The specific viscosities in 1% solutions in DMF for the three polymers are 0.1, 0.6, and 1.0; the average molecular weight of polymer C was calculated to be 43,000.

Determination of Chelating Abilities.—Solutions of 0.02 *N* acid were prepared of each polymer by refluxing an aqueous solution of 1.26 g of the polymer and diluting this to 1 l. at room temperature. This solution was titrated potentiometrically with 0.1 *N* base in order to determine the dissociation constants of the acids. The titration was repeated with Cu(II), Co(II), or Ni(II) ions as perchlorates. The difference in acidity of the solutions for the same amount of base added is an indication of the amount of chelation between the acid and the metal ions.

Synthesis of Metal Complexes.—Samples of each ethylene maleic anhydride copolymer were weighed carefully (6.3 g) and hydrolyzed in aqueous DMF by stirring and warming. A theoretical amount of $Cu(NO_3)_2$ (6.04 g), $CoCl_2$ (5.95 g), or $NiCl_2$ (5.95 g) was added to each solution of polymer and the pH was adjusted to 6 with KOH. The precipitated complex was separated by filtration and centrifugation, and dried to constant weight under vacuum. The salts were analyzed for metal by standard EDTA titrations.

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New Compounds

Synthesis of 3-Hydroxy- and 3-Methoxyindole-2-carboxamides and Esters

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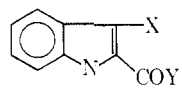
3-Alkoxyindole-2-carboxylates and -2-carboxamides have been shown to possess antiemetic properties.[1] Most of the compounds studied have alkyl or dialkylaminoalkyl side chains. In this communication the preparation of some 3-hydroxyindole-2-carboxamides with aromatic side chains is reported (Table I).

TABLE I



No.	X	Y	Mp, °C	Recrystn[a] solvent	Yield, %	Formula[b]
1	OH[c]	NHPh	220	A	58	$C_{15}H_{12}N_2O_2$
2	OH[c]	$NHC_6H_4OCH_3$-*p*	238	B	58	$C_{16}H_{14}N_2O_3$
3	OH[c]	$NHC_6H_4OC_2H_5$-*p*	206	B	60	$C_{17}H_{16}N_2O_3$
4	OH[c]		169–170	A	60	$C_{13}H_{14}N_2O_3$
5	OH	OCH_2Ph	152–153	C	51	$C_{16}H_{13}NO_3$
6	OMe	NHPh	176	A	52	$C_{16}H_{14}N_2O_2$
7	OMe	$NHC_6H_4OC_2H_5$-*p*	211	A	54	$C_{18}H_{18}N_2O_3$
8	OMe		150	A	55	$C_{14}H_{16}N_2O_3$
9	H	NHPh	200	A	76	$C_{15}H_{12}N_2O$
10	H	$NHC_6H_4OC_2H_5$-*p*	219	A	71	$C_{19}H_{16}N_2O_2$
11	H		179	A	73	$C_{13}H_{14}N_2O_2$

[a] A = EtOH, B = MeOH, C = C_6H_6–petroleum ether (bp 60–80°). [b] All the analyses were performed for C, H, and N and results were in the range ±0.4%. [c] These compounds first darken and then melt.

Experimental Section[2]

3-Methoxyindole-2-carboxamides (Table I).—Indoxylic ester was prepared by cyclization of *o*-carbomethoxyphenylglycine methyl ester in the presence of NaOMe.[3] The ester was methylated and hydrolyzed with ethanolic KOH.[4] 3-Methoxyindole-2-carboxylic acid (1 g, 0.005 mole) was converted to its acid chloride with $SOCl_2$ (1.42 g, 0.012 mole) in dry Et_2O. After standing for 1 hr at room temperature, Et_2O was removed under reduced pressure and the residual acid chloride was flushed with dry Et_2O to remove the last traces of $SOCl_2$. The acid chloride was then taken up in Et_2O and treated with ethereal $PhNH_2$ (0.96 g, 0.01 mole). The reaction mixture was left for 1.5 hr at 30°, Et_2O was removed, and the solid residue was washed (5% HCl, 5% $NaHCO_3$, H_2O), dried, and crystallized (EtOH), mp 176°, 0.66 g (52%). *Anal.* ($C_{18}H_{14}N_2O_2$) C, H, N.

3-Hydroxyindole-2-carboxamides (Table I).—Chloroacetyl derivatives of amines and benzyl alcohol were prepared by the usual methods.[5]

(a) *o*-Carbomethoxyphenylglycine-*p*-methoxyanilide (Table II).—Chloroacetyl-*p*-anisidine (6.0 g, 0.03 mole) and methyl anthranilate (18.12 g, 0.12 mole) were heated on a steam bath for 8 hr under anhydrous conditions. Dry C_6H_6 (100 ml) was added, and methyl anthranilate hydrochloride was filtered off. C_6H_6 was then removed under reduced pressure and the residue was heated again for another 6 hr and then the hydrochloride was removed as before. The hydrochloride which separated weighed

(1) Société d'Etudes scientifiques et industrielles de l'Ile-de-France, French Patent 1527 (Nov 12, 1962); *Chem. Abstr.*, **58**, 7911*a* (1963).

(2) Melting points are uncorrected.

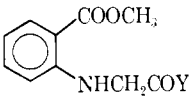
(3) A. Robertson, *J. Chem. Soc.*, 1937 (1927).

(4) N. T. Modi, *Ph.D. Thesis*, Aligarh Muslim University, 1966.

(5) (a) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 103 (1915); (b) P. Malatesta and G. Migliaceso, *Farmaco, Ed. Sci.*, **11**, 113 (1956); (c) A. L. Remizov and N. V. Khromov Borizov, *Zh. Obshch. Khim.*, **26**, 1471 (1956).

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).