2-Formyl-3-phenyl-5-chlorobenzofuran Isonicotinoylhydrazone (XXIII). A solution of compound XXIII (4.5 g, 0.0175 mole) and isonicotinic acid hydrazide (2.4 g, 0.0175 mole) in a mixture of ethanol (20 ml) and dioxane (10 ml) was refluxed for 3.5 h. After cooling the precipitate was filtered off. The yield was 3.7 g (54%), mp 150°C (from methanol). Found, %: C 64.21; H 4.09; Cl 9.00; N 10.67. $C_{21}H_{14}ClN_3O_2$. Calculated, %: C 64.04; H 4.09; Cl 9.00; N 10.67.

2-Formyl-3-phenyl-5-bromobenzofuran Nicotinoylhydrazone (XXIX) was prepared in the same way as compound XXVIII. The yield was 69%, mp 233-235°C. Found, %: C 57.93; H 3.64; Br 18.34; N 9.51. $C_{21}H_{14} \cdot BrN_3O_2 \cdot H_2O$. Calculated, %: C 57.55; H 3.68; Br 18.23; N 9.59.

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SYNTHESIS AND PHARMACOLOGICAL STUDY OF CONDENSED HETEROCYCLIC DERIVATIVES OF QUINUCLIDINE

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Earlier work has shown that 2-methylene-3-oxoquinuclidine (I), which is a bicyclic α, β-unsaturated ketone, readily adds nucleophiles – malonate esters, water, alcohols, amines, and phenols [1-6] – forming 2-substituted 3-oxoquinuclidines. We have attempted to move from the unsaturated ketone (I) to condensed heterocyclic derivatives of quinuclidine and to study their biological properties by examining the reactions of I with some bifunctional nucleophiles, notably o-phenylenediamine and its C-methyl derivatives.

o-Phenylenediamines react with I at both functional groups to form 11,11a-dihydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (II) and its 7,8-dimethyl derivative (III). We carried out the reaction at room temperature in protic (alcohols) and aprotic (dioxane) solvents. The yield of compound II was substantially lower in the latter.

We examined the properties of the synthetic polycyclic derivatives of quinuclidine. Compound II is unstable toward acidic reagents; ethereal or alcoholic hydrogen chloride cleaves II to form 2-[(2-aminophenyl)·amino]methyl-3-oxoquinuclidine dihydrochloride (IV), which regenerates the tetracyclic compound II on treatment with aqueous sodium bicarbonate. Compound II is stable toward weaker acids forming a tartrate with tartaric acid, and is also stable when heated with water. (see scheme on following page).

Sodium borohydride reduction of II and III generates the 4a,5,11,11a-tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepines (V) and (VI). The benzodiazepine compound (V) forms the 10-acetyl (VII) or 5,10-diacetyl (VIII) derivative, depending on the reaction conditions. Conversely heating with two equivalents of benzoyl

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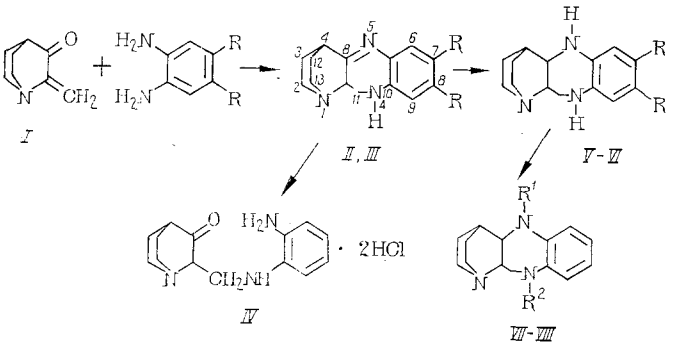

II : R = H; III : R = CH_3; VII : R^1 = H, R^2 = $COOH_3$; VIII : R^1 = R^2 = $COOH_3$;
IX : R^1 = H, R^2 = COC_6H_5; X : R^1 = H, R^2 = COC_6H_4Cl –p

chloride or p-chlorobenzoyl chloride in pyridine forms only the 10-benzoyl (IX) and 10-(p-chlorobenzoyl) derivatives. We were unable to carry out the reaction of II with 3,4,5-trimethoxybenzoyl chloride under equivalent conditions, recovering the original compound unchanged.

To verify the structure of the synthetic compounds, identify their configurations, and locate the acetyl substituent in the monoacetyl derivatives, we examined the ^1H- and ^{13}C-NMR spectra (Tables 1 and 2) of quinuclidinobenzodiazepines II, III, and V-X. The presence in the ^1H-NMR spectra of compounds II and III of the symmetrical quintet at $\delta \approx 2.76$ ppm with splitting about 2.2 Hz due to the proton in position 4 demonstrates the preservation of the quinuclidine ring, which has no hydrogen atoms at C_{4a}. This carbon atom is responsible for the signal at $\delta \approx 177$ ppm in the ^{13}C-NMR spectrum. This sort of chemical shift points to the presence of an exocyclic C=N bond at this position of the quinuclidine ring. In all these compounds the numbers of quaternary carbon atoms, CH, CH_2, and CH_3 groups derived from the ^{13}C-NMR spectra with partial proton decoupling, support the conjectured structures.

To locate the acyl substituent in the monoacyl derivatives VII, IX, and X we compared their ^1H-NMR spectra to that of diacetate (VIII). Of all the protons of the CH and CH_2 groups of the quinuclidine and azepine rings, one of the protons of the azepine CH_2 group appears furthest downfield – δ = 4.40, 4.69, and 4.71 ppm in monoacetates VII, IX, and X respectively. We may conclude that the downfield position of this signal in VII, IX, and X is due to the effect of the adjacent electronegative substituent, the acyl group at N10. This is supported by the ^1H-NMR spectrum of diacetate (VIII), in which the C_{4a}–H proton (δ = 5.09 ppm) lies furthest downfield of the signals of the quinuclidine and azepine rings, implying that an acetyl group is also present at N5 in compound VIII.

Compounds V-X, which contain two asymmetric carbon atoms, can exist as two diastereoisomers. The ^1H- and ^{13}C-NMR spectra show that the synthetic compounds are single diastereoisomers. We used the $J(H_{11a}H_{4a})$ coupling constant, which in the diacetyl compound (VIII) is ~ 10 Hz, to establish their configurations. The coupling constants $J^{cis}(H_2H_3) > 7$ Hz and $J^{trans}(H_2H_3) < 6.5$ Hz respectively are typical of the cis- and trans-isomers of 2,3-disubstituted quinuclidines [7, 8]. On this basis we assign the synthetic compounds V-X as the cis-isomers with respect to the C_{11a}–C_{4a} bond.

We then used the synthetic polycyclic quinuclidine derivatives, which incorporate the 1,5-benzodiazepine fragment (a component of numerous biologically active compounds) in pharmacological tests.

EXPERIMENTAL PHARMACOLOGY

Since active psychotropic preparations (neuroleptics, antidepressants, etc.) can be found among tricyclic compounds, we examined the newly synthesized compounds II, V, and VII-X in terms of indices of their general effect and several indices characterizing their psychotropic activity.

We examined the general effect and toxicity in white mice on subcutaneous and internal administration. In tests on mice we also examined the action of these compounds on the depressant effects of reserpine (hypothermia and ptosis, 2 mg/kg intraperitoneally), the effects of phenamine (hyperthermia, 7.5 mg/kg subcutaneously), effect of L-DOPA (hypothermia, 200 mg/kg intraperitoneally), the effect of apomorphine (hypothermia, 10 mg/kg subcutaneously), the convulsant activity of 5-hydroxytryptophan (head shaking, 50 mg/kg intraperitoneally), arecoline, and nicotine (hyperkinesia 15 and 10 mg/mg subcutaneously, respectively). We were thus able to assess the effect of the compounds on the central adreno-, dopamino-, serotonino-, and cholinoreactive structures. We also examined their effect on the length of hexenal-induced sleep (tests on rats, 50 mg/kg intravenously). Compounds II and V have LD_{50} 175 and 127 mg/kg, respectively, in mice on subcutaneous

TABLE 1. ^{1}H-Chemical Shifts of Quinuclidinobenzodiazepines II, III, and VII-X (δ, ppm)

Compound	11aH	$11CH_2$	4aH	4H	3, $13CH_2$	2, $12CH_2$	$H_{arom.}$	Other groups	Solvent
II	3,41	3,74; 3,50	—	2,76	~1,95	2,8—3,1	6,68; 7,00 6,82; 7,34	—	$CDCl_3$
III	3,35	3,72; 3,45	—	2,77	1,95	2,8—3,1	6,52; 7,08	2,17 (..... CH_3) (..... CH_3)	$CDCl_3$
VII	~3,50	4,43; ~3,60	~3,65	1,98	1,4—1,8	2,6—3,1	6,6—7,1	~3,85 (NH); 2,16 ($COCH_3$)	$CDCl_3$
VIII	3,66	4,75; 2,88	5,10	~1,80	0,9—1,9	2,1—2,8	7,0—7,2	1,81; 1,74 ($COCH_3$)	C_6D_5Br (90°C)
IX	~3,43	4,68; ~3,80	~3,90	2,05	1,3—1,9	2,6—3,1	6,4—7,5	—	$CDCl_3$
X	~3,40	4,67; 3,78	~3,90	2,08	1,35—1,9	2,6—3,2	6,4—7,5		$CDCl_3$

TABLE 2. ^{13}C-Chemical Shifts of Quinuclidinobenzodiazepines III, V, VII, and IX (δ, ppm)

Compound	C (quaternary)	CH	CH_2	CH_3	Solvent
III	177,07; 137,36; 135,36; 132,09; 126,93	132,72; 119,41; 66,11; 36,82	50,54; 49,16; 42,91; 27,36; 25,84	19,15; 18,39	$CDCl_3$ (30°C)
V	138,17; 136,68	120,64; 118,72; 118,58; 116,32; 59,75; 57,24; 28,06	48,46; 44,53; 41,92; 25,51; 19,87	—	$CDCl_3$ (30°C)
VII	170,31; 142,44; 127,90	127,26; 126,78; 117,37; 117,37; 56,49; 53,11; 27,85	48,02; 46,90; 41,96; 25,04; 19,80	22,83	$CDCl_3$ (30°C)
IX	168,97; 141,49; 136,15; 128,68	129,40; 128,85(2); 128,32; 127,58(2); 126,15; 117,56; 117,27; 57,77; 53,66; 28,03	49,10; 47,27; 42,02; 25,22; 19,92	—	$CDCl_3$ (30°C)

adminstration and compounds VII, VIII, and IX, 250, more than 500, mg/kg in mice on internal administration. The interaction with reserpine revealed that compound V (10 mg/kg subcutaneously) reduces blepharoptosis in mice from 3.7 ± 0.6 points to 2.2 ± 0.4 points while the other compounds have little effect on the action of reserpine.

None of these polycyclic quinuclidine derivatives have any marked effect on phenamine hyperthermia and L-DOPA and apomorphine hypothermia.

Compounds VII and IX enhance the convulsant activity of 5-hydroxytryptophan. Thus head shaking was apparent in five out of ten mice after adminstration of V (25 mg/kg internally) and in three out of ten mice after adminstration of IX (30 mg/kg internally). Head shaking was not observed in the control mice, which received only 5-hydroxytryptophan. The other compounds did not enhance the effect of 5-hydroxytryptophan. The tested quinuclidine derivatives did not reduce the intensity or duration of the convulsant activity of arecoline and nicotine and did not alter the length of hexenal sleep.

Thus, among these compounds, V displayed the elements of antidepressant activity antagonism of the effect of reserpine, enhancing the effect of 5-hydroxytryptophan . The other compounds are relatively inactive in terms of the chosen indices.

EXPERIMENTAL CHEMISTRY

The following spectra were recorded: IR: on a UR-20 as Vaseline oil mulls; ^{1}H NMR: on a Varian XL-100A-12 at 100 MHz and a Bruker WH-360 at 360 MHz; ^{13}C NMR: on a Varian XL-100A-12 at 25.2 MHz with complete and partial proton decoupling. The standard was tetramethylsilane (σ = 0); the solvents are listed in Tables 1 and 2.

11,11a-Dihydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (II). Method A. To a solution of o-phenylenediamine (2.6 g, 24 mmole) in methanol (30 ml) was added I (3.3 g, 24 mmole). The reaction mixture was kept at room temperature for 20 h. The precipitate was then filtered off. The yield was 3.87 g (70.5%), mp 213-215°C (with decomposition; from ethanol). IR spectrum (ν, cm^{-1}): 1652 (C=N), 3240 (NH). Found, %: C 73.86; H 7.37; N 18.24. $C_{14}H_{17}N_3$. Calculated, %: C 73.97; H 7.54; N 18.49.

Method B. A mixture of o-phenylenediamine (3.1 g, 27.8 mmole) and ketone I (3.9 g, 28.7 mmole) in ethanol (25 ml) was left at room temperature for 70 h. The yield was 5 g (77.3%), mp 213-215°C (with decomposition).

Method C. A mixture of o-phenylenediamine (2.6 g, 24 mmole) and ketone I (3.3 g, 24 mmole) in dioxane (20 ml) was left at room temperature for 70 h. The yield was 1.6 g (32.3%), mp 213-215°C (with decomposition).

Tartrate. To a suspension of II (0.5 g, 2.2 mmole) in ethanol (15 ml) was added a solution of d-tartaric acid (0.66 g, 4.4 mmole) in ethanol (10 ml). After 15 min stirring, the precipitate of base (II) disappeared and the tartrate began to precipitate from the homogeneous solution, being filtered off after 2 days. The yield was 0.76 g (91.5%), mp 180-182°C (with decomposition). Found, %: C 57.30; H 6.48; N 10.87. $C_{14}C_{17}N_3 \cdot C_4H_6O_6$. Calculated, %: C 57.40; H 6.16; N 11.14.

2-[(2-Aminophenyl)amino] methyl-3-oxoquinuclidine Dihydrochloride (IV). To a suspension of II (2 g) in ethanol (20 ml) was added alcoholic hydrogen chloride until acidic. The precipitate was triturated, kept at 4°C for 1 h, filtered off, and washed with acetone. The yield was 2.75 g (98%), mp 229-231°C (with decomposition; from 90% ethanol). IR spectrum (ν, cm^{-1}): 1700 (C=O), 3140, 3200-3400 (NH,NH$_2$). Found, %: Cl 22.13; N 13.14. $C_{14}H_{19}N_3O \cdot 2HCl$. Calculated, %: Cl 23.31; N 13.19.

Treatment of IV with 6% aqueous sodium bicarbonate regenerated the tetracyclic compound (II), mp 213-215°C (with decomposition).

7,7-Dimethyl-11,11a-dihydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (III). A solution of 4,5-dimethyl-1,2-diaminobenzene (1.9 g, 14 mmole) and I (1.92 g, 14 mmole) in methanol (10 ml) was left at room temperature for 70 h. The reaction mixture was evaporated under vacuum and the residue was triturated with ether. The yield was 2.5 g (65.3%), mp 180-182°C (from acetone). Found, %: C 75.31; H 8.26; N 16.33. $C_{16}H_{21}N_3$. Calculated, %: C 75.25; H 8.29; N 16.46.

4a,5,11,11a-Tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (V). To a suspension of II (4.2 g, 18.5 mmole) in ethanol (90 ml) was added, with stirring, sodium borohydride (2 g). Stirring was continued at room temperature for 6 h. The resulting solution was evaporated under vacuum and water (30 ml) was added to the residue, which was extracted with chloroform. The chloroform was stripped off and the residue was

triturated with ether. The yield was 3.1 g (73.5%), mp 140-142°C (with decomposition). IR spectrum (ν, cm^{-1}): 3280, 3370 (NH). Found, %: C 73.53; H 8.45; N 18.22. $C_{14}H_{19}N_3$. Calculated, %: C 73.52; H 8.35; N 18.33.

Dihydrochloride, mp 270-271°C (with decomposition). Found, %: C 55.74; H 7.13; Cl 23.78; N 13.92. $C_{14}H_{19}N_3 \cdot 2HCl$. Calculated, %: C 55.76; H 6.99; Cl 23.54; N 13.90.

7,8-Dimethyl-4a,5,11,11a-tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (VI). To a solution of III (1.1 g, 4 mmole) in ethanol (20 ml) was added, with stirring, sodium borohydride (1 g). The mixture was heated at 50°C for 1 h, left at room temperature for 20 h, and evaporated under vacuum. Water (20 ml) was added to the residue, which was then extracted with chloroform. The chloroform was stripped off and the residue was triturated with ether. The yield was 0.8 g (72%), mp 159-161°C (with decomposition). IR spectrum (ν, cm^{-1}): 3270, 3355 (NH). Found, %: C 74.70; H 8.86; N 16.41. $C_{16}H_{23}N_3$. Calculated, %: C 74.66; H 9.07; N 16.33.

10-Acetyl-4a,5,11,11a-tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (VII). A mixture of II (2.7 g, 12 mmole), acetic anhydride (6 ml), and dry pyridine (25 ml) was left at room temperature for 7 days. The reaction mixture was evaporated under vacuum. The residue was treated with 15% potassium carbonate solution (30 ml) and extracted with chloroform. The chloroform was stripped off and the residue was triturated with petroleum ether. The yield was 3 g (92.8%), mp 214-215°C (from acetone–ethanol). IR spectrum (ν, cm^{-1}): 1648 (N–C), 3360 (NH). Found, %: C 70.64; H 7.96; N 15.29. $C_{16}H_{21}N_3O$. Calculated, %: C 70.85; H 7.80; N 15.45.

Hydrochloride, mp 132-133°C (with decomposition; from ether–ethanol). Found, %: C 58.81; H 7.37. $C_{16}H_{21}N_2O \cdot HCl \cdot H_2O$. Calculated, %: C 58.98; H 7.42.

5,10-Diacetyl-4a,5,11,11a-tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (VIII). A solution of compound II (1 g, 4.4 mmole) in acetic anhydride (10 ml) was refluxed for 4 h and then evaporated under vacuum. The residue was triturated with ether. The yield was 1.1 g (84.7%), mp 190-191°C (from acetone). IR spectrum (ν, cm^{-1}): 1665 (N–CO, broad). Found, %: C 68.61; H 7.3; N 13.59. $C_{18}H_{23}N_3O$. Calculated, %: C 68.78; H 7.40; N 13.37.

Hydrochloride, mp 254-255°C (with decomposition; from ethanol–methanol). Found, %: Cl 10.09. $C_{18}H_{23} \cdot N_3O_2$. Calculated, %: Cl 10.13.

10-Benzoyl-4a,5,11,11a-tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (IX). A solution of II (1 g, 4.4 mmole), benzoyl chloride (1.23 g, 8.8 mmole), and dry pyridine (20 ml) was heated at 90-100°C for 5 h. The reaction mixture was evaporated under vacuum. The residue was made alkaline with 10% potassium carbonate solution and extracted with chloroform. The chloroform was stripped off and the residue was triturated with acetone. The yield was 1.1 g (75.5%), mp 264-265°C (from methanol). IR spectrum (ν, cm^{-1}): 1628 (N–CO), 3350 (NH). Found, %: C 75.35; H 6.83; N 12.42. $C_{21}H_{23}N_2O$. Calculated, %: C 75.65; H 6.95; N 12.60.

Hydrochloride, mp 290-292°C (from ethanol). Found, %: Cl 9.41. $C_{21}H_{23}N_3O \cdot HCl$. Calculated, %: Cl 9.58.

10-(p-Chlorobenzoyl)-4a,5,11,11a-tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (X) was prepared like compound IX. Chloroform was stripped off and the residue was triturated with petroleum ether and then recrystallized from methanol. The yield was 62%, mp 243-245°C. Found, %: C 68.66; H 6.24; Cl 9.73; N 11.30. $C_{21}H_{22}ClN_3O$. Calculated, %: C 68.55; H 6.02; Cl 9.63; N 11.42.

Hydrochloride, mp 215-217°C (with decomposition; from acetone–ethanol). Found, %: Cl 16.64. $C_{21}H_{22} \cdot ClN_3O \cdot HCl \cdot H_2O$. Calculated, %: Cl 16.80.

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