The **hydrochloride salt** was recrystallized from ethanol, m.p. 185–186°.

3-(β-Hydroxyphenethylamino)pyridazine (XVI).—A stirred mixture of 15.0 g. (0.06 mole) of XV, 2 g. of 10% palladium-on-carbon, 25 ml. of 64% hydrazine, and 200 ml. of ethanol was boiled on the steam bath for 1.5 hr. The cooled mixture was filtered and the filtrate concentrated to a tan solid residue that was washed with water and crystallized from isopropyl alcohol–water to yield 8.8 g. (68%) of XVI, m.p. 141–142°.

The **hydrochloride salt of XVI,** crystallized from isopropyl alcohol, melted at 122–124°.

2-(β-Hydroxyphenethylamino)-3-methylpyrazine (XVII).—A mixture of 18.0 g. (0.14 mole) of 2-chloro-3-methylpyrazine, 18.0 g. (0.13 mole) of β-hydroxyphenethylamine, 23.2 g. (0.14 mole) of potassium carbonate, and 0.5 g. of copper powder was heated in an oil bath maintained at 160° for 7 hr. The mixture was triturated with benzene and the solution filtered and concentrated to a dark oil that was vacuum distilled to yield 8.3 g. (28%) of product, b.p. 195–201° (0.5 mm.).

The **hydrochloride** salt was crystallized from isopropyl alcohol–ethyl acetate to give tan crystals, m.p. 111–113°.

2-(β-Hydroxyphenethylamino)-s-triazine (XVIII).—A solution of 13.8 g. (0.05 mole) of β-hydroxyphenethylguanidine hydrobromide[3] and 4.2 g. (0.05 mole) of *s*-triazine in 25 ml. of dry ethanol was heated on the steam bath for 20 hr. The precipitated solid was collected and crystallized from methanol to give 4.3 g. (40% yield) of XVIII, m.p. 211–212°.

2-(β-Hydroxyphenethylamino)-4,6-diamino-s-triazine (XIX).—To a slurry of 72.8 g. (0.5 mole) of 2,4-diamino-6-chloro-*s*-triazine and 71.3 g. (0.52 mole) of β-hydroxyphenethylamine in 500 ml. of water was added, dropwise at steam-bath temperature, a solution of 74.4 g. (0.6 mole) of sodium carbonate monohydrate in 160 ml. of warm water. The addition required approximately 1 hr. after which the mixture was heated for an additional 3 hr. and then cooled and filtered. The water-washed precipitate was recrystallized from ethanol to yield 66.7 g. (54%) of white crystals, m.p. 176–178°.

2-(β-Hydroxyphenethylamino)-4,6-diamino-s-triazine hydrochloride, recrystallized from ethanol, showed m.p. 231–232°.

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Synthesis and Antitussive Activity of a New Heterocyclic Ring System. Some 1,2-Diazabicyclo[2.2.2]octanes

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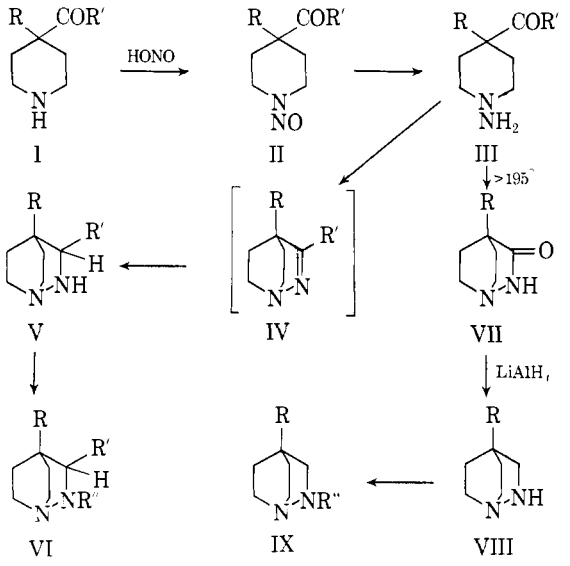
Two routes to the previously unknown 1,2-diazabicyclo[2.2.2]octane ring system have been developed. The parent heterocycle, 1,2-diazabicyclo[2.2.2]octane, as well as a number of substituted derivatives, has been synthesized. The most effective compound is similar to codeine in antitussive potency and is devoid of analgesic activity.

The use of 4-acyl-4-phenylpiperidines for the preparation of the corresponding 1-alkyl derivatives has been reported previously.[2] The same intermediates are suitable starting materials for the synthesis of the previously unknown[3] 1,2-diazabicyclo[2.2.2]octane ring system. The preparation of the parent compound, 1,2-diazabicyclo[2.2.2]octane, as well as a series of 2- and 3-substituted derivatives has now been accomplished.

SCHEME I



The 3-alkyl-4-phenyl-1,2-diazabicyclo[2.2.2]octanes (V) listed in Table II were prepared as shown in Scheme I. Addition of a slight excess of aqueous sodium nitrite to aqueous solutions of the hydrochlorides of the amino ketones (I) gave very good yields of the corresponding 1-nitrosopiperidines (II). These are listed in Table I. In all cases, the products as obtained from the reaction mixture were analytically pure and were used directly in the next step. Any attempts at recrystallization or distillation resulted in partial decomposition. Reduction of the nitroso ketones (II) with zinc dust and acetic acid at 15–20° gave basic materials which proved to be the 3-alkyl-4-phenyl-1,2-diazabicyclo[2.2.2]octanes (V). No other products could be isolated. Apparently, cyclization of the 1-amino derivatives (III) occurs to yield what are probably the cyclic hydrazones (IV). Under the conditions of the reaction, these are further reduced to the saturated heterocycle (V).

The method of synthesis, elemental analyses, and the infrared and n.m.r. spectra of representative compounds are all consistent with the bicyclic structure assigned for the products (V). The infrared spectrum of 4-phenyl-3-propyl-1,2-diazabicyclo[2.2.2]octane (V, R = C_6H_5; R′ = C_3H_7) hydrochloride, a typical compound in this series, shows a broad absorption band at 4.20–4.32 μ, which is indicative of a disubstituted >NH+ function. The carbonyl band at 5.92 μ

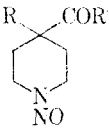
(1) This paper is taken in part from the thesis of Philip M. Carabateas, submitted to Rensselaer Polytechnic Institute, Troy, N. Y., in partial fulfillment of the requirements for the Ph.D. degree.

(2) B. Elpern, P. M. Carabateas, and L. Grumbach, *J. Org. Chem.*, **26**, 4728 (1961).

(3) The literature records examples of 1,3-, 1,4-, 2,3-, and 2,6-diazabicyclo[2.2.2]octanes; C. Harries, *Ann.*, **294**, 362 (1897); O. Hromatka and O. Kraup, *Monatsh.*, **82**, 880 (1951); J. Pirsch and J. Jorgl, *Ber.*, **68B**, 1324 (1935); D. E. Piper and G. F. Wright, *J. Am. Chem. Soc.*, **72**, 1669 (1950).

TABLE I

N-NITROSO PIPERIDINES



R	R′	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
C_6H_5	OC_2H_5	44.4–47.6	100	$C_{14}H_{18}N_2O_3$	10.68	10.78
C_6H_5	CH_3	58–60	68	$C_{13}H_{16}N_2O_2$	12.06	12.32
C_6H_5	C_2H_5	82–83	98	$C_{14}H_{18}N_2O_2$	11.38	11.10
C_6H_5	C_3H_7	94–95.5	89.2	$C_{15}H_{20}N_2O_2$	10.76	10.72
C_6H_5	C_4H_9	Oil	91.5	$C_{16}H_{22}N_2O_2$	10.21	10.58
C_6H_5	C_7H_5	Oil	71.2	$C_{19}H_{23}N_2O_2$	8.86	8.75
H	C_3H_7	Oil	93	$C_9H_{16}N_2O_2$	15.21	15.29
H	OCH_3	Oil	93.4	$C_7H_{12}N_2O_3$	16.28	16.07
		$n^{27}D$ 1.4920				

and the N-nitroso band at 6.9 μ which are present in the nitroso ketones (II) are absent in V. There are no bands which would indicate the presence of intermediates containing a > C=N linkage.

The n.m.r. spectrum of a 20% solution of the 4-phenyl-3-propyl compound (V, R = C_6H_5; R′ = C_3H_7) in deuteriochloroform shows a strong aromatic C–H signal at 472 c.p.s. and a number of saturated aliphatic C–H signals at 50–250 c.p.s. The integration trace of the above compound showed an aromatic C–H to aliphatic C–H ratio of 5 to 16. The formation of a monoacetyl compound (VI, R = C_6H_5; R′ = C_2H_5; R″ = CH_3CO) from the corresponding diazabicyclooctane (V, R = C_6H_5; R′ = C_2H_5) is also consistent with the proposed structure.

It was desirable to synthesize 3-propyl-1,2-diazabicyclo[2.2.2]octane in which the 4-phenyl group is missing to make it available for pharmacological studies. The synthesis of this compound was similar to that shown in Scheme I. In this instance, 4-cyanopiperidine, which was prepared in 70% yields by a modification of the procedure described by Gardner, *et al.*,[4] was treated with *n*-propyllithium to give 4-butyrylpiperidine (I, R = H; R′ = C_3H_7) which was then nitrosated with aqueous sodium nitrite to give 4-butyryl-1-nitrosopiperidine (II, R = H; R′ = C_3H_7). Reduction of the latter afforded 3-propyl-1,2-diazabicyclo[2.2.2]octane (V, R = H; R′ = C_3H_7) in 19% yield.

Compounds unsubstituted in the 3-position of the 1,2-diazabicyclo[2.2.2]octane nucleus were prepared from the appropriate ester as shown in Scheme I. Treatment of 4-carbethoxy-4-phenylpiperidine (I, R = C_6H_5; R′ = OC_2H_5) with sodium nitrite gave 4-carbethoxy-1-nitroso-4-phenylpiperidine (II, R = C_6H_5, R′ = OC_2H_5) which was readily reduced with zinc dust and acetic acid to 1-amino-4-carbethoxy-4-phenylpiperidine (III, R = C_6H_5; R′ = OC_2H_5). Cyclization of the latter in Dowtherm A at 240° afforded 3-oxo-4-phenyl-1,2-diazabicyclo[2.2.2]octane (VII, R = C_6H_5) in 40–50% yields. Quaternization of VII, R = C_6H_5, with methyl iodide in acetonitrile followed by exchange of iodide ion for chloride ion using IRA-400 ion exchange resin gave the methochloride, while reduction with lithium aluminum hydride in tetrahydrofuran proceeded smoothly to give 4-phenyl-1,2-diazabicyclo[2.2.2]octane (VIII, R = C_6H_5) in 95.5% yield.

Addition of chloral to the cyclic hydrazine (VIII, R = C_6H_5) according to the general procedure of Blicke, *et al.*,[5] yielded the 2-formyl compound (IX, R = C_6H_5; R″ = CHO). Reduction of this compound with lithium aluminum hydride gave 2-methyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane (IX, R = C_6H_5; R″ = CH_3) in good yield. The cyanomethyl derivative (IX, R = C_6H_5; R″ = CH_2CN) was readily synthesized by adding excess aqueous glycolonitrile to VIII. The phenylurea (IX, R = C_6H_5; R″ = $CONHC_6H_5$) was obtained by addition of phenyl isocyanate.

The parent heterocycle, 1,2-diazabicyclo[2.2.2]octane (VIII, R = H), was prepared as follows. 4-Carbomethoxypiperidine (I, R = H; R′ = OCH_3) hydrochloride was converted to the oily 1-nitroso derivative (II, R = H; R″ = OCH_3) by treatment with sodium nitrite. Reduction of the nitroso compound to the hydrazine using zinc dust and acetic acid was unsatisfactory. This was probably due to hydrolysis of the ester group of III (R = H; R′ = OCH_3) in the strongly basic medium which was required for the work-up of the reduction. The desired 1-amino-4-carbomethoxypiperidine (III, R = H; R′ = OCH_3) was finally obtained in yields ranging from 59–71% using amalgamated aluminum as the reducing agent. This reagent has been used for the preparation of hydrazines from nitrosamines[6] and for reduction of esters to alcohols.[7] However, in the present work no alcohol formation was observed. Cyclization of III (R = H; R′ = OCH_3) in Dowtherm A at 195–200° for 3 hr. in a nitrogen atmosphere gave 3-oxo-1,2-diazabicyclo[2.2.2]octane (VII, R = H) in 34–47% yield. Reduction of this 3-oxo compound with lithium aluminum hydride in tetrahydrofuran gave the desired 1,2-diazabicyclo[2.2.2]octane (VIII, R = H) in 93% yield. The product was obtained as a white solid which retained traces of moisture and organic solvents. This strong base also readily absorbs carbon dioxide from the atmosphere. Purification was effected by sublimation at reduced pressure or by distillation in a nitrogen atmosphere. In common

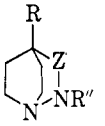
(4) T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, **22**, 984 (1957).

(5) F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(6) L. A. Carpino, A. A. Santilli, and R. W. Murray, *ibid.*, **82**, 2728 (1960).

(7) J. N. Ray, A. Mukherji, and N. D. Gupta, *J. Indian Chem. Soc.*, **38**, 705 (1961).

TABLE II
1,2-DIAZABICYCLO[2.2.2]OCTANES



No.	R	Z	R″	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Antitussive activity—ED$_{50}$ mg./kg., P.O.	Antitussive activity—Standard error (±)
1	C_6H_5	$CHCH_3$	H	330.0–332.0	33.5	$C_{13}H_{18}N_2\cdot HCl$			14.84[a]	14.96[a]	11.73	11.55	39.0[b]	8.7
2	C_6H_5	CHC_2H_5	H	325.0–327.0	32.0	$C_{14}H_{20}N_2\cdot HCl$			14.03[a]	14.26[a]	11.08	11.00	77.0	26.0
3	C_6H_5	CHC_3H_7	H	245.0–247.0	65.9	$C_{15}H_{22}N_2\cdot HCl$	67.51	67.47	8.69	8.49	13.29[a]	13.17[a]	11.6	4.6
4	C_6H_5	CHC_4H_9	H	218.0–219.2	39.3	$C_{16}H_{24}N_2\cdot HCl$	68.43	68.61	8.97	8.96	9.98	9.89	26.0	6.5
5	C_6H_5	$CH(CH_2)_6CH_3$	H	222.2–224.0	25.3	$C_{19}H_{30}N_2\cdot HCl$	70.66	70.99	9.68	9.62	8.68	8.82	19.0	7.7
6	C_6H_5	CHC_2H_5	$COCH_3$	127.2–128.6	62.2	$C_{16}H_{23}NO$	74.36	74.07	8.58	8.37	5.42	5.50	35.0[c]	
7	H	CHC_3H_7	H	223.0–224.8	19.3	$C_9H_{18}N_2\cdot HCl$			18.59[a]	18.29[a]	14.66	14.77	28.0[c]	
8	C_6H_5	C=O	H	248.0–249.2	46.4	$C_{12}H_{14}N_2O$	71.25	71.37	6.98	6.95	6.93	7.06	29.0[c]	
9	C_6H_5	CH_2	H	208.2–208.8	95.5	$C_{12}H_{16}N_2\cdot HCl$	64.13	64.31	7.63	7.73	15.78[a]	15.58[a]	28.5	5.9
10	C_6H_5	CH_2	$COCH_3$	89.0–91.0	94.1	$C_{14}H_{18}N_2O$	73.01	73.12	7.88	8.01	12.17	12.35	30.0[c]	
11	C_6H_5	CH_2	$CONHC_6H_5$	196.4–198.2	71.6	$C_{19}H_{21}N_3O$	74.23	74.49	6.89	6.63	13.67	13.40	19.0[c]	
12	C_6H_5	CH_2	CH_2CN	72.4–74.0	58.7	$C_{14}H_{17}N_3$	73.99	74.11	7.54	7.61	18.49	18.28	21.0[d]	
13	C_6H_5	CH_2	CHO	104.4–105.6	69.5	$C_{13}H_{16}N_2O$	72.19	72.46	7.46	7.47	12.95	13.02	42.0[c]	
14	C_6H_5	CH_2	CH_3	196.4–198.6	70.0	$C_{13}H_{18}N_2\cdot HCl$	65.38	65.42	8.02	7.72	14.84[a]	14.85[a]	19.0[c]	
15	H	C=O	H	170.8–173.4	47.2	$C_6H_{10}N_2O$	57.10	57.40	7.99	7.90	22.20	22.05	37.0[c]	
16	H	CH_2	H	264.0–265.8	93.4	$C_6H_{12}N_2\cdot HCl$	48.49	48.49	8.81	8.84	23.86[a]	23.67[a]	43.0[c]	
17	H	CH_2	$CSNHC_6H_5$	125.5–127.2	76.8	$C_{13}H_{17}N_3S$	63.11	63.29	6.93	6.70	16.98	16.66		
Codeine													9.3	1.2

[a] Analyzed for chlorine. [b] Intraperitoneal. [c] Per cent inhibition at 40 mg./kg. [d] Per cent inhibition at 20 mg./kg.

with other compounds of a similar "cage" structure,[8] VIII (R = H) has a narrow liquid range, m.p. 137–140°, b.p. 170–175° (760 mm.). The compound was characterized as its hydrochloride salt as well as its phenylthiocarbamyl derivative (IX, R = H; R″ = $CSNHC_6H_5$).

Melting points, yields, and analytical data for V, VI, VII, VIII, and IX are given in Table II.

Pharmacology.—In recent years, a good deal of effort has been devoted to the search for effective nonnarcotic antitussive agents.[9–14] These compounds have ranged in structure and activity from local anesthetics[9,11] to phenothiazines.[14] The disadvantages of the opium derivatives which are used for the control of cough are numerous. In addition to the hazards of tolerance and addiction, other side effects seen with these agents include respiratory depression, nausea, constipation, drowsiness, dizziness, and sensitivity reactions.

In the present series of novel 1,2-diazabicyclo[2.2.2]-octane derivatives, a number of compounds have been found which are active antitussive agents in animals. One of these (**3**, Table II) was promising enough to warrant clinical trial and was shown to suppress cough equivalent to codeine.[15]

The antitussive activity in animals was determined by a modification of the method of May and Widdicombe.[16] Cats (2–4 kg.) were anesthetized with diallylbarbituric acid–urethane[17] and prepared for the recording of blood pressure, lead (II) electrocardiograph, and cough response, on a Grass Model II polygraph. Blood pressure was obtained from the femoral artery *via* a Statham P-23-AC pressure transducer. Cough response was recorded from a bonded strain gauge stitched to the chest wall at the second to third intracostal space. Coughs were elicited by plunging a rounded glass rod into the larynx through a hole cut in the trachea. Care was taken to maintain a uniform procedure for inducing cough. The larynx was stimulated regularly every 4 min. A control period of 4 coughs was carried out. The compounds, dissolved in distilled water, were then administered by stomach tube 2 min. after the last control cough. Coughs were regularly elicited for an additional 64 min. The control-cough height was obtained from an average measurement of the 2 control coughs preceding medication. The degree of cough inhibition was determined by obtaining the average cough height from the 60 and 64 min. readings and expressing this as per cent reduction of the control. With codeine, peak activity is also obtained at 1 hr.

Groups of 5 or more cats were given graded doses of the test compound and the 60-min. response means were plotted against log-dose on probit paper to obtain an ED_{50} (dose which produced a 50% reduction of the control cough) and its standard error.[18] If an inhibition of less than 50% was obtained at a dose of 40 mg./kg., a complete dose–response relationship was not established.

The results are shown in Table II. The unsubstituted compound (**9**) has fair activity which is reduced

(8) A. Farkas, G. A. Mills, W. E. Erner, and J. B. Maerker, *Ind. Eng. Chem.*, **51**, 1299 (1959).

(9) E. Levis, S. Preat, and F. Moyersoons, *Arch. Intern. Pharmacodyn.*, **103**, 200 (1955).

(10) A. David, F. Levth-Ross, and D. K. Vallance, *J. Pharm. Pharmacol.*, **9**, 446 (1957).

(11) J. Chen, H. F. Biller, and E. G. Montgomery, Jr., *J. Pharmacol. Exptl. Therap.*, **128**, 384 (1960).

(12) B. Silvestrini and C. Pozzatti, *Arch. Intern. Pharmacodyn.*, **129**, 249 (1960).

(13) K. D. Phillips and E. W. Couillaime, *Practitioner*, **238** (1961).

(14) M. Grozman, I. O. Berker, and F. Casimir, *Appl. Therap.*, **3**, 95 (1961).

(15) M. Grozman, personal communication.

(16) A. J. May and J. G. Widdicombe, *Brit. J. Pharmacol.*, **9**, 335 (1954).

(17) Dial-Urethane,(R) kindly supplied by Dr. A. J. Plummer, Ciba Pharmaceutical Products, Inc.

(18) L. C. Miller and M. L. Tainter, *Proc. Soc. Exptl. Biol. Med.*, **57**, 261 (1944).

by introduction of a 1-carbon (**1**) or 2-carbon (**2**) chain. However, the propyl compound (**3**) is considerably more active than (**9**). With the butyl and heptyl compounds, the activity seems to recede again.

Acylation, alkylation, or other substitution of the nitrogen function (compounds **6**, **10–14**) appears to attenuate the antitussive activity. Again, removal of the 4-phenyl group also leads to a lessening of effect (**7** *vs.* **3**, **16** *vs.* **9**). It is difficult to ascribe a rational explanation of the changes in activity seen with the structural changes. However, optimal activity in this limited series appears to lie in the 4-phenyl-3-propyl-1,2-diazabicyclo[2.2.2]octane derivative (**3**) which was found to be nearly equivalent to codeine.[19]

All of the compounds were tested for analgesic activity using the rat tail-flick procedure.[20] None of the compounds showed activity in this test procedure. Since there is a high correlation between activity in the rat tail-flick procedure with analgesia and narcotic activity in man, one might anticipate that the present series of antitussives would be devoid of narcotic effects. In addition, these compounds were tested for their general CNS activity in mice using the photocell activity cage.[21] Unlike most antitussive agents, the diazabicyclo[2.2.2]octane derivatives produced a mild stimulation of spontaneous activity. Thus, it would appear that these compounds represent a new class of nonnarcotic, nondepressant antitussive agents.

Experimental[22]

4-Carbomethoxypiperidine (methyl isonipecotate) was purchased from Reilly Tar and Chemical Corp., and 1-benzyl-4-cyano-4-phenylpiperidine and 4-carbethoxy-4-phenylpiperidine were obtained from Winthrop Laboratories.

1-Benzyl-4-octanoyl-4-phenylpiperidine.—This compound was prepared by the general method of Eisleb[23] in 59.4% yield. One recrystallization from *n*-pentane gave 59.4% of product, m.p. 71.5–72.5°.

Anal. Calcd. for $C_{26}H_{35}NO$: C, 82.71; H, 9.35. Found: C, 82.04; H, 9.29.

The propionyl[23] and butyryl[24] analogs were prepared similarly, whereas the acetyl and valeryl[3] analogs were prepared using the appropriate alkyllithium as described by Perrine[24] for 4-acetyl-1-benzyl-4-phenylpiperidine. The alkyllithium method is preferable to the Grignard procedure for the preparation of 4-acylpiperidines from the nitriles.

4-Octanoyl-4-phenylpiperidine Hydrochloride.—This was prepared by debenzylation of 1-benzyl-4-octanoyl-4-phenylpiperidine according to the general procedure described in ref. 2. A 66.8% yield of product melting at 124.5–126° was obtained.

Anal. Calcd. for $C_{19}H_{29}NO \cdot HCl$: Cl, 10.95. Found: Cl, 11.33.

The acetyl, propionyl, butyryl, and valeryl analogs[3] were prepared in a similar manner.

1-Nitroso-4-octanoyl-4-phenylpiperidine (II, R = C_6H_5; R′ = C_7H_{15}).—Sodium nitrite (14.5 g., 0.21 mole) in 50 ml. of water was added all at once to a stirred solution of 4-octanoyl-4-phenylpiperidine hydrochloride (63.8 g., 0.196 mole) in 600 ml. of water and 1 ml. of concentrated hydrochloric acid. The resulting white oil, which separated immediately, was extracted with ethyl acetate. The ethyl acetate solution was washed well with water, dried over sodium sulfate, and concentrated *in vacuo* to 44.2 g. of a thick oil which was used without further purification.

The other nitroso piperidines (Table I) were prepared in the same manner, except that the solid nitroso compounds were removed by filtration, washed with water, and dried over phosphorous pentoxide.

3-Heptyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane Hydrochloride (V, R = C_6H_5; R′ = C_7H_{15}).—A solution of 1-nitroso-4-octanoyl-4-phenylpiperidine (44.2 g., 0.14 mole) in 100 ml. of acetic acid and 75 ml. of ethanol was added dropwise during 1 hr. to a well stirred suspension of 90% zinc dust (72.5 g., 1.0 g.-atom) in 150 ml. of ethanol and 75 ml. of water. The temperature was maintained at 15–20° during the addition by means of an ice bath. Stirring was continued for 1 hr. at 15–20° after the addition was completed and for 1 hr. at room temperature. The solution was heated to the boiling point, filtered hot, and the zinc dust washed well with 95% ethanol. The filtrate and washings were concentrated to about 100 ml., diluted with 200 ml. of water, and made strongly basic with 35% sodium hydroxide. The resulting oil was extracted with ether, washed with water, and the ether solution concentrated to an oil which was dried by azeotroping with benzene. The orange oil was taken up in ether and treated with ethereal hydrogen chloride which precipitated a white solid. The solid was recrystallized successively from acetone, acetonitrile, and ethyl methyl ketone: yield, 11.4 g.

The other 3-alkyl-4-phenyl-1,2-diazabicyclo[2.2.2]octanes were similarly prepared, but in most cases required only one recrystallization from ethanol for purification.

2-Acetyl-3-ethyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane (VI, R = C_6H_5; R′ = C_2H_5; R″ = $COCH_3$).—A solution of 3-ethyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane hydrochloride (5.0 g., 0.02 mole) in 20 ml. of water was made basic with 35% sodium hydroxide and extracted with ether. The ether extracts were concentrated to an oil, 10 ml. of acetic anhydride was added, and the solution was heated on a steam bath for 4 hr. The mixture was poured into water and made basic with sodium hydroxide. The precipitated material was separated by filtration, washed with water, dried, and recrystallized twice from cyclohexane: yield, 3.2 g.

4-Cyanopiperidine.—Phosphorus oxychloride (575 g., 3.75 moles) was added to 4-piperidinecarboxamide[25] (143 g., 1.12 moles) at a rate causing vigorous refluxing of the phosphorus oxychloride. The solution was refluxed for 1.5 hr. and the excess phosphorus oxychloride removed by distillation *in vacuo*. The viscous residue was poured onto 600 g. of ice, while still warm, with vigorous stirring and allowed to come to room temperature. A clear, orange solution resulted. Addition of more ice was sometimes necessary to prevent the temperature of the mixture from rising above 25–30°. The solution was neutralized with solid potassium carbonate, made basic with 35% sodium hydroxide, and extracted 4 times with chloroform. The extracts were concentrated to an oil which was distilled to give 90.2 g. (73.3% of product, b.p. 100–105° (12 mm.), $n^{27}D$ 1.4738; lit.[25] b.p. 100° (7 mm.), $n^{25}D$ 1.4741.

4-Butyrylpiperidine (I, R = H; R′ = C_3H_7) Hydrochloride.—A solution of 4-cyanopiperidine (22.0 g., 0.2 mole) in 100 ml. of ether was added at a rate causing reflux, to a solution of *n*-propyllithium prepared from propyl bromide (86 g., 0.7 mole) and lithium shot (9.8 g., 1.4 g.-atom) in 300 ml. of ether. The mixture turned yellow-brown in color. Stirring was continued for 3 hr., after which the reaction was allowed to stand overnight. Hydrolysis was effected by cautious addition of 100 ml. of water followed by 200 ml. of concentrated hydrochloric acid. The aqueous layer was separated and refluxed for 5 hr. After cooling, the solution was made basic with 35% sodium hydroxide and extracted with ether. The ether extracts were concentrated to a red oil which was dried by azeotropic distillation with benzene. Distillation gave 18.6 g. of colorless oil, b.p. 60–65° (0.15 mm.), $n^{25}D$ 1.4681. The hydrochloride was prepared (ethereal hydrogen chloride) and recrystallized from acetone: yield, 15.4 g. (40.2%); m.p. 128–129.5°.

Anal. Calcd. for $C_9H_{17}NO \cdot HCl$: C, 56.39; H, 9.46; Cl, 18.46. Found: C, 56.63; H, 9.67; Cl, 18.68.

3-Propyl-1,2-diazabicyclo[2.2.2]octane Hydrochloride (V, R =

(19) A detailed report on the pharmacology of this compound will be published at a later date.

(20) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941); W. B. Bass and N. J. Vander Brook, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 569 (1962).

(21) L. S. Harris and F. C. Uhle, *J. Pharmacol. Exptl. Therap.*, **132**, 251 (1961).

(22) Melting points were taken in a Hershberg apparatus and are corrected.

(23) O. Eisleb, U. S. Patent 2,248,018.

(24) T. D. Perrine, *J. Org. Chem.*, **22**, 1484 (1957).

(25) C. A. Grob and L. Renk, *Helv. Chim. Acta*, **37**, 1672 (1954).

H; R′ = C_2H_7).—Reduction of 4-butyryl-1-nitrosopiperidine (13.7 g., 0.0745 mole) in a manner similar to that described for the octanoyl analog gave 3-propyl-1,2-diazabicyclo[2.2.2]octane hydrochloride.

1-Amino-4-carbethoxy-4-phenylpiperidine (VI, R = C_6H_5; R′ = C_2H_5).[26] Hydrochloride.—A solution of 4-carbethoxy-1-nitroso-4-phenylpiperidine[26] (154.2 g., 0.59 mole) in 300 ml. of acetic acid and 300 ml. of ethanol was added dropwise during 1.5 hr. to a vigorously stirred suspension of 90% zinc dust (145 g., 2.0 g.-atom) at 17–20°. Ice cooling was necessary. Another 50 ml. of acetic acid was added at 17–20°, after which the mixture was stirred for 2 hr. at room temperature. The mixture was filtered, the filter cake was washed well with ethanol, and the filtrate and washings were concentrated to a volume of approximately 500 ml. The solution was made strongly basic with 35% sodium hydroxide and the resulting oil extracted 3 times with benzene. The extracts were washed well with water and concentrated *in vacuo* to an oil which crystallized on cooling; m.p. 52–56°, 127.9 g. (87.5%). A portion was converted to the hydrochloride and recrystallized from ethanol; m.p. 177.4–179.6°.

Anal. Calcd. for $C_{14}H_{21}ClNO$: C, 59.04; H, 7.43. Found: C, 59.11; H, 7.57.

3-Oxo-4-phenyl-1,2-diazabicyclo[2.2.2]octane (VII, R = C_6H_5).—1-Amino-4-carbethoxy-4-phenylpiperidine (10 g., 0.04 mole) and 25 ml. of Dowtherm A[27] were heated at 240° under nitrogen for 2 hr. The heat source was removed, and the dark solution was poured into 150 ml. of ethyl acetate. The resulting white solid had m.p. 241–245° and was of satisfactory purity for further reactions. Purification was effected by crystallization from acetic acid–ethyl acetate; yield 3.4 g.

3-Oxo-4-phenyl-1,2-diazabicyclo[2.2.2]octane *p*-Toluene Sulfonate.—A mixture of 3-oxo-4-phenyl-1,2-diazabicyclo[2.2.2]-octane (4.04 g., 0.02 mole), *p*-toluenesulfonic acid monohydrate (3.8 g., 0.02 mole), and 50 ml. of methanol was boiled for 5 min. After all solid had dissolved, the solution was filtered hot and allowed to cool. There was obtained 6.7 g. (89.5%), m.p. 217.8–219.4°.

Anal. Calcd. for $C_{19}H_{22}N_2O_4S$: C, 60.93; H, 5.92; N, 7.48. Found: C, 61.37; H, 5.91; N, 7.59.

3-Oxo-4-phenyl-1,2-diazabicyclo[2.2.2]octane Methochloride.—A mixture of 3-oxo-4-phenyl-1,2-diazabicyclo[2.2.2]octane-(4.04 g., 0.02 mole), methyl iodide (5.7 g., 0.04 mole), and 50 ml. of acetonitrile was refluxed for 7 hr. All the solid dissolved in 0.5 hr. The solution was concentrated to a yellow solid which was dissolved in methanol. The methanolic solution was passed through a column of IRA-400 ion-exchange resin, and the eluate was concentrated to a white solid which was recrystallized from ethanol. There was obtained 3.5 g. (69.2%) of product, m.p. 221.8–222.6°.

Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 61.77; H, 6.78; Cl, 14.03. Found: C, 61.96; H, 6.80; Cl, 13.90.

4-Phenyl-1,2-diazabicyclo[2.2.2]octane (VIII, R = C_6H_5) Hydrochloride.—Finely powdered 3-oxo-4-phenyl-1,2-diazabicyclo[2.2.2]octane (101.1 g., 0.5 mole) was added in portions with vigorous stirring to a slurry of lithium aluminum hydride (38.0 g., 1.0 mole) in 1 l. of tetrahydrofuran. The mixture was refluxed with stirring for 22 hr., cooled, and hydrolyzed by dropwise addition of 40 ml. of water. A saturated solution of potassium sodium tartrate in 250 ml. of water was then added slowly and the mixture stirred for 2 hr. more. The mixture was filtered, the filter cake washed well with tetrahydrofuran, and the filtrate and washings concentrated to an orange oil which was dried by azeotroping with benzene. The oil crystallized on slight cooling. The crystals were dissolved in ether, the solution was filtered, and the ether evaporated, giving 90 g. of product, m.p. 90–95°, suitable for further reactions. The hydrochloride was prepared (ethereal hydrogen chloride) and recrystallized from ethanol–ether.

2-Acetyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane (IX, R = C_6H_5, R″ = $COCH_3$).—This compound was prepared as described for 2-acetyl-3-ethyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane.

4-Phenyl-2-phenylcarbamyl-1,2-diazabicyclo[2.2.2]octane (IX, R = C_6H_5, R″ = $CONHC_6H_5$).—Phenylisocyanate (2.5 g., 0.02 mole) was added to 4-phenyl-1,2-diazabicyclo[2.2.2]octane (3.6 g., 0.02 mole) in 30 ml. of benzene. A white solid crystallized; a further quantity was obtained by evaporating the filtrate. Recrystallization from toluene gave 4.4 g. of product.

2-Formyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane (IX, R = C_6H_5, R″ = CHO).—4-Phenyl-1,2-diazabicyclo[2.2.2]octane (5.0 g., 0.027 mole) in 10 ml. of chloroform was treated with chloral (4.4 g., 0.03 mole) in 5 ml. of chloroform. The solution became hot and crystallized on slight cooling. After washing with *n*-hexane, the product was crystallized from cyclohexane using charcoal; yield 4.0 g.

2-Methyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane Hydrochloride (IX, R = C_6H_5, R″ = CH_3).—Reduction of 2-formyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane (4.0 g., 0.02 mole) with lithium aluminum hydride (1.5 g., 0.04 mole) in 100 ml. of tetrahydrofuran was carried out as described for VIII (R = C_6H_5). The base was converted to its hydrochloride (ethereal hydrogen chloride) which was recrystallized from 2-propanol to give 3.0 g.

2-Cyanomethyl-4-phenyl-1,2-diazabicyclo[2.2.2]octane (IX, R = C_6H_5, R″ = CH_2CN).—A 70% aqueous solution of glycolonitrile (4.07 g., 0.05 mole) was added to VIII (R = C_6H_5) (4.7 g., 0.05 mole). The solution became warm. After briefly heating to boiling, the mixture was allowed to stand for 2 hr. and poured into water. The resulting oil crystallized on scratching, and the solid was recrystallized from ethanol–water, then cyclohexane with decolorizing charcoal, to give 3.0 g.

1-Amino-4-carbomethoxypiperidine (III, R = H, R′ = OCH_3).—Granulated 8–20 mesh aluminum (24.3 g., 0.9 g.-atom) was treated with 5% sodium hydroxide solution until a vigorous evolution of hydrogen occurred. The solution was decanted and the aluminum washed with water by decantation. The aluminum was covered with 100 ml. of a 2% mercuric chloride solution for 2 min., the mercuric chloride solution was decanted, and the aluminum again washed by decantation successively with water, ethanol, and ether. The aluminum was covered with 500 ml. of U.S.P. ether and stirred gently while 4-carbomethoxy-1-nitrosopiperidine (II, R = H; R′ = OCH_3, 51.7 g., 0.3 mole) was added dropwise at a rate causing gentle reflux. The addition required 1.5 hr. and ice cooling was occasionally necessary. Water (16 ml.) was then added at a rate causing vigorous reflux, after which the mixture was stirred 15 min. more. The mixture was filtered, and the filtrate was concentrated to a yellow oil weighing 33.7 g. (71%), $n^{27}D$ 1.4782. The oil was found to be satisfactorily pure without distillation, which, in any case, caused partial decomposition. On a 2-mole scale, the yield in the above reaction was 59.6%.

Anal. Calcd. for $C_7H_{14}N_2O_2$: N, 17.17. Found: N, 16.99.

3-Oxo-1,2-diazabicyclo[2.2.2]octane (VII, R = H).—A solution of III (R = H, R′ = OCH_3, 125.8 g., 0.79 mole) in 1 l. of Dowtherm A was heated to 175° in 1 hr. under nitrogen. Heating was continued at 195–200° for 3 hr., after which the solution was allowed to cool overnight under nitrogen. The dark solution was poured into 6 l. of *n*-pentane, and the solid was filtered, washed with *n*-pentane, and recrystallized from propionitrile to give 47.2 g.

1,2-Diazabicyclo[2.2.2]octane Hydrochloride (VIII, R = H).—Reduction of VII (R = H) (24.1 g., 0.19 mole) with lithium aluminum hydride (14.5 g., 0.38 mole) as described for the 4-phenyl analog gave a 93% yield of crude VIII (R = H). Sublimation of a small portion at 90° (0.1 mm.) gave a white, crystalline product, m.p. 137–140° and b.p. 170–175° (760 mm.). The hydrochloride was recrystallized from 2-propanol–ethyl acetate, then ethanol–ethyl acetate.

2-Phenylthiocarbamyl-1,2-diazabicyclo[2.2.2]octane (IX, R = H, R″ = $CSNHC_6H_5$).—Phenylisothiocyanate and 1,2-diazabicyclo[2.2.2]octane in benzene gave this product in 76.8% yield.

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(26) B. Elpern and L. N. Gardner, this laboratory, unpublished.

(27) A eutectic mixture of diphenyl and diphenyl ether.