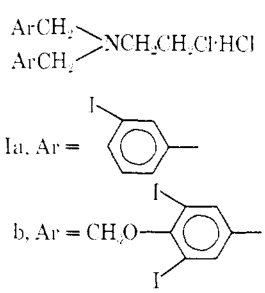
Though many derivatives of Dibenamine have been synthesized and evaluated biologically as adrenergic blocking agents, very few containing iodine have been prepared. We report here the preparation of two such compounds of potential interest. It is expected that the iodine atoms will confer sufficient 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.* ($C_{16}H_{17}Cl_2I_2N$) C, H, N.

2-[N,N-Bis(3,5-diiodo-4-methoxybenzyl)]ethanolamine (II). 3,5-Diiodo-4-methoxybenzyl chloride[3] (4.1 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.

(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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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]

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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.