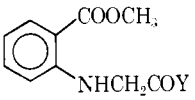
6 g, indicating a 90% completion of the reaction. Excess methyl anthranilate was removed by washing the C_6H_6 layer with 10% H_2SO_4, 10% Na_2CO_3, and H_2O. The C_6H_6 was dried, solvent was removed, and the resulting anilide was crystallized (EtOH), mp 158°, yield 6.3 g (66%). *Anal.* ($C_{17}H_{18}N_2O_4$) C, H, N.

TABLE II



No.	Y	Mp, °C	Recrystn[a] solvent	Yield, %	Formula[b]
1	NHPh	146	A	70	$C_{16}H_{16}N_2O_3$
2	$NHC_6H_4OCH_3$-*p*	158	A	66	$C_{17}H_{18}N_2O_4$
3	$NHC_6H_4OC_2H_5$-*p*	155	A	65	$C_{18}H_{20}N_2O_4$
4		152	A	60	$C_{14}H_{18}N_2O_4$
5	OCH_2Ph	77	C	55	$C_{17}H_{17}NO_4$

[a] A = EtOH, B = MeOH, C = C_6H_6–petroleum ether (bp 60–80°). [b] All compounds analyzed correctly for C, H, N.

(b) **3-Hydroxyindole-2-(N-*p*-methoxyphenyl)carboxamide.**—To a suspension of Na (0.26 g, 0.011 g-atom) in 20 ml of dry C_6H_6, a solution of *o*-carbomethoxyphenylglycine-*p*-methoxyanilide (3.14 g, 0.01 mole) in 15 ml of dry C_6H_6 and a few drops of absolute MeOH were added. The reaction mixture was warmed on a water bath with shaking for 30 min and then refluxed for 40 min under anhydrous conditions. After cooling, dry Et_2O was added, the Na salt was filtered and dissolved in a little cold H_2O, and the solution was acidfied with cold AcOH. The carboxamide which separated as a white precipitate was filtered, dried, and crystallized (MeOH), mp 238° (darkens at 225–236°), yield 1.63 g (58%). *Anal.* ($C_{16}H_{14}N_2O_3$) C, H, N.

The compounds listed in Table I were prepared by conversion of indole-2-carboxylic acid to the amides *via* the acid chlorides.

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Pyrimido[4,5-*e*][1,4]diazepin-5-ones and 4,4-Ethylenediaminobis(2-phenylpyrimidine-5-carboxylic acid) Diethyl Esters

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Since the discovery of the remarkable psychopharmacological activity of the 1,4-benzodiazepines,[1] work in this area has led to the development of several clinically useful drugs.[2] A pyridine analog, 1,3-dihydro-5-phenyl-2H-pyrido[4,3-*e*]-1,4-diazepin-2-one, has pharmacological effects in mice similar to those of the benzodiazepines.[3] No pyrimidine analog of the 1,4-benzodiazepines has yet been prepared for pharmacological evaluation.[4] This paper describes preliminary work on the synthesis of pyrimido[4,5-*e*][1,4]diazepin-5-ones and general CNS screening results.

Fusion of the diazepine ring to the pyrimidine nucleus was effected smoothly by allowing the 5-carbethoxy-4-chloro-2-phenylpyrimidine (IV) to react with N,N′-dialkylethylenediamine in ethanol under reflux (see Scheme I). Compound IV was obtained by treating 5-carbethoxy-4-hydroxy-2-phenylpyrimidine with $SOCl_2$. The pyrimidodiazepinone structures of Ia,b were confirmed by elemental analyses, ir lactam carbonyl absorption bands at 6.1 μ, and nmr spectra.

It was thought interesting to prepare the bicyclodiazepinone II, in which the two diazepine nitrogens of I are fixed rigidly by the ethylene linkage. Treatment of IV with piperazine under similar conditions used for the preparation of Ia,b, however, failed to give II, but afforded III. Attempted cyclization of III under various conditions was not successful.

When the reaction of IV with N,N′-dialkylethylenediamine was carried out in DMF, the reaction took an alternative path to form open-chain bis compounds Va–c which showed ir ester carbonyl absorptions at 5.86 μ. Similarly, piperazine and *o*-phenylenediamine yielded VI and VII, respectively, under these conditions. Ethylenediamine itself failed to afford a pyrimidodiazepine, but yielded only the open-chain bis compound Va.

Pharmacology.—In preliminary CNS screening, Ib showed moderate depressant activity accompanied by anticonvulsant effects. Compound Vc showed slight depressant activity.

Experimental Section[5]

5-Carbethoxy-4-chloro-2-phenylpyrimidine (IV).—A mixture of 5-carbethoxy-4-hydroxy-2-phenylpyrimidine[6] (73 g) and $SOCl_2$ (450 ml) was refluxed for 30 hr. The excess $SOCl_2$ was removed under reduced pressure, the residue was treated with a large amount of crushed ice, and the solid material was collected on a filter to give 75 g of product, mp 128–131°. Recrystallization of the product from petroleum ether raised the melting point to 130–131°. *Anal.* ($C_{13}H_{11}ClN_2O_2$) C, H, N.

6,9-Dimethyl-6,7,8,9-tetrahydro-2-phenyl-5H-pyrimido[4,5-*e*][1,4]diazepin-5-one (Ia).—Three grams of IV was added in small portions to a mixture of $MeNHCH_2CH_2NHMe$ (7.0 g) and Na_2CO_3 (0.6 g of powder) in 25 ml of absolute EtOH with vigorous stirring over a period of 10 min. Stirring was continued for another 25 min, then the mixture was heated to reflux for 15 min. The insoluble material was separated from the reaction mixture by filtration and the filtrate was chilled in ice. Crystals which deposited were collected on a filter and washed with absolute EtOH giving 3.0 g of product, mp 152–156°. Recrystallization of the product from cyclohexane gave an analytical sample: mp 155–157.5°; nmr (DMSO-d_6) δ 3.05 (s, 3 H, CH_3N), 3.27 (s, 3 H, CH_3N), 3.72 (s, 4 H, CH_2CH_2), 7.53 (m, 3 H, aromatic), 8.62 (m, 2 H, aromatic), and 8.82 ppm (s, 1 H, pyrimidine ring H). *Anal.* ($C_{15}H_{16}N_4O$) C, H, N.

6,9-Diethyl-6,7,8,9-tetrahydro-2-phenyl-5H-pyrimido[4,5-*e*][1,4]diazepin-5-one (Ib) was prepared as described for Ia. After the insoluble material was removed from the reaction mixture, the filtrate was concentrated under reduced pressure to an oil. Addition of water to the residual oil caused separation of a solid which was collected on a filter and washed with water, followed

(1) L. R. Hines, *Current Therap. Res.*, **2**, 227 (1960).

(2) (a) S. J. Childrss and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964); (b) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).

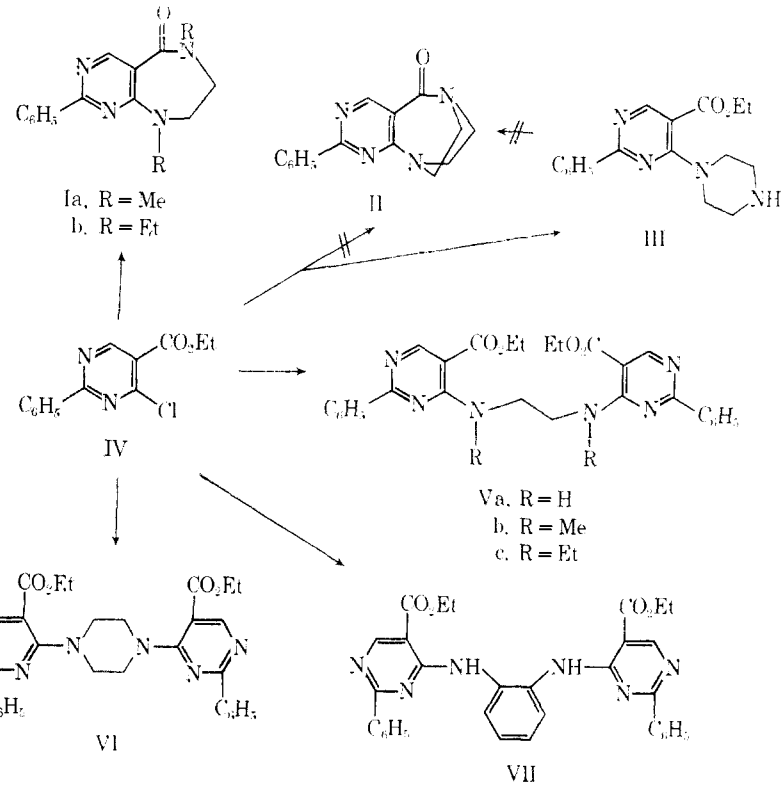
(3) R. Little and D. S. Allen, Jr., *J. Med. Chem.*, **8**, 722 (1965).

(4) The first report on this ring system describes the formation of 2-(2-hydroxyethyl)-3,8-dimethyl-4-formyl-4,5-dihydro-1H-pyrimido[4,5-*e*][1,4]-diazepine from thiamine by aqueous alkaline hydrolysis: H. Hirano, *Yakugaku Zasshi*, **77**, 1007 (1957).

(5) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Ir spectra (KBr) were obtained using a Perkin-Elmer Model 21 spectrophotometer, and nmr spectra (Me_4Si) were determined on a Varian A-60 spectrometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(6) P. C. Mitter and J. C. Bardhan, *J. Chem. Soc.*, 2179 (1923).

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.

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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.