of vehicle without drug had no significant effect on the reaction time. The animal was considered to be analgesic if it exhibited a response greater than 4 s. If the animal did not respond in 15 s, the tail response was considered to be completely inhibited and the warm water was withdrawn. Subsequent measurements were taken until the animal elicited normal response.

Acknowledgment. Our thanks to Janssen Pharmaceutica, who kindly furnished a sample of ketone **1a**.

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Synthesis and Pharmacological Activity and Some Derivatives of 1-Phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one

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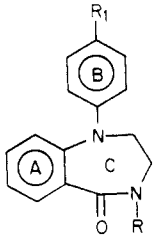
4-*N*-Alkylamino derivatives and corresponding ammonium quaternary salts of tetrahydro-1,4-benzodiazepin-5-one were synthesized and evaluated for psychotropic activity in mice by ip via. This study was also extended to some nitro and amino derivatives of tetrahydro-1,4-benzodiazepin-5-one. Compounds were devoid of tranquilizing activity and in comparison with two classical benzodiazepines, chlordiazepoxide and diazepam, they showed high toxicity and little or no effect on motor coordination, motor activity, and maximal electroshock. On some "in vitro" tests the compounds exhibited pharmacological properties when they were used at high concentrations.

At present a high number of molecules which belong to the class of 1,4-benzodiazepines are well known for their activity on the central nervous system.[1] In general, the sedative and tranquilizing activity of these compounds is such that their use in therapeutics is widespread. The compounds synthesized in our laboratories belong to the 1,4-benzodiazepine class (see structure A).



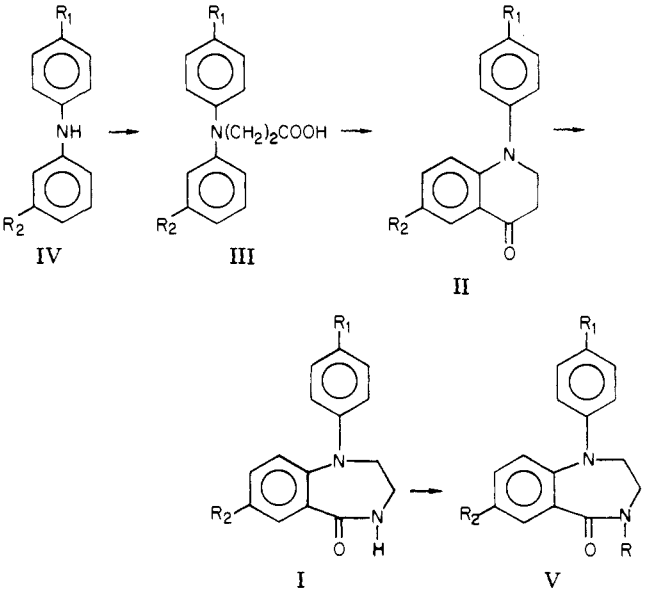
A

All the molecules possess the carbonyl group in position 5 and one phenyl group in position 1. In some cases the nitrogen atom in position 4 has been alkylated; the introduced side chain, linear or branched, contains at least 2 carbon atoms and either one aliphatic tertiary nitrogen atom or one which is part of a saturated heterocycle; the latter nitrogen atom may also be quaternized with methyl iodide. In some molecules nitro and amino groups have been introduced into rings A and B.

Chemistry. Compound I ($R_1 = R_2 = H$), from which most of the molecules described in this paper are derived, was prepared by starting from 1-phenyl-1,2,3,4-tetrahydroquinolin-4-one (II, $R_1 = R_2 = H$) by means of the Schmidt reaction under the conditions described by Misiti et al.[2] II was in turn prepared from diphenylamine in accordance with the general method described by Atwal et al.[3] for the preparation of tetrahydroquinolones (sequence IV → III → II, Scheme I).

The compounds studied in our laboratories are essentially *N*-alkylamino derivatives of benzodiazepinone I which are obtained by N-alkylation with ω-bromoalkyl tertiary amines[4] in the presence of sodium amide[5,6]

Scheme I



(compounds **1–6**, Table I). The latter, after treatment with methyl iodide,[7] gives the corresponding quaternary ammonium salts (compounds **7–12**, Table I).

In particular, the above compounds have the general formula V in which R represents the substitutions shown in Table I. The nitration of the starting quinolinone II ($R_1 = R_2 = H$) brings about the preferential formation of a dinitro derivative (II, $R_1 = R_2 = NO_2$) with nitro groups in the two aromatic rings, i.e., in position 6 and in position 4′. The structure of the dinitroquinolinone II ($R_1 = R_2 = -NO_2$) was assigned mainly on the basis of NMR data. Indeed, in the aromatic region of the NMR spectrum, a quartet of an AA′BB′ system at δ 8.03 (J_{AB} = 9 Hz), integrated for four protons, is present. This quartet should be assigned to the protons of a para-substituted aromatic ring bonded to the nitrogen atom.

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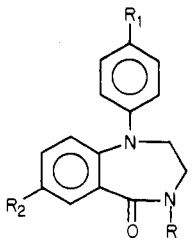
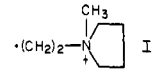
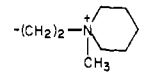
Table I



No.	R	R_1	R_2	Mp, °C	Purifcn solvent	Formula
1	$-(CH_2)_2N(CH_3)_2$	H	H	124-126	Hexane	$C_{19}H_{23}ON_3$
2	$-(CH_2)_3N(CH_3)_2$	H	H	125-127	Petr ether	$C_{20}H_{25}ON_3$
3	$-CH(CH_3)CH_2N(CH_3)_2$	H	H	107-108	Hexane	$C_{20}H_{25}ON_3$
4	$-(CH_2)_2N(CH_2CH_3)_2$	H	H	84-85	Hexane	$C_{21}H_{27}ON_3$
5	$-(CH_2)_2$-c-NC_4H_8	H	H	138-140	Petr ether	$C_{21}H_{25}ON_3$
6	$-(CH_2)_2$-c-NC_5H_{10}	H	H	118-120	Petr ether	$C_{22}H_{27}ON_3$
7	$-(CH_2)_2N^+(CH_3)_3$ I^-	H	H	256-258	Acetone	$C_{20}H_{26}IN_3O$
8	$-(CH_2)_3N^+(CH_3)_3$ I^-	H	H	258-259	Acetone	$C_{21}H_{28}ON_3I$
9	$-CH(CH_3)CH_2N^+(CH_3)_3$	H	H	224-226	Acetone	$C_{21}H_{28}ON_3I$
10	$-(CH_2)_2N^+CH_3[(CH_2CH_3)_2]$ I^-	H	H	190-192	Acetone	$C_{22}H_{30}N_3OI$
11		H	H	176-178	Acetone	$C_{22}H_{28}ON_3I$
12		H	H	190-192	Acetone	$C_{23}H_{30}ON_3I$
13	H	NO_2	NO_2	184-186	MeOH-*i*-PrOH	$C_{15}H_{12}N_4O_5$
14	H	NO_2	NH_2	243-245		$C_{15}H_{14}O_3N_4$
15	H	NH_2	H	268-270	EtOH	$C_{15}H_{15}ON_3$
16	H	$NHCOCH_3$	H	260-262	*i*-PrOH	$C_{17}H_{17}N_3O_2$

Moreover, the following ABX system was present: a doublet at δ 8.58 assigned to the aromatic proton in position 5 ($J_{H\text{-}5\text{-}H\text{-}7} \equiv J_{meta}$ = 3.5 Hz), a quartet at δ 8.12 assigned to the aromatic proton in position 7 ($J_{H\text{-}7\text{-}H\text{-}5} \equiv J_{meta}$ = 3.5 Hz and $J_{H\text{-}7\text{-}H\text{-}8} = J_{ortho}$ = 9 Hz), and finally one doublet at δ 6.98 assigned to the aromatic proton in position 8 ($J_{H\text{-}8\text{-}H\text{-}7} \equiv J_{ortho}$ = 9 Hz). The nitration carried out under milder conditions also gives the mononitro derivative in position 6, though at lower yields. The NMR spectrum of this mononitroquinolinone shows three characteristic signals of the aromatic protons respectively in positions 5, 7, and 8 (ABX system) which are identical with those present in the NMR spectrum of the dinitroquinolinone previously described.

On the contrary, in the same NMR spectrum, the characteristic AA'BB' system quartet of the para-substituted aromatic ring of the dinitroquinolinone is absent and a broad signal, integrating for five protons, occurs at δ 7.63.

The dinitroquinolinone is then converted into the benzodiazepinone **13** similarly to the other quinolinones which do not contain nitro groups. Consequently, the two nitro groups of the benzodiazepinone **13** resulted in positions 4' and 7, respectively. It is important to point out that the NMR spectrum of the last compound shows a significant change of the chemical shift of the signals assigned to the protons of the aromatic ring (H-6, H-8, and H-9) in comparison with the corresponding protons in positions 5, 7, and 8 of the starting quinolinone; at the same time no significant change for the aromatic protons of AA'BB' system occurs.

Alternatively, in order to obtain the dinitrobenzodiazepinone **13**, direct nitration on compound I ($R_1 = R_2$ = H) was attempted, but in this case, even under controlled conditions, complex nitrate mixtures are achieved and it is difficult to separate the individual compounds.

Dinitrobenzodiazepinone **13**, even when employing different reaction conditions, is partially reduced, giving only monoaminobenzodiazepinone **14** in which the $-NO_2$ group in position 7 is converted to $-NH_2$.

Also, structure **14** is supported by spectroscopic data. Indeed, the NMR spectrum shows a quartet (AA'BB' system) at δ 7.37 (J_{AB} = 9 Hz) in the aromatic region, identical with that present in the NMR spectrum of the dinitro derivative **13** which was assigned to the protons of the para-substituted aromatic ring. Moreover, a broad signal at δ 6.9 which should be assigned to the three protons of aromatic ring (H-6, H-8, and H-9) substituted with the $-NH_2$ group in position 7 was also present.

Lastly, even for obtaining the acetamidobenzodiazepinone **16**, it was necessary to prepare the acetamidoquinolinone II (R_1 = NHAc; R_2 = H) from the *p*-acetamidodiphenylamine IV (R_1 = NHAc; R_2 = H), in accordance with the above method. Generally, two different quinolinones are formed by ring closure;[8] in this case only one quinolinic ring was observed. Indeed, acetamidoquinolinone II ($R_1 = NHCOCH_3$; R_2 = H) was the only compound obtained and no amount of isomer II (R_1 = H; $R_2 = NHCOCH_3$) was present. The NMR spectrum was consistent with the structure assigned to the quinolinone II ($R_1 = NHCOCH_3$; R_2 = H). This last compound shows, in the aromatic region, a quartet (AA'BB' system) at δ 7.42 (J_{AB} = 9 Hz) assigned to the four protons of the para-substituted aromatic ring, as present in $>N\text{-}C_6H_4\text{-}p\text{-}NHCOCH_3$.

Moreover the NMR spectrum showed a pattern of signals, assigned to the four protons of the benzocondensed ring which were identical with those present in the NMR spectra of the unsubstituted tetrahydroquinolinones.[2,3,9,10] Compound **16** was obtained by the usual method; in consequence the acetamido group position will be unequivocally defined. The acidic hydrolysis of **16** brings

about the formation of compound **15**. The characteristics of the synthesized compounds are shown in Table I.

In the NMR spectra compounds **1–12** exhibit signals relative to the protons belonging to the 1,4-benzodiazepin-5-one group[2] and to the five protons of the aromatic B ring. The characteristic signals belonging to the protons of R for compounds **1–12** are in agreement with the proposed structures. NMR data for protons belonging to molecules **13–16** are reported in the Experimental Section. In the IR spectra all the compounds display the characteristic carbonyl band ν_{CO} at about 1630 cm^{-1} as well as the aromatic band.

Pharmacology. A preliminary pharmacological study of the new compounds was designed to investigate the acute toxicity and the following effects—tranquillizing, anxiolitic, and anticonvulsant—which are characteristic of the classic benzodiazepines: chlordiazepoxide, diazepam, etc. LD_{50}[11] was evaluated and behavioral changes were examined[12] together with the effects on spontaneous motor activity,[13] on motor coordination,[14] on barbiturate-induced sleep,[15] and on convulsive activity[16] due to cardiazol, strychnine, and electroshock.

The compounds (Table II) exhibited high toxicity in mice; that in **9–12** was remarkably evident when compared with benzodiazepines. No sedative action was noted, although two compounds, **1** and **13**, produced a reduction of spontaneous motor activity, −30 and −20% ($p = 0.05$), respectively, in comparison with control animals, and compound **13** displayed a marked reduction (−45%) in rotarod performance ($p = 0.01$) over controls. Barbiturate-induced sleep was increased by compounds **14** and **15** after the administration of somewhat high doses.

The anticonvulsive effect, present after low dosages of chlordiazepoxide, was completely absent when the new compounds were assayed in each of the three tests above. Conversely, and especially as regards electroshock-induced seizures, some compounds caused a reduction in latency time and an increase in the tonic–clonic seizure intensity.

The second part of the investigation included the study of amphetamine interactions[13,17,18] (hyperthermia, hypermotility, and group toxicity), reserpine interactions[19] (ptosis, catatonia, and hypothermia), the analgesic activity,[20] and the effects on conditioned avoidances.[21]

A study on isolated organs was then carried out: guinea pig ileum[22] for the response to histamine and acetylcholine, guinea pig atria[23] for the response to adrenaline, the rat caudal artery[24] for noradrenaline, and [^{3}H]tryptamine response were used.

Lastly, in order to investigate the possible mechanism of the high toxicity exhibited by some compounds, the curariform activity on the phrenic diaphragm isolated system[25] was studied.

The compounds (Table II) in some cases determined an increase in group toxicity, hypermotility, and hyperthermia induced by amphetamine and did not antagonize the reserpine effects. Analgesic activity was constantly absent, and deconditioning or facilitation of conditioning effects was not noted.

The activity on the isolated organs was evident at high concentrations and only when the compounds were present in the bath. On the phrenic diaphragm isolated system no curariform activity was present.

It may be concluded that, under the experimental condition used, the new compounds do not exert the same important effect on the CNS as those exhibited by the classical benzodiazepines at low concentrations; on the contrary, they apparently potentiate both the convulsant activity due to electroshock and to amphetamine in grouped mice. The mechanism of these effects may be related to their higher toxicity of the compounds.

It will therefore be the purpose of further studies to investigate the mechanism of high toxicity of this series of compounds. Furthermore, taking into account that also the original molecule[2] proved to be devoid of tranquillizing activity, it will be important to detect the structural change which gives rise to the difference between the activity of these derivatives and those of classical benzodiazepines.

Experimental Section

All melting points were determined on a Kofler hot-stage microscope and are uncorrected. The IR spectra (KBr) were recorded with a Beckman IR20 spectrophotometer. The NMR spectra were determined on a Varian A-60 spectrometer (60 MHz) in $CDCl_3$ or Me_2SO and using Me_4Si as the internal standard. Analytical results obtained for C, H, and N in the elemental analyses were within ±0.4% of the theoretical values for compounds **1–16**.

1-Phenyl-4-(2-dimethylaminoethyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**1**). To 1.45 g (6 mmol) of 1-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (I) in 90 mL of anhydrous benzene was added 0.24 g (6 mmol) of $NaNH_2$. The mixture was stirred for a few minutes and then 3.65 g (24 mmol) of 2-dimethylamino-1-bromoethane was added. The reaction mixture was stirred for 48 h at room temperature. Iced water (50 mL) was added in the same reaction vessel, thus separating the organic layer which was washed with H_2O and then extracted with 2 N HCl. The acid aqueous layer was first neutralized, then alkalinized with 6 N NaOH, and later extracted with ether. The organic phase was separated, washed several times with H_2O until alkalinity disappeared, and then dried ($MgSO_4$). The oily residue obtained by evaporating the solvent in vacuo was crystallized from hexane. Compound **1** (1.55 g, 75%) was thus obtained; compounds **2–6** were prepared in the same manner.

1-Phenyl-4-(2-trimethylammonioethyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one Iodide (**7**). 1-Phenyl-4-(2-dimethylaminoethyl)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**1**, 6 g, 19 mmol) was dissolved in a small amount of anhydrous acetone; under stirring 5 mL (80 mmol) of methyl iodide was added dropwise and at room temperature. The reaction mixture was stirred for several hours at room temperature; it became turbid since a white solid was precipitated. The precipitate was collected to give 8.4 g (98%) of compound **7** after crystallization from acetone. The other quaternary salts, **8–12**, were prepared in the same manner.

1-Phenyl-(4′-nitro)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**II, $R_1 = R_2 = NO_2$**). HNO_3 (15 mL of a 65% water solution) was added dropwise under stirring at 0 °C to 10 g (45 mmol) of 1-phenyl-1,2,3,4-tetrahydroquinolin-4-one previously dissolved in 200 mL of an acetic acid–acetic anhydride solution (1:1). The yellow precipitate was collected after diluting the solution with 150 mL of distilled water. The precipitate was washed with H_2O, dried in vacuo, and crystallized from MeOH–*i*-PrOH to yield 12.5 g (89%) of compound II ($R_1 = R_2 = NO_2$).

1-Phenyl-(4′-nitro)-7-nitro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**13**). Concentrated H_2SO_4 (60 mL) at 0 °C was added dropwise to a vigorously stirred solution of 16 g (0.25 mmol) of NaN_3 and 20 g (64 mmol) of 1-phenyl-(4′-nitro)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (II, $R_1 = R_2 = NO_2$) in 140 mL of $CHCl_3$. The reaction mixture was allowed to stand at room temperature for about 3 h and then neutralized with a Na_2CO_3 saturated solution. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The solid residue obtained was crystallized from ethyl acetate–hexane to give 14.5 g (69%) of **13**: NMR (Me_2SO-d_6) δ 3.70 (m, 4 H, $=NCH_2CH_2N=$), 6.90–8.70 (m, 7 H, aromatic).

1-Phenyl-(4′-nitro)-7-amino-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**14**). $SnCl_2 \cdot 2H_2O$ (25 g, 110 mmol) was added to 10 g (30 mmol) of 1-phenyl-(4′-nitro)-7-nitro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**13**) in 550 mL of MeOH and 200 mL of AcOH and refluxed for 10–12 h. Then the solution was partially concentrated in vacuo, diluted with water, alkalinized with a K_2CO_3 saturated solution, and extracted with ethyl acetate. The organic layer was washed with water and then extracted with

Table II. Pharmacological Profile of Compounds

Test[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	C[n]	D[o]
LD_{50},[b] mg kg^{-1} ip	100	116	130	75	80	75	35	50	15	15	10	15	>400	>400	>400	780	650
Motor act.[c]	−30[q]	−15	+4	+1	−10	−11	+20[p]	−5[p]	+1[p]	−3[p]	−8[p]	−20[p]	−21	−15	+2	−40	−50
Motor coordination[d]	−6	−12	−25	+11	−32	−27	−21[p]	+70[p]	−7[p]	+20[p]	+11	+8	−45[q]	+39	−20	−50	−40
Barbiturate-induced sleep[e]	+4	+35	+20	+40	+60	+45	−40	−25	−15	−40	+30	+20	+40	+70[q]	+90[r]	–	–
Barbiturate-induced sleep[f]	15	10	12.5	10	20	20	15	10	5	5	5	3	50	50	50		
Max electroshock[g]	50	10	12	5	–	25	15	10	5	5	3	–	–	–	–	(90)	(50)
Amphetamine-induced hyperthermia[h]	+0.6	–	–	–	−0.2	+1.4[q]	−0.3[p]	+1.2[p]	+0.3[p]	+1.4[p]	+1.6[p,q]	+0.9[p]	+1	+1.2	+1.4	–	–
Amphetamine-induced toxicity[i] in grouped mice	10	–	–	–	–	10	5	5	–	3	3	–	–	–	–	–	–
Antihistamine act.[j]	50	100	50	100	50	50	50	50	50	50	50	200	200	200	200	3	4
Antiacetylcholine act.[k]	100	100	50	100	100	100	50	50	200	50	100	50	200	50	200	3	–
Antinoradrenaline act.[l]	200	160	160	80	15	25	50	100	50	50	5	25	–	–	–	18	–
Anti[^{5}H]tryptamine act.[m]	50	50	50	50	50	25	50	50	15	15	50	50	–	–	–	20	–

[a] Albino mice of 20–25-g body weight and albino Wistar rats of 160–200-g body weight were used. Compounds usually were dissolved in physiological solutions and administered by ip via. Statistical analysis of the data was assessed in accordance with Student's t test. [b] Determination of lethality within an observation period of 24 h was evaluated in accordance with Weil[11] ($n = 6$; $k = 3$). [c] Translatory movements, in percent of control group; measurements were effected in mice by an activity cage (Basile) after a 10 mg kg^{-1} ip treatment. $N = 5$ per group. [d] Rotarod performance in mice after 10 mg kg^{-1}. Time of permanence in percent of controls. End point, 5 min of permanence. $N = 5$ per group. [e] Loss of righting reflex, minutes in percent of control, after pentobarbital (70 mg kg^{-1} ip) injection. Compounds were administered at a dose level of mg kg^{-1} ip. [f] Reported in 45 min before barbiturate. $N = 10$ per group. [g] Dose at which the maximal extensor seizure due to a maximal electroshock was increased more than 25% of controls. Numbers in parentheses indicate total prevention. [h] Body temperature variation 20 min after *dl*-amphetamine sulfate injection, 10 mg kg^{-1} ip. A dash indicates that compounds were administered at a dose level of 10 mg kg^{-1} ip 30 min before *dl*-amphetamine. $N = 6$ per group. [i] Dose at which the death induced by *dl*-amphetamine sulfate, 15 mg kg^{-1} ip, in grouped mice was increased more than 25%. $N = 8$ per group. [j] Dose level in μg/mL at which the response due to 0.2 μg/mL of histamine was decreased by 50–100% in the isolated guinea pig ileum. Agonist was introduced 5 min after compounds. [k] Dose level in μg/mL at which the response due to 0.02 μg/mL of acetylcholine was decreased by 50–100% in the isolated guinea pig ileum. Agonist was introduced 5 min after compounds. [l] Dose level, μg/6 mL/min, at which the response due to noradrenaline stimulation on an isolated rat caudal artery was decreased by 20–50%. Stimulations with agonist were effected 15 min after the compounds were perfused. [m] Dose level, μg/6 mL/min, at which the response due to [^{5}H]tryptamine stimulation on an isolated rat caudal artery was decreased by 20–50%. [^{5}H]Tryptamine stimulation was effected 15 min after the compounds were perfused. [n] Chlordiazepoxide. [o] Diazepam. [p] Compounds were administered at a dose level of 5 mg kg^{-1}. [q] $p = 0.05$. [r] $p = 0.01$; Student's t test.

a 2 N HCl solution. The acidic aqueous solution was cooled at 0 °C and then neutralized with a 2 N NaOH solution. The white precipitate was washed several times with water to give 5.4 g (59%) of 14: NMR (Me_2SO-d_6) δ 3.60 (m, 4 H, $=NCH_2CH_2N=$), 5.60 (br s, =NH), 6.50–8.50 (m, 7 H, aromatic).

1-Phenyl-(4′-acetylamino)-1,2,3,4-tetrahydroquinolin-4-one (II, R_1 = NHCOCH$_3$; R_2 = H). 4-Acetylamino-*N*,*N*-diphenyl-β-alanine (14 g, 47 mmol) was added to 131 g of polyphosphoric acid and kept under vigorous stirring at 100 °C for 2 h. The mixture was cooled, diluted with ice water, and then extracted with EtOAc. The organic layer was first washed with 1 N NaOH and then with water, dried, concentrated in vacuo, and crystallized from EtOAc to give 9.8 g (74%) of yellow solid II (R_1 = NHCOCH$_3$; R_2 = H).

1-Phenyl-(4′-acetylamino)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (16). Sodium azide (10 g, 150 mmol) was added to 10 g (36 mmol) of 1-phenyl-(4′-acetylamino)-1,2,3,4-tetrahydroquinolin-4-one (II, R_1 = NHCOCH$_3$; R_2 = H) in $CHCl_3$. Concentrated H_2SO_4 (50 mL) was then added at 0 °C under vigorous stirring. The reaction mixture was allowed to stand at room temperature for 3 h and then neutralized with a Na_2CO_3 saturated solution; the precipitate was collected by filtration. The organic layer was washed with water, dried (Na_2SO_4), and concentrated in vacuo; the small amount of the obtained compound was joined to the previously obtained precipitate. The combined residues were crystallized from acetone to give 7.8 g (74%) of 16: NMR (Me_2SO-d_6) δ 2.05 (s, 3 H, $-CH_3$), 3.40 (m, 4 H, $=NCH_2CH_2N=$), 6.70–7.80 (m, 8 H, aromatic).

1-Phenyl-(4′-amino)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (15). 1-Phenyl-(4′-acetylamino)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (16, 1 g, 3.4 mmol) was refluxed in 100 mL of absolute EtOH and HCl(g) allowed to bubble in slowly for 4–5 h. The solvent was evaporated in vacuo, and amine hydrochloride thus obtained was washed several times with ethyl alcohol, then dissolved in a small amount of water, and alkalinized with 1 N NaOH to give 0.5 g (58%) of compound 15: NMR (Me_2SO-d_6) δ 3.50 (m, 4 H, $=NCH_2CH_2N=$), 4.90 (br s, =NH), 6.70–7.60 (m, 8 H, aromatic).

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Antiallergic 9-Oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]benzopyrans

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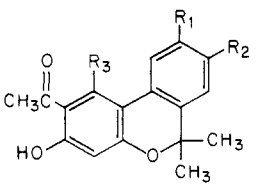
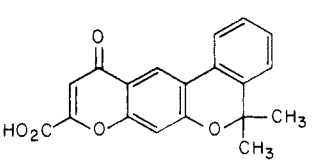
The synthesis and properties of the title compounds 1 are described. Several of these compounds, in addition to being potent inhibitors of the passive cutaneous anaphylaxis reaction of rats against egg albumin challenge, significantly block the effects of several mediators of anaphylaxis in isolated smooth muscle preparations. An improved procedure for the isolation and partial purification of SRS-A from chopped guinea pig lung tissue is also described.

We have investigated the antiallergic activities of acidic representatives of polycyclic heterocyclic systems.[1] The 9-oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]-benzopyrans (1), a short series of which is herein described, are members of this group which have been found to possess significant activity both in the PCA assay and the inhibition of the effects of several mediators of anaphylaxis in isolated smooth muscle preparations.

Chemistry. The synthetic route which was generally employed for the preparation of 1 (see Table I) involved the condensation of 2-acetyl-3-hydroxy-6*H*-dibenzo-[*b*,*d*]pyrans[1,2] (2) with diethyl carbonate in the presence of sodium hydride.



2



3

Results and Discussion

The PCA reaction can be altered by the inhibition of mast cell degranulation so that no vasoactive mediators are released after antigen challenge. Disodium

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