# Antifilarial Agents. Diazabicyclooctanes and Diazabicycloheptanes as Bridged Analogs of Diethylcarbamazine†

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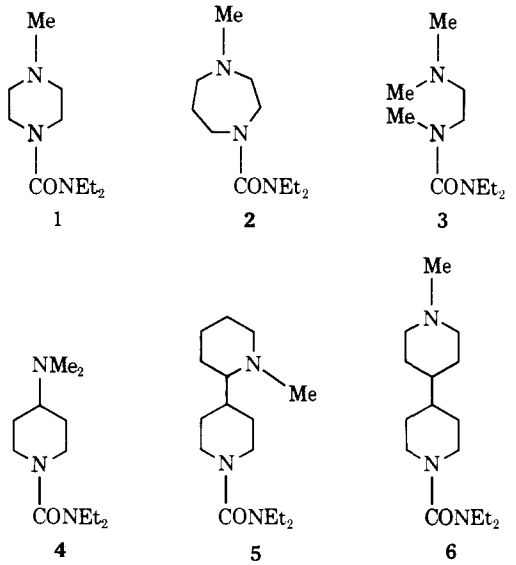
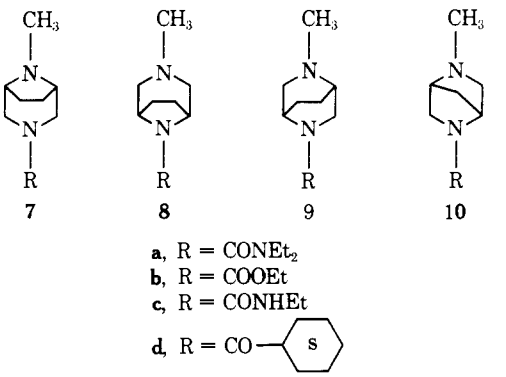
Twelve analogs of diethylcarbamazine (DEC) were prepared by acylation of 3- and 8-methyl-3,8-diazabicyclo[3.2.1]octane, 2-methyl-2,5-diazabicyclo[2.2.2]octane, and 2-methyl-2,5-diazabicyclo[2.2.1]heptane with diethylcarbamyl chloride, ethyl chloroformate, ethyl isocyanate, and cyclohexanecarbonyl chloride. These compounds are formally derived from DEC in possessing two- or one-carbon bridges over the piperazine ring. When evaluated against *Litomosoides carinii* in the gerbil, all compounds strongly suppressed blood microfilaremia levels but did not affect the adult worms. Several compounds were nearly equivalent to DEC in activity. The results are discussed in terms of molecular model studies and receptor site theory.

Diethylcarbamazine (DEC, 1) was described by Hewitt, *et al.*,[2] in 1947 and has since become the primary drug for the treatment of Bancroftian filariasis, Malayan filariasis, loaiasis, and the microfilaremia of onchocerciasis. In spite of the widespread occurrence of these diseases in tropical areas throughout the world,[3] and the well-known deficiencies of DEC,[4] there has been surprisingly little research on DEC analogs since that time.[5] The work reported here and in succeeding papers of the series was undertaken in an effort to use past work on DEC analogs to develop improved drug activity and define further the structural parameters leading to activity within the class. More specifically, we have been examining the biological effects of changes in the carbon skeleton that links the essential functional groups of DEC and its close relatives.

Structure-activity work related to DEC[2,6-20] has established that drugs displaying any effect against *Litomosoides carinii* microfilaria in rodents possess two aliphatic amine functions connected by a saturated carbon framework. One amine function must be basic and the other modified by coupling with some type of carbonyl function. Compounds 2-6 illustrate some of the types of carbon skeleton that have been employed in conjunction with the two functional groups. Homopiperazine (2) is one-fourth to one-half as active as DEC.[17] Acyclic analog 3 has been described as having slight[12] or no[14] antimicrofilarial properties. Compounds 4-6 displayed moderate activity but did not approach DEC in potency.[13]




Because of the lack of detail in published test data, it is not possible to compare quantitatively the potencies of these compounds except to say that DEC is the most effective. However, it is evident that all differ from DEC in having greater molecular flexibility and a greater distance between the functional groups. Compound 3, which has the greatest conformational freedom, is virtually inactive, and a variety of related open-chain congeners were also inactive.[14,18,20] For our study, we therefore elected to prepare compounds with functionality closely related to that of DEC but that had functional group separations equal to or less than that of DEC and that were conformationally more rigid. To that end, several DEC-related derivatives of 3,8-diazabicyclo[3.2.1]octane (**7a-d**, **8a-c**), 2,5-diazabicyclo[2.2.2]octane (**9a-c**), and 2,5-diazabicyclo[2.2.1]heptane (**10a,b**) were synthesized and evaluated for their capacity to reduce blood microfilaria levels in gerbils harboring experimentally induced *L. carinii* infections. The inclusion of carbethoxy (**b**),[14] ethylcarbamyl (**c**),[14] and cyclohexylcarbonyl (**d**),[21] as modifying groups, in addition to diethylcarbamyl (**a**), was based on earlier findings that these were nearly equivalent in microfilariacidal properties.




## Results and Discussion

Table I presents the biological results obtained in this study. The assay entailed a sliding daily dosage schedule. Drugs were administered at dosages of 25, 50, 100, and 200 mg/kg on days 0, 1, 2, and 3, respectively. Blood microfilaria levels were determined before treatment and on days 1, 3, 7, 9, and 14 of the experiment. Details of the assay are given in the Experimental Section. Data on DEC are

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**Table I.** Chemical and Antifilarial Properties of Bridged Diethylcarbamazine Analogs

| Compd | Formula[b] | Yield, % | Mp, °C | Microfilaria count, day 0 (range) | Antifilarial activity[a] % of day 0 count (std dev) Day 1 | 3 | 7 | 9 | 14 |
|---|---|---|---|---|---|---|---|---|---|
| 1 (DEC) | | | | 132 (56–194) | 6 (±3) | 0.1 (±0.2) | | 29 (±11) | 43 (±12)[c] |
| **7a** | $C_{12}H_{23}N_3O \cdot HCl$ | 89 | 202–205 | 208 (104–406) | 62 (±20) | 1 (+0.6) | 13 (±6) | 30 (±8) | 35 (±12) |
| **7b** | $C_{10}H_{18}N_2O_2 \cdot HCl$ | 73 | 200–205 | 232 (41–358) | 84 (±20) | 1 (+0.7) | 12 (±4) | 21 (±3) | 49 (±16) |
| **7c** | $C_{10}H_{19}N_3O \cdot HCl$ | 79 | 246–250 dec | 194 (59–539) | 92 (±35) | 3 (±2) | 18 (±8) | 32 (±9) | 46 (±12) |
| **7d** | $C_{14}H_{24}N_2O \cdot HCl$ | 58 | 263–268 | 86 (18–196) | 86 (±12) | 4 (±1) | 17 (±2) | 28 (±5) | 52 (±18) |
| **8a** | $C_{12}H_{23}N_3O \cdot C_4H_4O_4$[d] | 82 | 123–125 | 155 (77–338) | 26 (±9) | 6 (±3) | 21 (±8) | 23 (±20) | 63 (±28) |
| **8b** | $C_{10}H_{18}N_2O_2 \cdot HCl$ | 91 | 209–210 | 371 (84–1040) | 110 (±41) | 8 (±5) | 16 (±8) | 32 (±18) | 66 (±28) |
| **8c** | $C_{10}H_{19}N_3O \cdot HCl$ | 28 | 205–215 | 175 (14–312) | 152 (±48) | 25 (±14) | 33 (±13) | 54 (±29) | 45 (±10) |
| **9a** | $C_{12}H_{23}N_3O \cdot 2HCl$[e,f] | 60 | 144–157 | 280 (126–379) | 25 (±12) | 1 (+0.6) | 7 (±2) | 17 (±5) | 43 (±11)[g] |
| **9b** | $C_{10}H_{18}N_2O_2 \cdot HCl$[e] | 58 | 149–155 | 223 (39–765) | 16 (±9) | 0.1 (±0.2) | 8 (±4) | 19 (±9) | 66 (±18)[g] |
| **9c** | $C_{10}H_{19}N_3O \cdot HCl$ | 52 | 220–230 dec | 241 (96–365) | 93 (±30) | 6 (±4) | 14 (±3) | 31 (±9) | 68 (±14)[g] |
| **10a** | $C_{11}H_{21}N_3O \cdot C_4H_4O_4$[d] | 40 | 82–84 | 229 (166–273) | 87 (±27) | 6 (±3) | 20 (±7) | 31 (±12) | 79 (±25) |
| **10b** | $C_9H_{16}N_2O_2 \cdot C_4H_4O_4$[d] | 75 | 78–82 | 290 (141–678) | 96 (±34) | 20 (±9) | 31 (±13) | 41 (±21) | 82 (±25) |

[a] See Experimental Section for assay details. [b] Elemental analyses for carbon, hydrogen, and nitrogen were within ±0.4% of the theoretical values for these compounds. [c] This figure refers to day 11 rather than day 14. [d] Maleic acid salt. [e] Hygroscopic. [f] Loses HCl slowly with time. [g] This figure refers to day 15 rather than day 14.

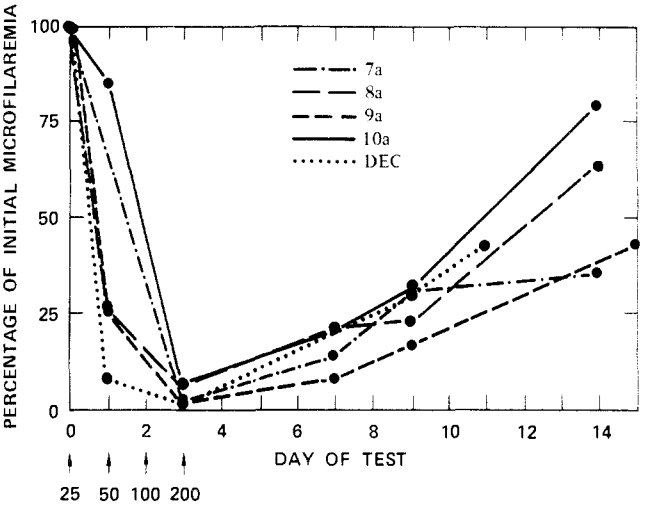



Figure 1. Antifilarial activity of diethylcarbamazine analogs.

given for comparison. Drug activity is indicated by a decrease in the microfilarial count. The average count on day 0 is given for each experimental group (four or five animals per group), but test data are presented as a percentage of the day 0 microfilaremia level. Figure 1 presents the data for DEC and compounds **7a**, **8a**, **9a**, and **10a** in graphical form.

DEC proved to have the most rapid onset of action and effected the lowest day-3 nadir among all of the drugs examined with the exception of **9a**, which appeared to be of about equal potency. Compared to DEC most of the new compounds produced comparatively modest effects on day 1, but by day 3 all had induced markedly lowered microfilaremia levels, in parallel with DEC. At necropsy the adult worms were found essentially unaffected by all treatments; this is reflected by the rapid rebound in microfilaremia levels upon cessation of therapy (days 7, 9, 14).

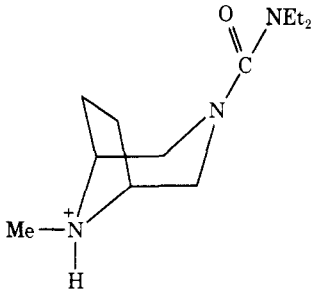
8-Methyl-3,8-diazabicyclo[3.2.1]octane (series **7**) and 2,5-diazabicyclo[2.2.2]octane (series **9**) provided compounds somewhat more potent than the other two ring systems (**8** and **10**), but the differences were not substantial. Two compounds from series **9** (**9a**,**b**) lowered the microfilarial count somewhat faster than the others and effected minima among the lowest encountered, but neither were clearly outstanding. Two derivatives of 3-methyl-3,8-diazabicyclo[3.2.1]octane (**8b**,**c**) apparently enhanced the microfilarial count on day 1, but both regained the common pattern by day 3.

In terms of the influence of the acylating function, diethylcarbamyl and carbethoxy appeared roughly equivalent within each ring system group. Ethylcarbamyl generally produced the least effective compounds (*e.g.*, **8c**) but the difference was not remarkable. The cyclohexylcarbonyl function of **7d** was essentially indistinguishable from other acyl groups employed in the study.

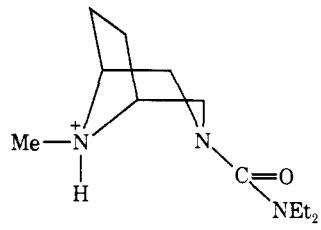
The most notable feature of these results is their comparative uniformity. All the new compounds were substantially active, and the differences, where they exist, are not highly marked. This phenomenon may be rationalized in terms of the stereochemistry of these molecules. Chart I presents stereoformulas of compounds **7a**–**10a**. The stereoformula of DEC may be visualized by deletion of the bridge from **7** or **8**. A possible boat form of **7** is given; a similar boat form for **8** is also possible.

Structure **11** is that of a fused bicyclic DEC analog that was reported by Saxena, *et al.*, during this work.[18,19] It is formally derived from DEC by connecting one of the ethyl

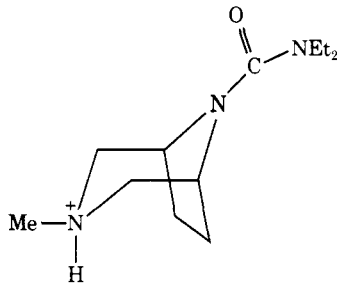
**Chart I**



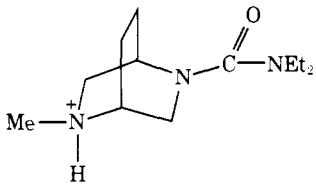
**7a**, chair



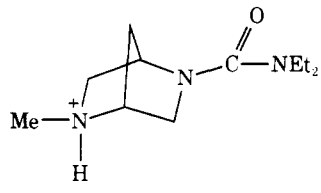
**7a**, boat



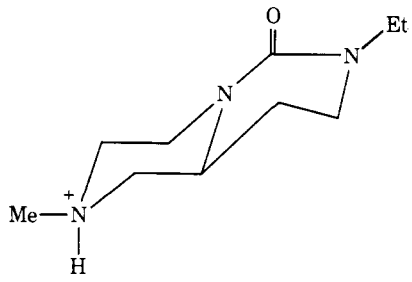
**8a**



**9a**



**10a**



11

groups to the 2 position of the piperazine ring. Compared with DEC, this compound was reported to have five times the potency, a higher therapeutic index, and increased duration of action against *L. carinii* in the cotton rat. In a more recent study, Thompson, *et al.*,[22] found 11 highly active against *L. carinii* in the gerbil as well as in the cotton rat but were not able to demonstrate obvious superiority over DEC. Of special importance to the present study, the bicyclic ring system of 11 provides markedly increased molecular rigidity and locks the urea moiety into a single rotational conformation. In contrast, the diethylcarbamyl group of DEC is free to rotate about all of its single bonds. Space-filling molecular models, as depicted in the formula, indicate that molecule 11 is approximately planar with the carbon-oxygen bond of the carbonyl and all the nitrogens of the molecule lying in the plane. Since this molecule is at least as effective as DEC, this conformation is apparently optimum.

Among the drugs reported in our study, models indicate that all can closely approximate the preferred geometry with regard to the relative positions of the carbonyl and nitrogen functions. However, they can also assume, as can DEC, alternate conformations because of rotational freedom in the diethylcarbamyl moiety. Although molecular models cannot provide definitive evidence, their study suggests that ring systems 8 and **10** provide substantially more steric hindrance to achieving the desired geometry than in 7 and **9**. The latter ring systems appear roughly comparable to DEC in permitting the diethylcarbamyl group to assume the conformation of **11**.

It is apparent from the assay data in Table I that the nature of the carbon structure connecting the essential amide and tertiary amine moieties is not critical. Although all the reported ring systems place the two pharmacophoric groups about the same distance apart (2.8 ± 0.1 Å between ring nitrogen atoms), they differ in other ways. The piperazine rings of 7 and 8 may exist either as boat or chair forms, as can DEC itself, with the chair the more likely. The piperazine rings of 9 and **10** are locked into boat forms. The ethylene bridges of 7-9 might be expected to cause marked effects because of steric hindrance of the amine or amide functions, but this does not occur to an obvious extent. As shown by models, the overall shape of these ring systems varies considerably, and it must be concluded that the receptor site involved in the action of this class of drugs possesses a comparatively low order of discrimination for the connecting carbon linkage.

One stereochemical point that the compounds prepared in the study do not address is the orientation of the *N*-methyl group. In each drug, the methyl group may assume at least two conformations because of the ability of the nitrogen atom to invert. In the cases of 7 and 8, the possible boat-chair equilibrium adds additional conformational possibilities for the *N*-methyl. This subject will be considered in a subsequent paper.

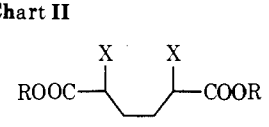
A sufficient supply of compound **7a** was available to treat one dog harboring an experimentally induced *Dirofilaria immitis* infection. The drug was given orally in two daily doses for 19 days. Individual doses ranged from 20 to 50 mg/kg/day with a total dose of 768 mg/kg. This treatment gradually resulted in a 90% decrease in microfilaremia, but the microfilarial count returned to pretreatment levels within 4 months of cessation of therapy, thus indicating little effect on the adult worms. It should be noted, however, that the total dose of **7a** was only about half that of DEC typically employed for heart worm treatment.

None of the compounds prepared in this study displayed toxicity under the conditions employed to obtain the data given in Table I. Compound **8a**—when subjected to a similar test employing 100, 200, and 400 mg/kg doses on days 0, 1, and 2, respectively—killed three out of five animals after the second treatment. In the two survivors, microfilaremia levels dropped to 0.4% on day 3 and recovered to only 10% by day 14.

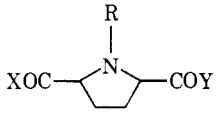
**Chemistry.** The 3,8-diazabicyclo[3.2.1]octane system of series 7 and 8 was obtained by a route closely related to that of Cignarella and colleagues[23,24] and also to that of Blackman and Baltzly.[25] The former authors prepared 8-methyl-3,8-diazabicyclo[3.2.1]octane (**28**), a key intermediate for series 7, by a seven-step sequence starting from diethyl *meso*-$\alpha,\alpha'$-dibromoadipate (**12**), but we were unable to reproduce their results reliably. However, a six-step variation on their method (**12** → **16** → **17** → **18** → **23** → **27** → **28**) proved effective. In general, the route proceeds by ring closure of **12** to *cis*-pyrrolidine-2,5-dicarboxylic acid derivatives **16**-**18** followed by a second ring closure to bicyclic imide **23**. Reduction of the latter provided the bridged piperazine **27** (Chart II).

The isomeric 3-methyl-3,8-diazabicyclo[3.2.1]octane (**30**) required for series 8 was obtained by a seven-step modification of the basic sequence (**12** → **20** → **21** → **25** → **22** → **26** → **29** → **30**). This route entails preparation of pyrrolidinedicarboxylic acid **21** and conversion to mo-

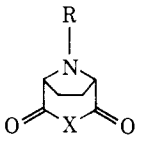
**Chart II**



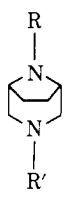
| | R | X |
|---|---|---|
| 12 | Et | Br |
| 13 | Et | phthalimido |
| 14 | H | $NH_2$ |
| 15 | Me | $NH_2$ |



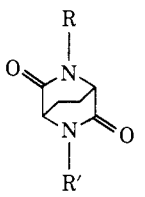
| | R | X | Y |
|---|---|---|---|
| 16 | $CH_3$ | OEt | OEt |
| 17 | $CH_3$ | OEt | $NHCH_2Ph$ |
| 18 | $CH_3$ | OH | $NHCH_2Ph$ |
| 19 | $CH_3$ | OH | OH |
| 20 | $CH_2Ph$ | OEt | OEt |
| 21 | $CH_2Ph$ | OH | OH |
| 22 | $CH_2Ph$ | OH | $NHCH_3$ |



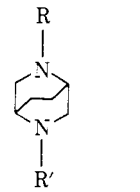
| | R | X |
|---|---|---|
| 23 | $CH_3$ | $NCH_2Ph$ |
| 24 | $CH_3$ | O |
| 25 | $CH_2Ph$ | O |
| 26 | $CH_2Ph$ | $NCH_3$ |



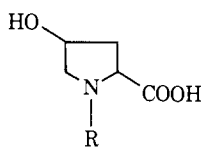
| | R | R′ |
|---|---|---|
| 27 | $CH_3$ | $NCH_2Ph$ |
| 28 | $CH_3$ | H |
| 29 | $CH_2Ph$ | $CH_3$ |
| 30 | H | $CH_3$ |



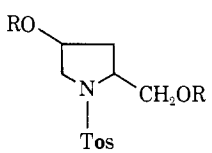
| | R | R′ |
|---|---|---|
| 31 | H | H |
| 32 | $CH_2Ph$ | $CH_2Ph$ |
| 33 | H | $CH_2Ph$ |
| 34 | $CH_3$ | $CH_2Ph$ |



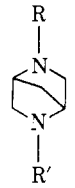
| | R | R′ |
|---|---|---|
| 35 | $CH_2Ph$ | $CH_2Ph$ |
| 36 | H | H |
| 37 | COPh | H |
| 38 | COPh | $CH_3$ |
| 39 | H | $CH_3$ |



40, R = H
41, R = Tos



42, R = H
43, R = Tos



| | R | R′ |
|---|---|---|
| 44 | $CH_2Ph$ | Tos |
| 45 | $CH_2Ph$ | H |
| 46 | $CH_2Ph$ | $CONEt_2$ |
| 47 | H | $CONEt_2$ |
| 48 | $CH_2Ph$ | COOEt |
| 49 | $CH_2Ph$ | $CH_3$ |
| 50 | H | $CH_3$ |

noamide **22** *via* bicyclic anhydride **25**. A similar route to **28** was originally envisioned (*i.e.*, **19** → **24** → **18**), but anhydride **24** proved too unstable to survive hot acetic anhydride, the reagent used to form it from diacid **19**. The sensitivity of monocyclic basic anhydrides related to **24** and **25** has been noted previously.[26]

The 2,5-diazabicyclo[2.2.2]octane system of target series **9** was obtained by a synthesis reported in the patent literature.[27] Starting material **12** was converted to $\alpha,\alpha$-diaminoadipic acid (**14**) *via* phthalimido derivative **13**. Esterification to **15**, followed by ring closure to dilactam **31**, proceeded essentially as described, but the reduction of **31** to **36** with lithium aluminum hydride proved intractable in our hands, apparently owing to the insolubility of **31** in organic solvents. This problem was solved by benzylating **31** to give **32**; reduction of **32** to **35** was readily achieved, as was catalytic debenzylation to **36**. The required asymmetry of N substitution required for the target drugs was incorporated by monobenzoylation to **37** under pH-controlled conditions as described.[27] Methylation to **38** followed by hydrolysis provided key intermediate **39**.

In an effort to avoid the additional steps to **39** entailed by the benzylation-debenzylation and benzoylation-hydrolysis steps, we attempted to monobenzylate **31** to **33**, thereby acquiring solubility in organic solvents and asymmetric N substitution in one step. Unfortunately, under a variety of solvent and stoichiometry conditions, monobenzyl intermediate **33** proved to be formed in much lower yields (maximum 18%) than the dibenzyl dilactam **32**. In the hope that useful amounts of *N*-methyl-*N*′-benzyl dilactam (**34**) could be formed by alkylation of **31** with mixtures of methyl iodide and benzyl chloride, the experiment was performed with a wide variety of alkylating agent ratios. Inexplicably, symmetrically substituted products predominated under all conditions, and **34** was obtained in a maximum yield of only 25%. This low yield would have been an acceptable exchange for a three-step decrease in the length of the synthesis of **39**, except that the separation of **34** from **32** and the corresponding *N*,*N*′-dimethyl dilactam was impractical on a useful scale.

The key intermediate (**45**) in the 2,5-diazabicyclo[2.2.1]heptane series (**10**) was prepared from hydroxyproline (**40**) essentially as described by Portoghese and Mikhail.[28] We found it convenient, however, to reduce acid **41** directly to diol **42** with diborane rather than prepare the methyl ester of **41** for subsequent lithium borohydride reduction. Target **10a** was obtained by conversion of **45** to diethylcarbamyl derivative **46**, followed by debenzylation to **47** and methylation. Treatment of **45** with ethyl chloroformate to give **48**, reduction to **49**, debenzylation to **50**, and reaction again with ethyl chloroformate yielded target **10b**.

## Experimental Section

**Antifilarial Evaluation.** Mongolian jirds (*Meriones unguiculatus*) of both sexes were purchased as weanlings from Rudolph R. Aussner, Collegedale, Tenn., and Lester Embry of Kansas City, Mo. They were infected with *Litomosoides carinii* using a modification of the tank exposure method of Hawking and Sewell[29] approximately 8–10 weeks before dosing was initiated. This entailed allowing large numbers of mites to feed on two jirds with patent *L. carinii* infections for 2 weeks and then allowing the mites to feed during an additional 2 weeks on the test animals. The entire infecting procedure was conducted in an insectary maintained at 80°F (26.6°) and 80% relative humidity. The animals used in an experiment were exposed concomitantly in the same tank. When placed on test, the jirds typically weighed 50–70 g.

Examinations for microfilariae were made in Giemsa-stained thick films of blood drawn from the retroocular sinus. Films were prepared by mixing 20 μl of blood with tap water and spreading the mixture on a 25 by 15 mm area of a microscope slide. At least 200 microfilariae were counted per slide and the number of fields noted (100× magnification). A minimum of five fields was counted. These were converted to numbers of microfilariae per μl of blood using conversion factors for the appropriate microscope. Microfilarial counts were done on days −5 or −4 of the experiment and on days 0, 1, 3, 7, 9 or 11, and 14.

Animals were divided into groups of four or five jirds according to their microfilariae counts. Each group had approximately the same mean microfilaremia. Animals not having microfilariae in 20 μl of blood were discarded.

Untreated infected control animals were included in each experiment to assure the stability of the infection. However, drug-treated animals served as their own controls because drug effects were determined by comparing pre- and posttreatment microfilaremia levels.

Water-soluble drugs were administered by gavage as aqueous solutions. Drugs insoluble in water were ultrasonicated for 10 min in aqueous 0.5% hydroxyethylcellulose and 0.1% Tween 80 and administered by gavage. Doses were expressed in terms of the free base and were given in two daily subdoses 5–6 hr apart. Control

animals were given the respective vehicle only. Dosing was initiated on day 0 immediately after determining the microfilarial count.

The experiments were terminated on day 14 when surviving animals were killed and examined for adult worms. The pleural and peritoneal cavities were thoroughly searched and the worms removed to petri dishes containing physiological saline. The peritoneal cavity only occasionally contained worms, and these were few in number. The number of live worms was counted. Dead worms were scored because they could not be accurately counted since most of them were encapsulated. The average live worm burden per animal was calculated to be approximately 33 worms.

**Chemistry.** All boiling and melting points are uncorrected. Melting points were determined using a Fisher block or a Mel-Temp apparatus. Infrared spectra were obtained on a Perkin-Elmer Infracord. Merck acid-washed alumina (71695) was used for column chromatography, and tlc data were obtained from alumina GF plates unless otherwise noted. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Corey-Pauling-Koltun atomic models (Ealing Corp.) were used in the molecular model studies.

**Diethyl *cis*-1-Methylpyrrolidine-2,5-dicarboxylate (16).** To liquid $CH_3NH_2$ (3.5 g, 0.113 mol), collected in the chilled glass liner of a 500-ml stainless steel bomb, was added a solution of **12**[30,31] (12.0 g, 0.0334 mol) in $C_6H_6$ (40 ml). The sealed bomb was then heated at 90° overnight. After cooling, the bomb was opened, the white solid ($CH_3NH_2$·HBr) was collected, and the filtrate evaporated *in vacuo* to a yellow oil. Fractionation through a Vigreux column yielded the product: 4.6 g (61%); bp 73–76° (0.2 mm). *Anal.* ($C_{11}H_{19}NO_4$) H, N; C: calcd, 57.6; found, 57.0.

***cis*-1-Methylpyrrolidine-2,5-dicarboxylic Acid (19).** Compound **16** (4.65 g, 0.0203 mol) in concentrated HCl (40 ml) was heated 2 hr at 90–100°. The reaction was then evaporated *in vacuo* to a light orange solid and triturated in hot absolute EtOH to afford a white solid (1.34 g), mp 292–300° dec (sublimed above 250°). Sublimation at 0.25 mm and 210° yielded 1.04 g (29%) of white solid with the same melting point. *Anal.* ($C_7H_{11}NO_4$) C, H, N. Analysis before sublimation indicated persistent, nonstoichiometric HCl contamination.

**Ethyl *cis*-5-(*N*-Benzylcarbamyl)-1-methylpyrrolidine-2-carboxylate (17).** A solution of compound **16** (10.95 g, 0.0478 mol) and benzylamine (5.2 ml, 0.048 mol) in xylene (30 ml) was refluxed 72 hr at 140°. After evaporation of the xylene *in vacuo*, the oily residue was fractionated on a Vigreux column. After an initial fraction of **16** (0.49 g), the product was collected: 7.11 g; bp 160° (0.25 mm). *Anal.* ($C_{16}H_{22}N_2O_3$) C, H, N.

**3-Benzyl-8-methyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (23).** Compound **17** (59.0 g, 0.203 mol) in 622 ml of 1 *N* NaOH (in 75% aqueous EtOH) was stirred at room temperature for 30 min. The reaction was neutralized with dry HCl (phenolphthalein end point), and the white solid (NaCl) was collected by filtration. The filtrate was evaporated *in vacuo*, redissolved in absolute EtOH, and reevaporated to a foamy glass. This material (crude **18**) was heated in $Ac_2O$ (565 ml) at 110° for 2 hr. The cooled, dark amber reaction mixture was filtered to remove precipitated inorganic salts (22 g). The filtrate was evaporated *in vacuo* to leave a dark brown crystalline solid (52.7 g). Recrystallization from $CHCl_3$–$Et_2O$ gave 38 g of brown solid, mp 92–95°. Filtration of this in $CHCl_3$ solution through 400 g of alumina afforded, after removal of solvent, 32.8 g (66%) of colorless product, mp 98–102°, which was suitable for subsequent reactions. An earlier reaction provided the analytical sample, mp 105.5–108°. *Anal.* ($C_{14}H_{16}N_2O_2$) C, H, N.

**3-Benzyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (27).** A solution of compound **23** (32.8 g, 0.135 mol) in dioxane (500 ml) was rapidly added dropwise to a suspension of $LiAlH_4$ (20.5 g, 0.54 mol) in dioxane (500 ml). The reaction was refluxed 18 hr, cooled, and worked up by slow and careful dropwise addition of water (stirring) until the grey suspension turned white. The mixture was filtered, the inorganic salts were washed with dioxane, and the combined filtrate and washing were evaporated *in vacuo* to leave a pale yellow oil (24.9 g). Chromatography on 370 g of alumina in $CHCl_3$ provided 17.7 g of pure oily free base. Treatment with 3 equiv of anhydrous ethanolic HCl in ether solution gave 19.1 g (41%) of the dihydrochloride salt which analyzed as the monohydrate after drying *in vacuo* (0.2 mm) at 100° for 18 hr. It melted at *ca.* 110°, resolidified, and remelted at 210–219°. *Anal.* ($C_{14}H_{20}N_2$·2HCl·$H_2O$) C, H, N.

**8-Methyl-3,8-diazabicyclo[3.2.1]octane (28).** A mixture of compound **27**·2HCl·$H_2O$ (18.1 g, 0.059 mol) in absolute EtOH (200 ml) and 10% Pd on charcoal (3.0 g) was hydrogenated for 2 hr at atmospheric pressure. Sufficient water was added to dissolve the insoluble HCl salt that had formed, and the reaction was filtered. The filtrate was evaporated *in vacuo*, residue was triturated in hot absolute EtOH, and the mixture was filtered to yield 8.98 g of **28**·2HCl, mp 315° dec. The mother liquor was treated with ethanolic dry HCl to afford an additional 2.28 g: yield, 12.26 g (96%). *Anal.* ($C_7H_{14}N_2$·2HCl) C, H, N.

**Diethyl *cis*-*N*-Benzylpyrrolidine-2,5-dicarboxylate (20).** The preparation of this compound from **12** and benzylamine proceeded as described[24] except that external heating was required to maintain the reaction temperature at the specified 83–85°.

***cis*-*N*-Benzylpyrrolidine-2,5-dicarboxylic Acid (21).** Compound **20** (103.5 g, 0.340 mol) was heated in concentrated HCl (1 l.) at 100° for 2 hr. Upon cooling, a crystalline solid precipitated. It was isolated by filtration, triturated with acetone–ether, and recrystallized from EtOH–$H_2O$ to give 41.3 g (49%) of partially hydrated product: ir 2.95 μ; mp 254–258°. This material was used for preparing anhydride **25**. A similar sample from an earlier experiment was analyzed. *Anal.* ($C_{13}H_{15}NO_4$·0.33$H_2O$) C, H, N. Crystallization by simply concentrating an EtOH–$H_2O$ solution led to anhydrous product melting at 247–250°. *Anal.* ($C_{13}H_{15}NO_4$) C, H, N. This latter product failed to produce cyclic anhydride **25** when submitted to the same conditions as the hydrated form.

***cis*-5-(*N*-Methylcarbamyl)-1-benzylpyrrolidine-2-carboxylic Acid (22).** Compound **21** (41.3 g, 0.166 mol) and $Ac_2O$ (206.5 ml) were heated carefully together to 100°; the solid gradually dissolved, and the mixture assumed a dark brown color. In typical experiments, solution was complete in 10–30 min, depending on the state of subdivision of **21**. Heating time should be minimized. Just before the last solid dissolved, the excess $Ac_2O$ was removed *in vacuo*, and the brown oily residue of crude **25** was taken up in 400 ml of $C_6H_6$. Anhydrous methylamine (0.33 mol as 9.9% solution in $C_6H_6$) was added in two portions, and the mixture was heated on the steam bath for 45 min. After cooling, the crude product (35.8 g) was collected by filtration, washed with $C_6H_6$, and recrystallized from EtOH: yield, 31.4 g (72%); mp 190–192°. *Anal.* ($C_{14}H_{18}N_2O_3$) C, H, N.

**8-Benzyl-3-methyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (26).** Compound **22** (32.3 g, 0.123 mol) and $Ac_2O$ (160 ml) were heated together at 100° for 45 min after all solid had dissolved. Removal of solvent *in vacuo* left a red-brown oil that was dissolved in minimum $C_6H_6$. After removal of 2.0 g of unreacted **22** by filtration, the solution of product was chromatographed on 900 g of alumina ($C_6H_6$ elution) to give 13.2 g (44%) of pure, oily product. Treatment of a sample with excess ethanolic HCl in $Et_2O$ solution produced a salt, mp 140–170°. *Anal.* ($C_{14}H_{16}N_2O_2$·HCl) C, H, N. A sample of the free base, mp 73–75°, was subsequently obtained by slow crystallization from $C_6H_6$.

**8-Benzyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (29).**[24] Reduction of 9.6 g (0.039 mol) of **26** with $LiAlH_4$ in THF by the procedure used for **23** gave 8.3 g of crude **29**. Chromatography on 124 g of alumina with $CHCl_3$ elution gave 6.9 g (81%) of pure, oily product. The HCl salt, formed in $Et_2O$ by addition of 3 equiv of ethanolic HCl, melted at 263.5–272° dec with sublimation above 180°. *Anal.* ($C_{14}H_{20}N_2$·2HCl) C, H, N.

**3-Methyl-3,8-diazabicyclo[3.2.1]octane (30).**[24] A solution of 8.2 g (0.038 (0.038 mol) of **29** in 80 ml of absolute EtOH containing 0.11 mol of HCl was hydrogenated in the presence of 1.5 g of 10% Pd on charcoal at ambient temperature and pressure for 20 hr. The precipitated product salt was dissolved by addition of a little water, and, after filtration, the solvent was removed carefully *in vacuo*. The crystalline residue (6.9 g) was triturated with EtOH–$Et_2O$ containing dry HCl to ensure complete formation of the somewhat unstable dihydrochloride salt. Filtration gave 6.0 g (79%) of pure product, mp 272–280° dec with sublimation above 200°. *Anal.* ($C_7H_{14}N_2$·2HCl) C, H, N.

**8-(*N*,*N*-Diethylcarbamyl)-3-methyl-3,8-diazabicyclo[3.2.1]octane (8a).** A solution of 1.17 g (0.0093 mol) of **30** (free base) in 15 ml of *tert*-BuOH was treated with 1.94 ml (0.014 mol) of triethylamine and 1.9 g (0.014 mol) of diethylcarbamyl chloride. The mixture was stirred at ambient temperature for 4 hr. Hot water (30 ml) was added and stirring was continued for 30 min; extraction with $CHCl_3$ followed by drying of the combined extracts ($Na_2SO_4$) and thorough removal of volatiles *in vacuo* gave 1.86 g of crude product. This was dissolved in ether and treated with 1 equiv of maleic acid dissolved in minimum absolute EtOH. The colorless precipitate of **8a** maleate (2.58 g, 82%) was collected by filtration. *Anal.* ($C_{12}H_{23}N_3O$·$C_4H_4O_4$) C, H, N.

**Diethyl 2,5-Diphthalimidoadipate (13).** To a cold (0°) solu-

tion of phthalimide (9.7 g, 0.0666 mol, dried at 85° for 2 hr) in dry DMF (40 ml) was added 2.85 g of 56.4% NaH in mineral oil followed by a solution of **12** (10.0 g, 0.028 mol) in dry DMF (70 ml). The reaction was heated at 80° for 1 hr, cooled, and filtered to remove a small amount of white solid. Mineral oil was removed by pentane extraction, and the DMF was removed *in vacuo*. The residue was taken up in $CHCl_3$ and extracted successively with water, 0.1 *N* NaOH, and water. Removal of solvent *in vacuo* left an oil that crystallized on cooling. Trituration with $Et_2O$ left 4.5 g (33%) of product, mp 133–136°. *Anal.* ($C_{26}H_{24}N_2O_8$) C, H, N.

**2,5-Diaminoadipic Acid (14).**[27] A stirred mixture of **13** (236.1 g, 0.48 mol) and 98–100% hydrazine hydrate (61 ml) in 2500 ml of absolute EtOH was refluxed for 1.5 hr. Solvent was removed *in vacuo*, and concentrated HCl (1270 ml) was slowly added to the solid residue while stirring. The mixture was refluxed 1 hr, cooled, and filtered to remove phthalhydrazide. The filtrate was evaporated to near dryness *in vacuo*, and a chilled solution of the residue in 2400 ml of water was treated with 4 *M* NaOH (*ca.* 800 ml) until neutrality (pH 7–8). The colorless product was collected by filtration: yield, 63.7 g (75.6%); mp 311° dec (lit.[27] mp 303° dec). *Anal.* ($C_8H_{16}N_2O_4 \cdot 2HCl$) C, H, N.

**Dimethyl 2,5-Diaminoadipate (15).**[27] A solution of 44.0 g (0.25 mol) of **14** in 2 l. of MeOH saturated with dry HCl was refluxed 20 hr. After chilling, the precipitated product was isolated as the dihydrochloride by decantation and triturated with $Et_2O$ [49.1 g; mp 233–237° dec (lit.[27] mp 201–203°)]. Evaporation of the supernatant *in vacuo* and trituration of the residue with hot EtOH provided 10.4 g of additional product: total yield, 59.9 g (86%). An analytical specimen was recrystallized from EtOH–$H_2O$: mp 230–240° dec. *Anal.* ($C_8H_{16}N_2O_4 \cdot 2HCl$) H, N; C: calcd, 34.7; found, 34.2.

**2,5-Diazabicyclo[2.2.2]octane-3,6-dione (31).**[27] Compound **15**·2HCl (60.0 g, 0.217 mol) was combined with NaOMe (25.8 g, 0.478 mol) in *n*-BuOH (6.0 l.) and refluxed 5 days at which time the ir of an evaporated aliquot indicated completion. The bulk of the *n*-BuOH was removed by distillation and the remainder by evaporation *in vacuo*. The still-wet tan solid was triturated in hot EtOH and chilled, and the mixture was centrifuged. The solid (49.0 g), a mixture of NaCl and product, was sublimed at 210–220° and 0.3 mm; the collected material was then triturated in hot $CHCl_3$, cooled, and filtered: yield, 17.0 g; mp 275–277° (lit.[27] mp 272–273°). The supernatant was evaporated *in vacuo* and dissolved in $CHCl_3$, and, after several days, an additional 1.3 g of product was collected: overall yield, 18.3 g (58%).

**2,5-Dibenzyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (32).** A hot solution of 36.6 g (0.262 mol) of **31** in 800 ml of dry DMF was added rapidly from a dropping funnel to 12.5 g (0.52 mol) of oil-free NaH. After stirring for 1 hr, the mixture was chilled and treated with 67.5 ml (0.59 mol) of benzyl chloride during a period of a few minutes. After stirring at room temperature for 18 hr, 1 l. of water was added cautiously, and the mixture was extracted with $CHCl_3$. The extracts were washed with $H_2O$, dried ($Na_2SO_4$), and evaporated to dryness to yield a crystalline residue. Trituration in $Et_2O$ provided 77.0 g (91%) of product as colorless needles, mp 168–170°. *Anal.* ($C_{20}H_{20}N_2O_2$) C, H, N.

When only 1 equiv of benzyl chloride was employed in the above reaction leading to **32**, an 18.5% yield of 2-benzyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (**33**, mp 175–177°) could be separated from admixture with **31** and **32** by preparative tlc (silica gel, $CHCl_3$). *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

Use of 1 equiv of an equimolar mixture of methyl iodide and benzyl chloride as the alkylating reagent produced a mixture from which 2-benzyl-5-methyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (**34**, mp 135–137°) could be separated in 24% yield by sequential chromatography on silicic acid columns (EtOAc, $CHCl_3$ elution), silica gel preparative plates (EtOAc), and alumina preparative plates ($CHCl_3$). *Anal.* ($C_{14}H_{16}N_2O_2$) C, H, N.

Another reaction in which 1.5 equiv of an equimolar solution of methyl iodide and benzyl chloride in DMSO was used to alkylate **31** in the presence of NaH and DMSO gave a 24% yield of 2,5-dimethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (mp 205–206°) isolated from a mixture of **32** and **34** by preparative tlc (silica gel, $CHCl_3$). *Anal.* ($C_8H_{12}N_2O_2$) H, N; C: calcd, 57.1; found, 56.5.

**2,5-Dibenzyl-2,5-diazabicyclo[2.2.2]octane (35).** Reduction of 6.1 g (0.019 mol) of **32** by the procedure employed to prepare **29** gave 4.9 g (88%) of this compound as a colorless oil. *Anal.* ($C_{20}H_{24}N_2$) C, H, N.

**2,5-Diazabicyclo[2.2.2]octane (36).**[27] Catalytic debenzylation of **35** (8.00 g, 0.0274 mol) under conditions used to prepare **30** produced 4.15 g (82%) of pure **36**·2HCl after trituration of the crude product with anhydrous MeOH. It decomposed slowly from 300°, without melting, to 360° (lit.[27] mp 335° dec). *Anal.* ($C_6H_{12}N_2 \cdot 2HCl$) C, H, N.

**2-Benzoyl-2,5-diazabicyclo[2.2.2]octane (37).**[27] A solution of **36**·2HCl (25 g, 0.135 mol) in 500 ml of 50% aqueous acetone was adjusted to pH 3.0 (pH meter) by addition of a few drops of 2 *N* HCl. Benzoyl chloride (17.5 ml, 0.157 mol) was added to the stirred mixture in small increments, interspersed with small portions of 50% aqueous NaOAc, in such a manner that the pH was held near 3.0 and was not allowed to go below 2.2. After the addition was complete (6 hr), the mixture was chilled and the colorless precipitate (3.8 g) of by-product 2,5-dibenzoyl-2,5-diazabicyclo[2.2.2]octane [mp 189–190° (lit.[27] mp 181–183°)] was removed by filtration. *Anal.* ($C_{20}H_{20}N_2O_2$) C, H, N.

The filtrate was saturated with $K_2CO_3$ and extracted with $CHCl_3$ to give 15 g of oily material. Chromatography on 150 g of alumina with $CHCl_3$ elution gave 5.0 g of crystalline **37**, mp 119–121° (lit.[27] mp 109–111°). *Anal.* ($C_{13}H_{16}N_2O$) C, H, N. An additional 9.6 g of **37** was obtained by making the alkaline filtrate highly basic with solid NaOH and extracting repeatedly with $CHCl_3$: total yield, 14.6 g (50%). Compound **37** formed an HCl salt, mp 240–244°. *Anal.* ($C_{13}H_{16}N_2O \cdot HCl$) C, H, N.

**2-Benzoyl-5-methyl-2,5-diazabicyclo[2.2.2]octane (38).** To 7.4 ml of 88% HCOOH (0.17 mol) was added 14.6 g (0.0675 mol) of **37** with stirring at 0°. Aqueous formaldehyde (6.0 ml, 36%, 0.078 mol) was added, and, after visible gas evolution had ceased, the mixture was heated at 80° until renewed gas evolution had stopped (1 hr). After 3 hr at 90–100°, volatiles were removed *in vacuo*. The residue was dissolved in water, made alkaline with 20% NaOH, and extracted with $CHCl_3$. After drying ($Na_2SO_4$), the extracts yielded 15.6 g (100%) of colorless oily **38** that was homogenous by tlc. It was characterized as the oxalate salt, mp 167–169° dec. *Anal.* ($C_{14}H_{18}N_2O \cdot H_2C_2O_4$) C, H, N.

**2-Methyl-2,5-diazabicyclo[2.2.2]octane (39).** A solution of **38** (17.2 g, 0.074 mol) in concentrated HCl (172 ml) was refluxed 48 hr. The solution was evaporated to dryness *in vacuo* and the residue triturated with ether. The supernatant, after centrifugation, was decanted, and the procedure was repeated using absolute EtOH. The hygroscopic residue of **39**·2HCl (12.1 g, 81.5%) was dried *in vacuo*. It slowly decomposed above 300°. *Anal.* ($C_7H_{14}N_2 \cdot 2HCl$) C, H, N.

***N*-Tosylhydroxy-L-prolinol (42).** A solution of *N*-tosylhydroxyproline[28] (182.6 g, 0.642 mol) in 800 ml of dry THF was added over a 3-hr period to 1300 ml of 1 *M* $BH_3$ in THF with stirring at 0°. The reaction mixture solidified into a white, opaque gel. This was broken up by hand, 800 ml of THF was added, and the mixture was refluxed 2.5 hr with mechanical stirring. During this time, most of the solid redissolved. After 18 hr at ambient temperature, the reaction mixture was chilled, and 6 *N* HCl was carefully added until gas evolution ceased. Water (1 l.) was added, and the homogenous solution was diluted with $CHCl_3$ until two phases formed. The aqueous phase was separated and extracted with additional $CHCl_3$. The combined organic phases were washed with water, dried ($Na_2SO_4$), and evaporated *in vacuo* to leave a semisolid residue (159.6 g) that gave 80.0 g (50.5%, mp 130–132°) of **42** upon crystallization from EtOAc (lit.[28] mp 131–133°).

**2-Benzyl-5-(*N*,*N*-diethylcarbamyl)-2,5-diazabicyclo[2.2.1]heptane (46).** A two-phase mixture of 2-benzyl-2,5-diazabicyclo[2.2.1]heptane dihydroiodide (**45**)[28] (6.0 g, 0.0135 mol), 27 ml of 20% NaOH, and 50 ml of $CHCl_3$ was stirred 1 hr at 0°. Diethylcarbamyl chloride (2.75 g, 0.0202 mol) in 5 ml of $CHCl_3$ was added and the mixture stirred at 0° for 1 hr. After 68 hr at ambient temperature, 50 ml of hot water was added, and 30 min later the organic phase was isolated. One $CHCl_3$ extract of the aqueous phase was combined with the original organic phase, and the solution was dried ($Na_2SO_4$). Evaporation to dryness *in vacuo* left 4.87 g of oily crude product that was chromatographed on alumina with $CHCl_3$ elution. The purified product in 100 ml of ether was converted to the salt by addition of dry 5.9 *M* ethanolic HCl. The tacky precipitate was triturated with ether–acetone to give pure **46**·HCl (3.2 g, 80%, mp 147–149°). *Anal.* ($C_{17}H_{25}N_3O \cdot HCl$) C, H, N.

**2-(*N*,*N*-Diethylcarbamyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane (10a).** Compound **46**·HCl (3.2 g, 0.0099 mol) in 50 ml of 95% EtOH was hydrogenated at ambient temperature and pressure in the presence of 0.5 g of 10% Pd on charcoal. When the debenzylation was complete (2 hr), the mixture was filtered, and volatiles were removed *in vacuo*. Ether was added to the residue followed by ethanolic 5.9 *M* HCl until further additions induced no more cloudiness. Chilling at 0° effected crystallization of the

oily precipitate of **47**·HCl. Upon isolation by filtration, this proved to be very hygroscopic, and the oily free base (1.85 g, 95%) was regenerated by $CHCl_3$ extraction of an alkaline solution of the salt.

The free base **47** was mixed at 0° with 1.02 ml of 88% HCOOH (0.024 mol) and 0.80 ml of 33% aqueous HCHO (0.01 mol) and heated 30 min on the steam bath (gas evolution ceased). After heating a further 18 hr at 90°, the reaction mixture was chilled, made basic with 20% NaOH, and extracted with $CHCl_3$. Evaporation of the extract left 1.3 g (66%) of oily **10a** that was homogeneous by tlc (alumina-$CHCl_3$). The maleic acid salt was obtained from ether by addition of 0.605 g of maleic acid dissolved in a small volume of EtOH. The slightly hygroscopic salt was recrystallized from acetone–ether to afford 1.24 g (40%) of pure **10a** maleate, mp 82–84°. *Anal.* ($C_{11}H_{21}N_3O \cdot C_4H_4O_4$) C, H, N.

**2-Benzyl-5-carbethoxy-2,5-diazabicyclo[2.2.1]heptane (48).** Using the procedure for preparing **46**, 29.0 g of **45**·2HI was treated with 1.5 equiv of ethyl chloroformate to yield crude **48**. Dry column chromatography[32] on 1700 g of alumina ($CHCl_3$ development) provided 11.6 g (68%) of pure product, characterized as the maleate salt, mp 124–128°. *Anal.* ($C_{15}H_{20}N_2O_2 \cdot C_4H_4O_4$) C, H, N.

**2-Benzyl-5-methyl-2,5-diazabicyclo[2.2.1]heptane (49).** A solution of 11.6 g (0.045 mol) of **48** in 400 ml of dry THF was added dropwise rapidly to a stirred suspension of 6.77 g (0.178 mol) of $LiAlH_4$ in 100 ml of dry THF at 0°. The mixture was refluxed 18 hr, cooled, and cautiously treated with water to decompose excess $LiAlH_4$. When the grey color of the inorganic salts had changed to white, the mixture was filtered, and the solvents were removed *in vacuo*. The oily residue (6.5 g) was dissolved in ether, and the solution was filtered and treated with 11 ml of 5.9 *M* ethanolic HCl. The precipitate was collected and partitioned between ether and water; the aqueous phase was made basic (40% NaOH) and extracted with ether. The combined extracts were dried ($Na_2SO_4$) and evaporated to leave 4.78 g of oily product that was homogeneous by tlc (alumina/$CHCl_3$). This was reconverted to the dihydrochloride salt (6.03 g, 47.5%, mp 80–200° dec). *Anal.* ($C_{13}H_{18}N_2 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

**2-Methyl-2,5-diazabicyclo[2.2.1]heptane (50).** Catalytic hydrogenolysis of 6.03 g (0.0219 mol) of **49**·2HCl·0.5$H_2O$ in 95% EtOH using 0.90 g of 10% Pd on charcoal at atmospheric pressure was complete in 0.5 hr. Filtration, followed by evaporation of the solvent and trituration of the residue with absolute EtOH, gave 2.0 g of light yellow solid product, mp 264° dec. Drying at 100° (1 mm) for 18 hr removed persistent water of hydration. An additional 1.3 g of **50**·2HCl was obtained by treating the EtOH supernatant with additional ethanolic HCl: total yield, 3.3 g (81.5%). *Anal.* ($C_6H_{12}N_2 \cdot 2HCl$) C, H, N.

**General Procedure. Acyl Derivatives of *N*-Methyldiazabicyclooctanes and -heptanes.** The parent amine dihydrochloride (**28**, **30**, **39**, or **50**) was stirred in a chilled, two-phase mixture of 10% NaOH (small excess over that required to neutralize the amine salts) and an equal volume of $CHCl_3$. A 50–100% excess of acylating agent (diethylcarbamyl chloride, ethyl chloroformate, or ethyl isocyanate) was added and the mixture stirred 18 hr at room temperature. In the case of **7d**, 1 equiv of cyclohexylcarbonyl chloride was employed as acylating agent. The phases were separated, the aqueous layer was extracted once with $CHCl_3$, and the combined organic phases were dried ($Na_2SO_4$) and evaporated *in vacuo*. If tlc indicated that the crude products were homogeneous (alumina-$CHCl_3$), they were converted to HCl or maleic acid salts by treatment of ether solutions with ethanolic solutions of the acids (small excess). For **8c**, **9a**, and **9b**, it was necessary to chromatograph the crude products on alumina ($CHCl_3$ elution for **8** and **9**; ether elution for **9a**) to render them sufficiently pure to form the crystalline salts. Yield and melting point data are reported in Table I.

Target compounds **8a** and **10a** were obtained by different procedures that have been described separately.

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