5-Amino-6-oxo-1-phenyl-3-ethoxycarbonyl-1,6-dihydro-1,2,4-triazine (III). A 0.88 g portion (8 mmoles) of hydrazine II was added to a suspension of 1.37 g (4 mmoles) of triazine VI in 20 ml of absolute ethanol. The reaction mixture was held while stirring for 3 h at 20°C, and 0.18 g (17%) of triazine III was filtered off, which according to the IR spectrum and the melting point of a mixed sample was identical to an authentic sample [1]. The alcoholic mother liquor was evaporated, and the residue was ground with ether. From ether, a precipitate was filtered off which, according to the mass spectral data, contained hydrochloride VII. Mass spectrum of a base of VII, m/z (I, %): 108 $[M_{base}]^+$ (100), 92 $[PhNH]^+$ (40), 91 $[PhH]^+$ (14), 77 $[Ph]^+$ (41).

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SYNTHESIS OF TRICYLIC SYSTEMS INCORPORATING THE AZEPINE RING

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Some tricyclic compounds (derivatives of pyrazino[2,1-a]benzazepine, diazepino[7,1-a]isoquinoline, and some pyrimido[6,1-a]isoquinolines) which are analogs of the anthelmintic praziquantel have been synthesized.

Tricyclic compounds incorporating the benzene ring and nonaromatic six- and seven-membered diazaheterocycles have received much less attention than the corresponding bicyclic heterocycles. Nevertheless, several of them have shown biological activity of various types [1-4]. The most important of these is the hexahydropyrazino[2,1-*a*]isoquinoline praziquantel (Ia), an anthelmintic with a wide spectrum of action [5]. It was therefore of interest to examine related systems.

The aim of the present investigation was to obtain analogs of praziquantel (Ia), namely the pyrazinobenzazepine (Ib), diazepinoisoquinolines (II) and (III), and pyrimidoisoquinolines (XVIa, b) and (XVII) (see scheme on page 1384).

The pyrazinobenzazepine (Ib) was obtained by cyclization of the ω-hydroxylatam, with the intermediate formation of the acylammonium cation [6]. The synthesis of (Ib) by cyclization of the hydroxypiperazinone (IV) to the pyrazinobenzazepine (V) followed by removal of the protection and acylation has been described [1]. This reaction requires the intermediate forma-

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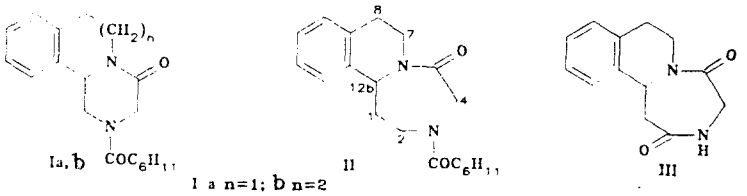
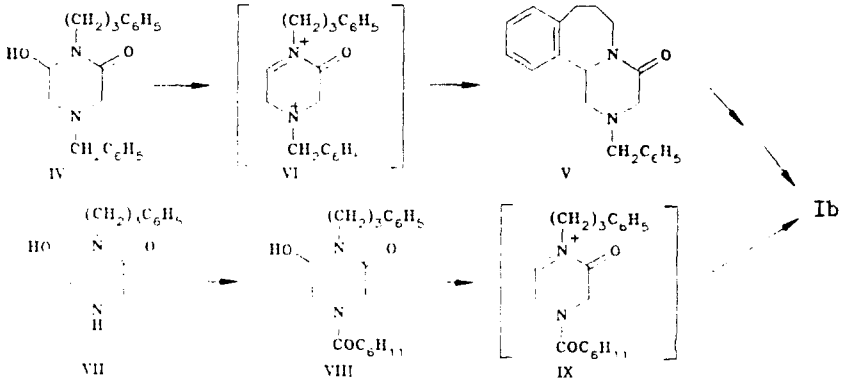
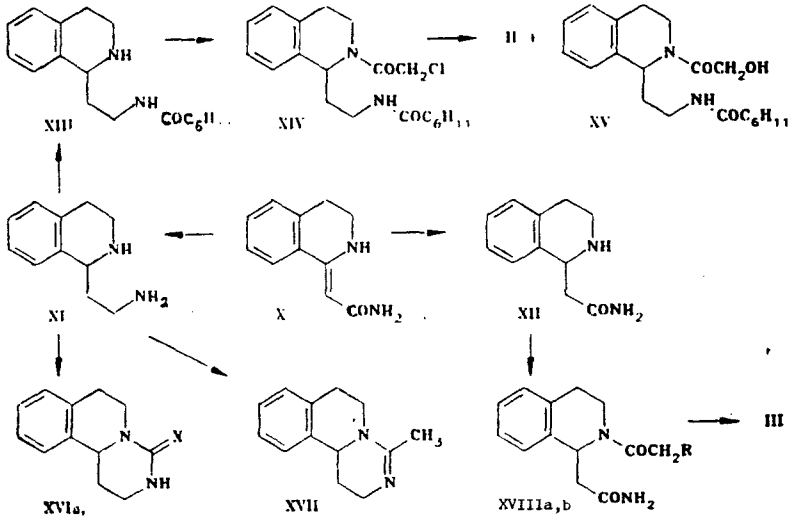


I a n=1; b n=2

tion of the dication (VI), so that the formation of the tricyclic compound (V) requires severe conditions (polyphosphoric acid, 160°C), and the yield is low (only 38%). We have devised a route involving cyclization of the compound (VIII), which is converted in HCl at 20°C (apparently via the monocation (IX)) into (Ib) in 59% yield:



The diazepinoisoquinolines (II) and (III) were obtained from (X) [7], which may be reduced either to the diamine (XI) [8], or the amide (XII). Selective acylation of the primary amino-group in (XI) with cyclohexylcarbonyl chloride afforded the monoacyl derivative (XIII) (cf. [9]), which on treatment with chloroacetyl chloride gave the diamide (XIV). Intramolecular cyclization of ω-haloamides has been effected by phase-transfer catalysis [10]. We adopted this simple method, using triethylbenzylammonium chloride as catalyst under a variety of conditions. In all cases, the diamide (XIV) gave a mixture of (II) and the hydrolysis product (XV), which was resolved by column chromatography. The highest yield of the diazepinoisoquinoline (II) (63%) was obtained in the system benzene–solid caustic alkali, the use of 50% aqueous sodium hydroxide giving mainly the compound (XV). The structure of (II) was confirmed by elemental analysis and IR and PMR spectroscopy. In the PMR spectrum, in addition to signals for the aromatic protons (a multiplet at 6.85-7.40 ppm), signals for the methine and methylene protons of the cyclohexane ring were seen as a multiplet at 0.9-2.0 ppm, and for the protons at $C_{1,2,4,7,8,\ 12b}$ (four multiplets in the range 2.5-5.0 ppm) (cf. [11]). In addition, the diamine (XI) was reacted with diethyl carbonate, formalin or triethyl orthoacetate to give the pyrazinoquinolines (XVIa, b) and (XVIII), respectively:



XVI a X=O; b X=H$_2$; XVIII a R=Cl; b R=OCH$_3$

Compound (III) was obtained by intramolecular cyclization of the chloroacetyl derivative (XVIIIa), which, unlike (XIV), did not require a phase-transfer catalyst, in the system methylene chloride–50% aqueous sodium hydroxide. The structure of the diazepinoisoquinoline (III) was confirmed by elemental analysis, IR and mass spectroscopy.

Attempts to form the 2,5-dioxodiazepine ring by heating the chloroacetyl derivative (XVIIIa) in sodium methoxide solution (cf. [12]) were unsuccessful, the methoxy-compound (XVIIIb) being the sole product.

EXPERIMENTAL

IR spectra were obtained on a UR-20 in KBr disks. PMR spectra were recorded on a Tesla BS-467 A spectrometer (60 MHz) in $CDCl_3$, internal standard HMDS. The mass spectrum was obtained on a Varian MAT-112 (West Germany) with direct sample introduction into the ion source. The ionizing electron energy was 70 eV, ionization chamber temperature 180°C. The reactions were followed and the purity of the products established by TLC on Silufol UV-254 plates in the system ether–acetone, 4:1, visualized with iodine vapor.

The elemental analyses were in agreement with the calculated values.

1-(3-Phenylpropyl)-6-hydroxypiperazin-2-one (VII, $C_{13}H_{18}N_2O_2$). To a solution of 4.8 g (15 mmoles) of (IV) [1] in 50 ml of alcohol was added 2 g of 5% Pd–C, and hydrogenation carried out at atmospheric pressure and 40-50°C. When uptake of hydrogen ceased (~5 h), the catalyst was filtered off, the alcohol removed under reduced pressure, and the residue recrystallized from benzene–hexane. Mp 89-90°C, IR spectrum: 3320-3370 (NH, OH), 1620 cm^{-1} (C=O). Yield 2.3 g (65%).

1-(3-Phenylpropyl)-4-cyclohexylcarbonyl-6-hydroxypiperazin-2-one (VIII, $C_{20}H_{28}N_2O_3$). To a solution of 2.3 g (10 mmoles) of (VII) in 50 ml of chloroform were added 1.7 ml (12 mmoles) of triethylamine and 1.6 ml (12 mmoles) of cyclohexanecarbonyl chloride with stirring at 20°C. The mixture was stirred for 2 h at 20°C, then washed with water (2 × 20 ml), 5% HCl (10 ml), water (30 ml), 5% NaOH (10 ml), and again with water (2 × 20 ml), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was recrystallized from benzene–hexane. Mp 107-108°C, IR spectrum: 3380-3550 (OH); 1645 cm^{-1} (C=O). Yield 2.3 g (68%).

2-Cylohexylcarbonyl-4-oxo-1,2,3,4,5,6,7,8,12*b*-octahydropyrazino[2,1-*a*][2]-benzazepine (Ib, $C_{20}H_{26}N_2O_2$). To 12 ml of concentrated sulfuric acid at 0°C was added 2.4 g (7 mmoles) of (VIII). The mixture was stirred for 1 h at 0°C, then for 2 h at 20°C, poured onto 100 g of ice, and extracted with methylene chloride (3 × 30 ml). The organic layer was separated, washed with 5% NaOH (2 × 20 ml) and water (2 × 20 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue recrystallized from ethyl acetate–hexane. Mp 187-189°C (the literature [1] gives 187-190°C). IR spectrum: 1660, 1641 cm^{-1} (C=O). Yield 1.3 g (59%).

1-Cyclohexylcarbonylaminoethyl-1,2,3,4-tetrahydroisoquinoline (XIII, $C_{18}H_{26}N_2O$). To a suspension of 6.5 g (25 mmoles) of (XI) dihydrochloride [8] in 75 ml of acetonitrile was added with stirring 12.5 ml (25 mmoles) of 2 N sodium hydroxide and 2.5 ml (30 mmoles) of pyridine. To the resulting solution was added over 1 h with stirring 5.4 ml (30 mmoles) of cyclohexanecarbonyl chloride, the mixture stirred for 3 h at 20°C, the acetonitrile removed under reduced pressure, the residue diluted with 100 ml of water, acidified with 25% HCl to pH 5-6, and extracted with ether (4 × 50 ml). The organic layer was separated, and the aqueous layer basified with 25% NaOH to pH 10. The oil which separated was extracted with methylene chloride (3 × 70 ml), the organic layer separated, washed with water (4 × 20 ml) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was triturated with ether, and the solid filtered off to give 4.0 g (57%) of product, mp 78-80°C. IR spectrum: 3350 (NH); 1655 cm^{-1} (C=O).

1-Cyclohexylcarbonylaminoethyl-2-chloroacetyl-1,2,3,4-tetrahydroisoquinoline (XIV, $C_{20}H_{27}ClN_2O_2$). To a solution of 5.6 g (20 mmoles) of (XIII) in 40 ml of methylene chloride was added 5.3 ml (100 mmoles) of 50% NaOH, then gradually with stirring over 15-20 min 1.8 ml (24 mmoles) of chloroacetyl chloride. When the addition was complete, the mixture was stirred for 1 h at 20°C, diluted with 50 ml of water, the organic layer separated, washed with water (2 × 30 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue boiled for 3-4 min with 20 ml of acetone, cooled, and the solid filtered off to give 4.5 g (64%) of product, mp 142-145°C. IR spectrum: 3340 (NH), 1660 cm^{-1} (C=O).

3-Cyclohexylcarbonyl-5-oxo-2,3,4,5,6,7,8,12*b*-octahydro[1,4]diazepino-[7,1-*a*]isoquinoline (II) and 1-Cyclohexylcarbonylaminoethyl-2-hydroxyacetyl-1,2,3,4-tetrahydroisoquinoline (XV). A. To a suspension of 0.36 g (1 mmole) of the diacyl compound (XIV) in 25 ml of benzene were added 0.3 g (7 mmoles) of powdered NaOH and 11.3 mg (5%) of triethylbenzylammonium chloride. The mixture was boiled with stirring for 6 h, cooled, 20 ml of water added, the organic layer separated, washed with water (10 ml), 5% HCl (10 ml), and again with water (2 × 10 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue (0.32 g, consisting according to TLC of

a mixture of two compounds with R_f 0.6 and 0.2) separated on a column (3 × 15 cm) of 100/250 μ silica gel, eluting first with chloroform, then after isolation of (II) with a mixture of chloroform and ethanol (95:5). There were obtained 0.2 g (63%) of (II) (R_f 0.6) and 0.07 g (20%) of (XV) (R_f 0.2). Compound (II), $C_{20}H_{26}N_2O_2$, mp 117-119°C, IR spectrum: 1660, 1645 cm^{-1} (C=O). PMR spectrum: 0.9-2.0 (11H, m, cyclohexane ring); 2.5-2.9 (2H, m); 3.4-4.0 (4H, m); 4.5-5.0 (2H, m); 6.8-7.4 ppm (4H, m, atom.). Compound (XV), $C_{20}H_{25}N_2O_3$, mp 92-95°C, IR spectrum: 3250-3600 (NH and OH), 1660, 1645 cm^{-1} (C=O).

B. To a solution of 0.36 g (1 mmole) of the diacyl compound (XIV) in 20 ml of methylene chloride was added 0.27 ml (5 mmoles) of 50% NaOH and 11.3 mg (5%) of triethylbenzylammonium chloride. The mixture was boiled with stirring for 6 h, and worked up as described in method A to give 0.09 g (28%) of (II) and 0.18 g (53%) of (XV).

1-Carbamoylmethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (XII, $C_{11}H_{14}N_2O \cdot HCl$). To a solution of 19.8 g (90 mmoles) of (X) hydrochloride [7] in a mixture of 120 ml of alcohol and 40 ml of water was added 1.8 g of Pd–C, and hydrogenation carried out at atmospheric pressure and 20°C until uptake of hydrogen ceased (2-3 h). The catalyst was then filtered off, the filtrate evaporated to dryness, and the residue recrystallized from alcohol to give 18.2 g (91%) of (XII) hydrochloride, mp 193-195°C, IR spectrum: 1680 cm^{-1} (C=O).

1-Carbamoylmethyl-2-chloroacetyl-1,2,3,4-tetrahydroisoquinoline (XVIIIa, $C_{13}H_{15}ClNO_2$). To a solution of 6.0 g (26 mmoles) of (XII) hydrochloride in 40 ml of methylene chloride was added with stirring 5 ml (95 mmoles) of 50% NaOH, followed over 15 min by a solution of 2.4 ml (32 mmoles) of chloroacetyl chloride in 10 ml of dry methylene chloride. The mixture was stirred for 40 min at 20°C, then diluted with 40 ml of water, the organic layer separated, washed with 5% HCl (2 × 10 ml) and water (2 × 20 ml), and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from chloroform–petroleum ether to give 6.6 g (93%) of product, mp 123-125°C, IR spectrum: 3360, 3200 (NH_2), 1690, 1645 cm^{-1} (C=O).

2,5-Dioxo-2,3,4,5,6,7,8,12*b*-octahydro[1,4]diazepino[7,1-*a*]isoquinoline (III, $C_{13}H_{14}N_2O_2$). To a suspension of 5.3 g (20 mmoles) of (XVIIIa) in 100 ml of methylene chloride was added 10 ml (180 mmoles) of 50% NaOH. The mixture was stirred for 3 h at 20°C, diluted with 70 ml of water, the organic layer separated, washed with water (2 × 40 ml), and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from alcohol to give 2.8 g (63%) of product, mp 178-180°C, IR spectrum: 3240 (NH); 1670, 1640 cm^{-1} (C=O). M^+ 230. M 230.

1-Carbamoylmethyl-2-methoxyacetyl-1,2,3,4-tetrahydroisoquinoline (XVIIIb, $C_{14}H_{18}N_2O_3$). To a solution of sodium methoxide, obtained from 0.12 g (5 mmoles) of sodium and 50 ml of methanol, was added 1.3 g (5 mmoles) of (XVIIIa). The mixture was stirred at the boil for 6 h, the methanol removed under reduced pressure, the residue diluted with 30 ml of water, extracted with methylene chloride (3 × 20 ml), the organic layer separated, washed with water (2 × 20 ml), and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from alcohol to give 0.77 g (54%) of product, mp 198-200°C, IR spectrum: 3370, 3190 (NH), 2840 (OCH_3), 1690, 1670 cm^{-1} (C=O).

4-Oxo-1,2,3,4,6,7-hexahydropyrimido[6,1-*a*]isoquinoline (XVIa, $C_{12}H_{14}N_2O$). To a solution of sodium ethoxide obtained from 2.8 g (120 mmoles) of sodium and 120 ml of absolute ethanol, was added 12 ml (100 mmoles) of diethyl carbonate followed by 2.5 g (11 mmoles) of (XI) dihydrochloride. The mixture was boiled for 5 h with stirring, then cooled and filtered. The filtrate was evaporated, and the residue treated with 100 ml of water. The resulting solution was extracted with chloroform (4 × 30 ml), and the chloroform solution dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 1.8 g (89%) of product, mp 149-151°C (from ethyl acetate), IR spectrum: 3210 (NH), 1660 cm^{-1} (C=O).

1,2,3,4,6,7-Hexahydropyrimido[6,1-*a*]isoquinoline (XVIb, $C_{12}H_{16}N_2$). To a suspension of 3.7 g (15 mmoles) of (XI) dihydrochloride in 20 ml of alcohol was added 4.5 ml (32 mmoles) of triethylamine. The mixture was stirred, and 35% formaldehyde (1.3 ml, 15 mmoles) added gradually. The resulting solution was stirred for 1 h at 100°C, then the alcohol was removed under reduced pressure. The residue was dissolved in 10 ml of water, and the solution basified with ammonia to pH 8-9. The solid which separated was filtered off and washed with water, mp 158-160°C (from alcohol), IR spectrum: 3450 cm^{-1} (NH). Yield 0.98 g (35%).

4-Methyl-1,2,6,7-tetrahydropyrimido[6,1-*a*]isoquinoline Hydrochloride (XVII, $C_{13}H_{16}N_2 \cdot HCl$). To a solution of 7.5 g (30 mmoles) of (XI) dihydrochloride in 20 ml of butanol was added 14.5 g (90 mmoles) of triethyl orthoacetate, and the mixture boiled for 15 h. The butanol was distilled off under reduced pressure, and the residue boiled for 2-3 min with 100 ml of acetone, cooled, and the solid filtered off. Mp 181-183°C (from propan-2-ol), yield 5.1 g (71%).

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AMINOMETHYLATION OF PEMOLINE

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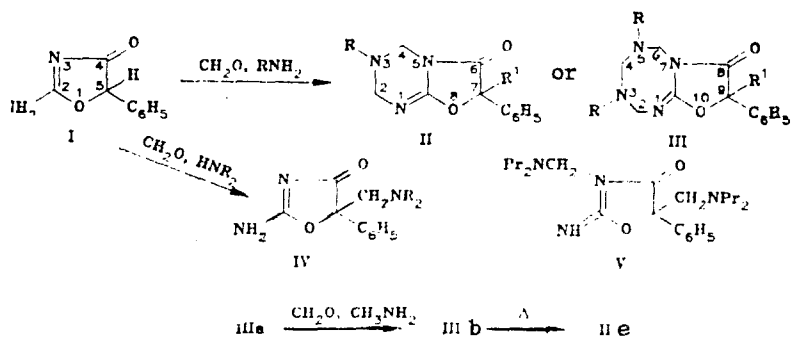
Aminomethylation of pemoline with primary amines has given the corresponding oxazolo[3,2-a]-1,3,5-triazines or oxazolo[3,2-a]-1,3,5,7-tetrazocines. When secondary amines were used, the 5-amino- or 3,5-bis(aminomethyl) derivatives were obtained.

2-Amino-5-phenyl-4-oxazolinone (pemoline, I) is an efficient psychic stimulant [1]. Its aminomethyl derivatives, which may be regard as prodrug forms of the compound [2], have not been examined. We here report the Mannich reaction of (I) with primary amines.

The structures of the Mannich bases obtained depend in the first instance on the amine used. When butylamine, tert-butylamine, N,N-dimethylpropane-1,3-diamine, or aniline is used as the amino-component, the oxazolo[3,2-*a*]-1,3,5-triazines (IIa-d) are obtained, while methylamine and cyclohexylamine give the oxazolo[3,2-*a*]-1,3,5,7-tetrazocines (IIIa-c) (Table 1).

The structures of compounds (IIa-d) were confirmed by the presence in their PMR spectra of signals for the protons of the two methylene groups of the annelated tetrahydrotriazine ring [3, 4] (Table 1), and for the protons of one R radical.

The PMR spectra of (IIa, b, d) also show pairs of doublets for the prochiral methylene protons of the $C_{(7)}$–CH_2OH methylene group, while that of (IIc) shows two doublets for the analogous protons of the $C_{(7)}$–$CH_2NHC_4H_9$-t aminomethyl group. In the IR spectra of this compound, the absorption for the nonassociated NH group at 3300 cm^{-1} is unusual in appearance, being narrow and intense.



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