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



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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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|---------------------------|--|----------|-----------------|---------------------|-----------------|-----------------|------------------|---------------|---------------------|
| - ح | | | | Microfilaria count, | | % OI 03 | y v count (sta a | lev) | |
| Compd | ${ m Formula}^b$ | Yield, % | Mp, °C | day 0 (range) | Day 1 | ĉ | 7 | 6 | 14 |
| 1 (DEC) | - | | | 132 (56-194) | 6 (±3) | $0.1(\pm 0.2)$ | | $29 (\pm 11)$ | $43 (\pm 12)^{c}$ |
| 7a C ₁ . | $_{2}$ H $_{23}$ N $_{3}$ O·HCl | 89 | 202 - 205 | $208 \ (104 - 406)$ | $62~(\pm 20)$ | 1 (+0.6) | $13~(\pm 6)$ | $30 (\pm 8)$ | $35 (\pm 12)$ |
| 7b C ₁₆ | $H_{18}N_2O_2 \cdot HCI$ | 73 | $200 \cdot 205$ | 232 (41 - 358) | $84~(\pm 20)$ | $1 (\pm 0.7)$ | $12~(\pm4)$ | $21 (\pm 3)$ | $49~(\pm 16)$ |
| 7c C ₁₆ | H ₁₉ N ₈ O · HCl | 62 | 246-250 dec | 194 (59 539) | $92~(\pm 35)$ | $3 (\pm 2)$ | 18 (±8) | $32~(\pm 9)$ | $46 (\pm 12)$ |
| 7d C ₁ , | $H_{24}N_{20} \cdot HCI$ | 58 | 263 - 268 | 86 (18-196) | $86~(\pm 12)$ | $4 \; (\pm 1)$ | $17~(\pm 2)$ | $28~(\pm 5)$ | $52~(\pm 18)$ |
| 8a C ₁ | ${}_{2}^{0}H_{23}N_{3}O \cdot C_{4}H_{4}O_{4}N_{4}$ | 82 | 123 - 125 | 155(77 - 338) | $26 (\pm 9)$ | $6(\pm 3)$ | $21 (\pm 8)$ | $23~(\pm 20)$ | $63 (\pm 28)$ |
| 8b C ₁ | ${}_{0}H_{18}N_{2}O_{2} \cdot HCI$ | 91 | 209 - 210 | 371 (84 - 1040) | $110 (\pm 41)$ | $8 (\pm 5)$ | 16(±8) | $32~(\pm 18)$ | $66(\pm 28)$ |
| 8e C ₁ | 0.H1.0.HCl | 28 | 205 - 215 | $175\ (14-312)$ | $152~(\pm 48)$ | $25~(\pm 14)$ | $33~(\pm 13)$ | $54~(\pm 29)$ | $45 (\pm 10)$ |
| 9a C ₁ | ${}_{2}H_{23}N_{3}O \cdot 2HCl^{\epsilon,f}$ | 60 | 144 - 157 | 280(126 - 379) | $25 \ (\pm 12)$ | $1 (\pm 0.6)$ | $7 (\pm 2)$ | 17(+5) | $43(\pm 11)^{g}$ |
| 9b C. | ${}_{0}\mathrm{H}_{18}\mathrm{N}_{2}\mathrm{O}_{2}\cdot\mathrm{HCl}^{e}$ | 58 | $149 \ 155$ | 223 (39 - 765) | 16(+9) | $0.1~(\pm 0.2)$ | $8 (\pm 4)$ | $19 (\pm 9)$ | $66(\pm 18)''$ |
| 9c C ₁₀ | $H_{19}N_{3}O \cdot HCI$ | 52 | 220230 dec | 241(96-365) | $93~(\pm 30)$ | $6(\pm 4)$ | $14 \ (\pm 3)$ | $31(\pm 9)$ | $68~(\pm 14)^{\mu}$ |
| 10a C ₁ | $_{1}H_{21}N_{3}O \cdot C_{4}H_{4}O_{4}$ | 40 | 82 - 84 | $229 \ (166-273)$ | $87~(\pm 27)$ | $6 \ (\pm 3)$ | $20 \ (\pm 7)$ | $31 (\pm 12)$ | $79~(\pm 25)$ |
| 10b C ₅ | $H_{16}N_2O_2 \cdot C_4H_4O_4{}^d$ | 75 | 78-82 | 290(141 - 678) | $96~(\pm 34)$ | $20~(\pm 9)$ | $31 \ (\pm 13)$ | $41 (\pm 21)$ | $82~(\pm 25)$ |

Table I. Chemical and Antifilarial Properties of Bridged Diethylcarbamazine Analogs



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



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 \pm 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- α, α' -dibromoadipate (12), but we were unable to reproduce their results reliably. However, a six-step variation on their method ($12 \rightarrow 16 \rightarrow 17 \rightarrow 18 \rightarrow 23 \rightarrow 27 \rightarrow 28$) 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 $(12 \rightarrow 20 \rightarrow 21 \rightarrow 25 \rightarrow 22 \rightarrow 26 \rightarrow 29 \rightarrow 30)$. This route entails preparation of pyrrolidinedicarboxylic acid 21 and conversion to mo-





noamide 22 via bicyclic anhydride 25. A similar route to 28 was originally envisioned (*i.e.*, $19 \rightarrow 24 \rightarrow 18$), 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 α, α -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 benzovlation-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 $N_i N'_j$ 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 Sewell²⁹ 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 μ l 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 μ l 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 $20 \,\mu$ l of blood were discarded.

Untreated infected control animals were included in each experiment to assure the stability of the infection. However, drugtreated 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 $\pm 0.4\%$ 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 CH₃NH₂ (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 C₆H₆ (40 ml). The sealed bomb was then heated at 90° overnight. After cooling, the bomb was opened, the white solid (CH₃NH₂·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. (C₁₁H₁₉NO₄) 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. (C₇H₁₁NO₄) 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. (C₁₆H₂₂N₂O₃) 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 Ac₂O (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 CHCl3-Et₂O gave 38 g of brown solid, mp 92-95°. Filtration of this in CHCl₃ 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. (C14H16N2O2) 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 LiAlH₄ (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 CHCl₃ 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. (C₁₄H₂₀N₂·2HCl·H₂O) C, H, N.

8-Methyl-3,8-diazabicyclo[3.2.1]octane (28). A mixture of compound $27 \cdot 2HCl \cdot H_2O$ (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. (C₇H₁₄N₂.2HCl) C, H, N.

Diethyl cis-N-Benzylpyrrolidine-2,5-dicarboxylate (20). The preparation of this compound from 12 and benzylamine proceeded as described²⁴ except that external heating was required to maintain the reaction temperature at the specified $83-85^{\circ}$.

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-H₂O 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. (C₁₃H₁₅NO₄.0.33H₂O) C, H, N. Crystallization by simply concentrating an EtOH-H₂O solution led to anhydrous product melting at 247-250°. Anal. (C₁₃H₁₅NO₄) 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 Ac₂O (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 Ac₂O was removed *in vacuo*, and the brown oily residue of crude 25 was taken up in 400 ml of C₆H₆. Anhydrous methylamine (0.33 mol as 9.9% solution in C₆H₆) 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 C₆H₆, and recrystallized from EtOH: yield, 31.4 g (72%); mp 190-192°. Anal. (C₁₄H₁₈N₂O₃) 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 Ac₂O (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 C₆H₆. After removal of 2.0 g of unreacted 22 by filtration, the solution of product was chromatographed on 900 g of alumina (C₆H₆ elution) to give 13.2 g (44%) of pure, oily product. Treatment of a sample with excess ethanolic HCl in Et₂O solution produced a salt, mp 140-170°. Anal. (C₁₄H₁₆N₂O₂·HCl) C, H, N. A sample of the free base, mp 73-75°, was subsequently obtained by slow crystallization from C₆H₆.

8-Benzyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (29).²⁴ Reduction of 9.6 g (0.039 mol) of 26 with LiAlH₄ in THF by the procedure used for 23 gave 8.3 g of crude 29. Chromatography on 124 g of alumina with CHCl₃ elution gave 6.9 g (81%) of pure, oily product. The HCl salt, formed in Et₂O by addition of 3 equiv of ethanolic HCl, melted at 263.5-272° dec with sublimation above 180°. Anal. (C₁₄H₂₀N₂·2HCl) 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-Et₂O 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. (C₇H₁₄N₂·2HCl) 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 CHCl₃ followed by drying of the combined extracts (Na₂SO₄) 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. (C₁₂H₂₃N₃O·C₄H₄O₄) 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 CHCl₃ 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 Et₂O left 4.5 g (33%) of product, mp 133-136°. Anal. (C₂₆H₂₄N₂O₈) 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.* (C₈H₁₆N₂O₄·2HCl) 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 Et₂O [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-H₂O: mp 230-240° dec. *Anal.* (C₈H₁₆N₂O₄·2HCl) 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 CHCl₃, cooled, and filtered: yield, 17.0 g; mp 275-277° (lit.²⁷ mp 272-273°). The supernatant was evaporated *in vacuo* and dissolved in CHCl₃, 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 oilfree 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, 11. of water was added cautiously, and the mixture was extracted with CHCl₃. The extracts were washed with H₂O, dried (Na₂SO₄), and evaporated to dryness to yield a crystalline residue. Trituration in Et₂O provided 77.0 g (91%) of product as colorless needles, mp 168-170°. Anal. (C₂₀H₂₀N₂O₂) 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-diaza-bicyclo[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, CHCl₃). Anal. (C₁₃H₁₄N₂O₂) 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-3,6dione (34, mp 135-137°) could be separated in 24% yield by sequential chromatography on silicic acid columns (EtOAc, CHCl₃ elution), silica gel preparative plates (EtOAc), and alumina preparative plates (CHCl₃). Anal. (C₁₄H₁₆N₂O₂) 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, CHCl₃). Anal. (C₈H₁₂N₂O₂) 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. (C₆H₁₂N₂·2HCl) 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 color-less precipitate (3.8 g) of by-product 2,5-dibenzoyl-2,5-diazabicy-clo[2.2.2]octane [mp 189-190° (lit.²⁷ mp 181-183°)] was removed by filtration. Anal. (C₂₀H₂₀N₂O₂) C, H, N.

The filtrate was saturated with K_2CO_3 and extracted with CHCl₃ to give 15 g of oily material. Chromatography on 150 g of alumina with CHCl₃ elution gave 5.0 g of crystalline 37, mp 119-121° (lit.²⁷ mp 109-111°). Anal. (C₁₃H₁₆N₂O) 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 CHCl₃: total yield, 14.6 g (50%). Compound 37 formed an HCl salt, mp 240-244°. Anal. (C₁₃H₁₆N₂O·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 CHCl₃. After drying (Na₂SO₄), the extracts yielded 15.6 g (100%) of colorless oily 38 that was homogenous by the. It was characterized as the oxalate salt, mp 167-169° dec. Anal. (C₁₄H₁₈N₂O·H₂C₂O₄) 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. (C₇H₁₄N₂·2HCl) C, H, N.

N-Tosylhydroxy-L-prolinol (42). A solution of *N*-tosylhydroxyproline²⁸ (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* BH₃ 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 1.) was added, and the homogenous solution was diluted with CHCl₃ until two phases formed. The aqueous phase was separated and extracted with additional CHCl₃. The combined organic phases were washed with water, dried (Na₂SO₄), and evaporated *in vacuo* to leave a semisolid residue (159.6 g) that gave 80.0 g (50.5%, mp 130-132°).

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 CHCl₃ was stirred 1 hr at 0°. Diethylcarbamyl chloride (2.75 g, 0.0202 mol) in 5 ml of CHCl₃ 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 CHCl₃ extract of the aqueous phase was combined with the original organic phase, and the solution was dried (Na₂SO₄). Evaporation to dryness in vacuo left 4.87 g of oily crude product that was chromatographed on alumina with CHCl₃ 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. (C₁₇H₂₅N₃O.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 CHCl₃. Evaporation of the extract left 1.3 g (66%) of oily 10a that was homogeneous by tlc (alumina-CHCl₃). 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. (C₁₁H₂₁N₃O·C₄H₄O₄) 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 chromatography³² on 1700 g of alumina (CHCl₃ 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 LiAlH₄ in 100 ml of dry THF at 0°. The mixture was refluxed 18 hr, cooled, and cautiously treated with water to decompose excess LiAlH₄. 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% $\mathrm{NaOH})$ 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/CHCl₃). This was reconverted to the dihydrochloride salt (6.03 g, 47.5%, mp 80-200° dec). Anal. (C13H18N2·2HCl·0.5H2O) 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·0.5H₂O 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. (C₆H₁₂N₂·2HCl) 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 CHCl₃. 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_a, and the combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. If tlc indicated that the crude products were homogeneous (alumina-CHCl₃), 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 (CHCl₃ 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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