(3) S. Sharma, B. Bindra, R. N. Iyer, and N. Anand, *J. Med. Chem.*, **18**, 913 (1975).
(4) H. Singh, S. Sharma, R. N. Iyer, and N. Anand, *Indian J. Chem.*, **14B**, 528 (1976).
(5) H. Singh, S. Sharma, R. N. Iyer, and N. Anand, *Indian J. Chem.*, **14B**, 532 (1976).
(6) S. Sharma, R. N. Iyer, and N. Anand, *Indian J. Chem.*, **13**, 468 (1975).
(7) R. Hewitt, E. White, W. Wallace, H. Stewart, S. Kushner, and Y. Subba Row, *J. Lab. Clin. Med.*, **32**, 1304 (1947).
(8) P. Brooke, R. Terry, and J. Walker, *J. Chem. Soc.*, 3165 (1957).
(9) R. Saxena, R. N. Iyer, and N. Anand, *J. Med. Chem.*, **14**, 929 (1971).
(10) P. E. Thompson, J. B. Ziegler, and J. W. McCall, *Antimicrob. Agents Chemother.*, **3**, 693 (1973).
(11) J. W. Reinertson and P. E. Thompson, *Antibiot. Chemother.*, **5**, 566 (1965).
(12) P. Sewell and F. Hawking, *Br. J. Pharmacol.*, **5**, 239 (1950).
(13) G. Lammler, H. Herzog, and H. R. Schutze, *Bull. W. H. O.*, **44**, 757 (1971).
(14) P. S. Wadia and N. Anand, *J. Sci. Ind. Res., Sect. B*, **17**, 24 (1958); *Chem. Abstr.*, **52**, 15549*d* (1958).
(15) P. S. Wadia, J. C. Asthana, N. Anand, and M. L. Dhur, *J. Sci. Ind. Res., Sect. B*, **17**, 11 (1958); *Chem. Abstr.*, **52**, 15547*e* (1958).
(16) H. Stewart, N. Quinones, E. Lee, and J. Denton, *J. Org. Chem.*, **18**, 1478 (1953).
(17) K. Howard, H. Stewart, E. Conroy, and J. Denton, *J. Org. Chem.*, **18**, 1484 (1953).
(18) E. Conroy and J. Denton, *J. Org. Chem.*, **18**, 1489 (1953).
(19) P. C. Das, B. B. Patra, S. B. Chandhuri, U. P. Basu, B. N. Kolay, and S. R. Maitra, *J. Med. Chem.*, 14, 890 (1971).
(20) J. Pecher and R. H. Martin, *Bull. Soc. Chim. Belg.*, **66**, 545 (1957); *Chem. Abstr.*, **53**, 583*g* (1959).
(21) A. Leo, P. Y. C. Jow, C. Silipo, and C. Hansch, *J. Med. Chem.*, **18**, 1865 (1975).
(22) W. T. Wipke, T. M. Dyott, and J. G. Werbalis, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971.
(23) W. T. Wipke, P. Gund, J. G. Werbalis, and T. M. Dyott, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept 1971.
(24) E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schlatter, *J. Am. Chem. Soc.*, **64**, 2696 (1942).
(25) T. S. Moore, M. Boyle, and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).
(26) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(27) R. A. W. Johnstone, D. W. Payling, and C. Thomas, *J. Chem. Soc. C*, 2223 (1969).

# Antifilarial Agents. 3-Aminopyrrolidine and 1,4-Diazabicyclo[3.2.1]octane Derivatives as Analogues of Diethylcarbamazine

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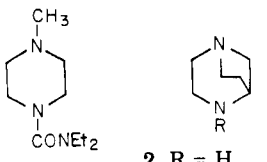
*Received March 2, 1977*

3-Aminopyrrolidines bearing acyl substituents on either nitrogen and N-acylated 1,4-diazabicyclo[3.2.1]octanes are potent microfilaricides in the *Litomosoides carinii* gerbil test system but have no effect on adult worms. The high activity of the pyrrolidine derivatives establishes that diethylcarbamazine (DEC) like antifilarial activity does not require that both pharmacophores be incorporated into one ring. Results with the 1,4-diazabicyclo[3.2.1]octanes establish that an axial conformation of the alkyl substituent corresponding to the equatorial *N*-methyl group of diethylcarbamazine is fully consistent with high activity. Other conformational considerations pertinent to DEC analogues are discussed.

In the preceding paper of this series, we discussed the reasoning behind our current work on diethylcarbamazine (DEC, **1**) analogues.[2] That study was concerned with defining the nature of the carbon skeleton connecting the two pharmacophoric groups of **1**. We concluded from the first study that there was a surprisingly low specificity for carbon skeleton structure among active DEC analogues if the approximate separation between the essential tertiary amine and the amide group seen in the parent compound was maintained.

In general, ring systems with more rigidity than **1** but with similar functional groups on the ring nitrogen displayed activity parallel to **1** against *Litomosoides carinii* in the gerbil. This paper reports the results of continued investigation in this area.

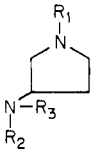
One stereochemical point not addressed in the first report was the preferred orientation of the *N*-methyl group of DEC and its active analogues. To evaluate the significance of orientation of the *N*-methyl group, we synthesized and evaluated the antifilarial activity of three 1,4-diazabicyclo[3.2.1]octanes (**2**–**4**) in which, because of the bridgehead nitrogen atom, the substituents on the tertiary amino group of the substituted piperazine were locked into a rigid conformation. In addition, we continued our investigation of DEC analogues with the synthesis and antifilarial evaluation of 3-aminopyrrolidine analogues of DEC (**5**–**8**). These compounds possess the functional groups shown to be consistent with significant activity in the piperazine[3,4] and bridged piperazine[2] congeners of DEC. Most importantly, however, compounds **5**–**8** maintain nearly the same interatomic distance between the pharmacophoric groups as that in the piperazine



**1**



**2**, R = H
**3**, R = $CO_2Et$
**4**, R = $CONEt_2$



**5**, $R_1 = CH_3$; $R_2 = CONEt_2$; $R_3 = H$
**6**, $R_1 = CH_3$; $R_2 = CO_2Et$; $R_3 = CH_3$
**7**, $R_1 = CONEt_2$; $R_2 = CH_3$; $R_3 = H$
**8**, $R_1 = CONEt_2$; $R_2 = R_3 = CH_3$

Table I. Chemical and Antifilarial Properties of Bridged Diethylcarbamazine Analogues

| Compd | Formula[b] | Mp, °C | Microfilaria count, day 0 (range) | Antifilarial act.[a] % of day 0 count (SD) 1 | 3 | 7 | 9 | 14 or 15 | 21 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | DEC | | 132 (56-194) | 6 (±3) | 0.1 (±0.2) | | 29 (±11) | 43 (±12)[c] | |
| **2** | $C_6H_{12}N_2 \cdot 2HCl$ | 330 | 131 (50-326) | 97 (±19) | 116 (±21) | 86 (±17) | 112 (±19) | 79 (±18) | |
| 3 | $C_9H_{16}N_2O_2 \cdot HCl$ | 179-182 | 118 (39-157) | 73 (±33) | 2 (±0.7) | 16 (±8) | 29 (±11) | 71 (±43) | |
| 4 | $C_{11}H_{21}N_3O \cdot HCl$ | 195-203 | 108 (37-222) | 49 (±11) | 0.8 (±0.4) | 12 (±4) | 28 (±13) | 87 (±38) | |
| 5 | $C_{10}H_{21}N_3O \cdot HCl$ | 150-155 | 270 (131-494) | 67 (±10) | 7 (±5) | 14 (±4) | | 51 (±18) | 82 (±37) |
| 6 | $C_9H_{18}N_2O_2$ | *d* | 277 (113-471) | 85 (±18) | 11 (±6) | 18 (±3) | | 80 (±26) | 139 (±87) |
| 7 | $C_{10}H_{21}N_3O \cdot C_4H_4O_4$ | 98-100 | 195 (132-322) | 105 (±21) | 39 (±15) | 46 (±25) | | 99 (±31) | 115 (±20) |
| 8 | $C_{11}H_{23}N_3O \cdot C_4H_4O_4$ | 121-123 | 424 (183-676) | 31 (±19) | 2 (±2) | 11 (±7) | | 62 (±31) | 79 (±37) |

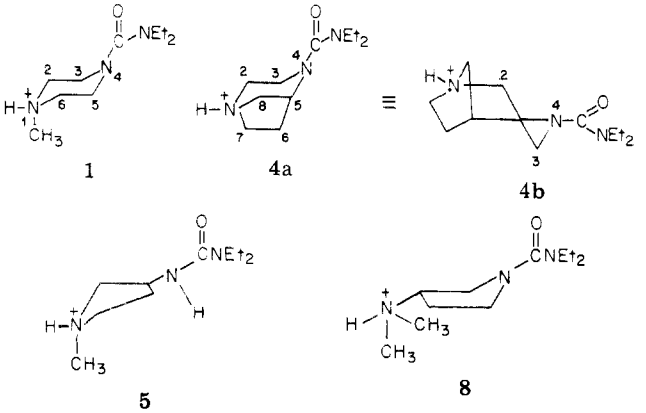
[a] Drugs administered at dosages of 25, 50, 100, and 200 mg/kg on days 0, 1, 2, 3, respectively. [b] Elemental analyses for carbon, hydrogen, and nitrogen were within ±0.4% of the theoretical values for these compounds. [c] This figure refers to day 11. [d] Bp 73-77 °C (0.55-0.65 mm).

derivatives but without a piperazine ring.

**Biological Activity.** Compounds **2-8** were evaluated against *Litomosoides carinii* in the gerbil by methods described in our previous publication.[2] The assay data are compared with those of DEC (1) in Table I. The parent 1,4-diazabicyclo[3.2.1]octane (**2**) gave no reduction of microfilaria count within the experimental error of the assay. However, acylated derivatives **3** and **4** were highly active and gave the typical pattern of microfilarial clearance seen with DEC and its earlier described analogues. For compounds **3** and **4**, day 1 microfilarial counts were reduced, but to a lesser extent than they were with DEC. By day 3, the microfilaria count was close to zero, and the usual rebound of microfilaremia was observed by day 14.

For the 3-aminopyrrolidine compounds **5-8**, a similar pattern of activity was seen. The low point of microfilaremia occurred on day 3 after dosing was initiated, and considerable rebound occurred by day 15. As in previous experiments, necropsy of the animals showed that neither DEC nor any of the new compounds had an effect on the adult worms.

The stereoformulas of compounds **1**, **4**, **5**, and **8** show DEC and analogues with the piperazine rings of **1** and **4** in their most probable (chair) conformations. In both cases, the piperazine ring also may assume the boat form, a conformation earlier found compatible with high activity in other bicyclic systems.[2] The *N*-methyl group of DEC is shown in the axial position to illustrate its equivalence to the 7-position methylene in structure **4a**. This methylene is part of a rigid carbon network that does not allow it to become equatorial relative to the piperazine ring portion of the molecule.

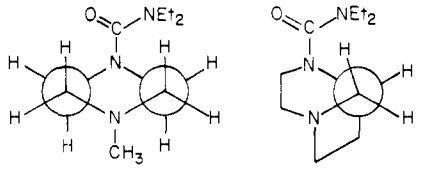


The extra methylene in **3** and **4** (carbon atom 6 in **4a**) would not be expected to seriously affect antifilarial activity, since the early work of Hewitt and co-workers[5,6] has shown that DEC analogues containing higher alkyl groups on the basic nitrogen atom retain substantial activity. In DEC and our earlier bicyclic analogues,[2] the *N*-methyl groups may assume either equatorial or axial conformations, although the equatorial conformation is known to be favored in *N*-methylpiperazine.[7] Because both **3** and **4** closely approach DEC in activity, we conclude that the axial position for the *N*-methyl group of DEC and its analogues although energetically unfavorable must be fully acceptable in the drug-receptor site complex. The alternate conclusion, that either conformation is acceptable in the receptor site, cannot be rigorously excluded because no DEC analogues with a conformationally immobile equatorial *N*-methyl (or equivalent group) are known.

Compounds **5** and **8** are presented in a twisted ring conformation. These compounds may assume a conformation that places the pharmacophoric groups in approximately the same relative spatial position as those in **1**, with a similar internitrogen distance. The poorest compound of this group, **7**, is the only one that contains a secondary amine as the basic amino functional group. In the early work on DEC analogues, Hewitt and coworkers found that compounds with a basic NH group had considerably less activity than DEC or were inactive.[5,6] DEC analogues with an NH in the urea moiety were in general still active but not as potent.[5] Compound **5**, bearing a proton on the acylated nitrogen, shows high activity but **8**, bearing no NH function in either pharmacophore, is the most potent of the pyrrolidine group.

This work demonstrates that high activity among DEC analogues is not dependent on both key nitrogen atoms of the two pharmacophores being contained within one ring. Previous work has shown that acyclic analogues of DEC are virtually inactive[8,9] and that piperidine analogues in which the basic amino pharmacophore is exocyclic at the 4 position are detectably active but not comparable to DEC.[10] We attribute the high activity seen with pyrrolidine derivatives **5-8** to their comparatively fixed conformation and the resulting preservation of a stereochemical relationship of the functional groups very close to other DEC analogues. This relationship can be conveniently demonstrated by consideration of Newman projection formulas[11] of the carbon-carbon bond connecting the key nitrogen atoms of DEC and its analogues (Chart I). DEC is projected in its most energetically probable conformation (chair), and the gauche relationship of the functional groups is evident. In compound **4**, because an approximate chair conformation is also most favored, the functional group relationship would also be gauche. In the pyrrolidine ring systems, illustrated with compound **5**, the five-membered ring requires a conformation in which the angle between the substituents is

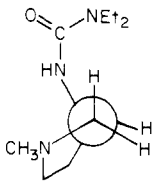
Chart I. Newman Projections of DEC and Analogues



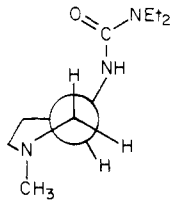
1



4



5a

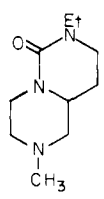


5b

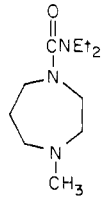
greater than the corresponding angle of DEC. However, the functional groups may still assume a skew relationship as in projection **5a**. A second possible rotational isomer (**5b**) presumably exists, but little energy barrier would be expected between the two forms and a high population of **5a** would be present. The same analysis applies to derivative 8.

It thus appears that all significantly active DEC analogues can or must assume the gauche or skew relationships discussed above. The highly effective fused bicyclic DEC analogues **9** recently reported by Saxena et al.[12,13] is rigidly constrained to the gauche rotational conformation. The somewhat less effective but still potent homopiperazine analogue **10**[14] has greater conformational mobility than DEC, but a high proportion of gauche rotamers would be expected. The nearly inactive, open-chain analogue **11**[9] is conformationally very flexible, and the gauche rotamer would be energetically unfavorable relative to the trans rotamer on the basis of steric interactions.

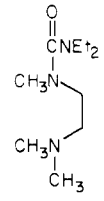
Studies with space-filling molecular models (CPK) show that the diethylcarbamyl, carbethoxy, and methyamino side chains of **5**–**8** can assume rotational conformations comparable to those of DEC and bicyclic analogue **9**. The



9



10

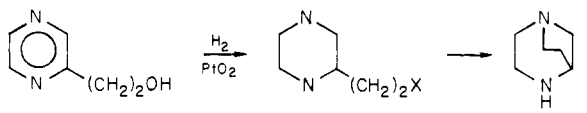


11

importance of the molecular rigidity imposed on DEC by fusing it with the tetrahydropyrimidone ring in **9** was discussed earlier.[2]

**Chemistry.** 2-(2-Hydroxyethyl)pyrazine[15] was reduced with $H_2$ and $PtO_2$ in MeOH to yield 2-(2-hydroxyethyl)-piperazine (**12**),[16] which was converted to the chloride **13**. Ring closure in base afforded **2**, which was acylated with ethyl chloroformate to give **3** or with diethylcarbamyl chloride to give **4**.

For synthesis of the 1-acylated pyrrolidines **7** and **8**, commerically available 3-pyrrolidinol was treated with diethylcarbamyl chloride to yield **14** according to a procedure used for tosylation of hydroxy-L-proline.[17] The 3-benzylamino analogue **15** was obtained by treatment of **14** with thionyl chloride followed by benzylamine.[18] Subsequent methylation of **15** successfully utilized Borch and Hassid's procedure[19] ($NaBH_3CN$ in acetonitrile) to yield compound **16**. Debenzylation of **16** gave the 3-



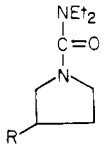
**12**, X = OH
**13**, X = Cl

**2**

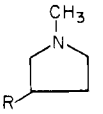
**3**, R = $CO_2Et$
**4**, R = $CONEt_2$

methylamino derivative **7** which was then methylated to yield **8**.

In the 1-methylpyrrolidine series, cyclization of 1,4-dibromo-2-butanol to yield **17**[20] was followed by chlorination to give **18**.[21] Substitution with benzylamine again provided the nitrogen substituent **19**, which was acylated



**14**, R = OH
**15**, R = $NHCH_2C_6H_5$
**16**, R = $N(CH_3)CH_2C_6H_5$



**17**, R = OH
**18**, R = Cl
**19**, R = $NHCH_2C_6H_5$
**20**, R = $N(CH_3)CH_2C_6H_5$
**21**, R = $NHCH_3$

with diethylcarbamyl chloride and debenzylated to yield compound **5**. Methylation[19] of **19** gave compound **20**, which was debenzylated to **21** and acylated with ethyl chloroformate to give compound **6**. Attempted acylation of **21** with diethylcarbamyl chloride gave primarily unreacted starting material.

## Experimental Section

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. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

**2-(2-Hydroxyethyl)piperazine (12).** A suspension of 30.0 g (0.242 mol) of 2-(2-hydroxyethyl)pyrazine[15] in 475 mL of MeOH and 7.5 g of 85% $PtO_2$ was hydrogenated in two equal portions on a Parr shaker. The reaction became quite warm to touch after 5 min of shaking. The shaker was stopped to allow for cooling (15–20 min) and then shaking continued for 24 h. Each reaction was filtered and combined with 1 g of fresh $PtO_2$, and the reaction was continued for another 24 h. Filtration and evaporation yielded 30.0 g (95%) of pale yellow oil. An earlier probe that behaved similarly had yielded a very hygroscopic HCl salt, mp 170–200 °C (lit.[16] mp 210 °C), and a dipicrate, mp 237–241 °C, from $H_2O$. Anal. ($C_6H_{14}N_2O \cdot 2C_6H_3N_3O_7 \cdot H_2O$) C, H, N.

**2-(2-Chloroethyl)piperazine Dihydrochloride (13).**[16] To 25.0 g (0.192 mol) of **12**, chilled in dry ice, 125 mL of $SOCl_2$ was added cautiously dropwise. After addition was complete, the mixture was cautiously heated on a steam bath with stirring for 2 h. The reaction mixture was cooled and treated cautiously with $H_2O$ until a solution resulted. The solution was evaporated to dryness to remove volatile by-products and the dark residue was redissolved in $H_2O$ and filtered. The dark filtrate was heated on the steam bath with decolorizing carbon for 30 min and filtered to yield a pale yellow solution. Acetone was added to precipitate the product in two crops: 29.3 g of white solid, mp 336–339 °C dec, and 11.6 g (total 96% yield) of pale-yellow solid, mp 330–350 °C dec (lit.[16] mp 348–350 °C dec).

**1,4-Diazabicyclo[3.2.1]octane (2).**[16] To a slowly stirring suspension of 11.6 g of **13** (0.0523 mol) in 8.7 mL of $H_2O$ was added a solution of 8.7 g (0.378 mol) of NaOH in 8.7 mL of $H_2O$, which

effected almost complete solution. The resulting solution was extracted three times with $CHCl_3$; the combined extracts were dried with $Na_2SO_4$, filtered, and evaporated to give 5.68 g of yellow oil. This was treated with excess concentrated HCl and evaporated to dryness. The semisolid was triturated in acetone and EtOH, quickly filtered, and dried under $N_2$ to yield 6.75 g (70%) dihydrochloride salt, mp 340 °C dec (lit.[16] mp 348 °C dec). Anal. ($C_6H_{12}N_2 \cdot 2HCl$) C, H, N.

**4-Carbethoxy-1,4-diazabicyclo[3.2.1]octane (3).** To 2.0 g (0.0108 mol) of **2**·2HCl and 1.73 g of NaOH (0.0432 mol) in 20 mL of $H_2O$ was added 20 mL of $CHCl_3$. After the mixture was stirred briefly at 0 °C, 1.76 g of ethyl chloroformate (1.56 mL, 0.0162 mol) was added, and the reaction was stirred for 2 h at room temperature. The two phases were separated, and aqueous phase was extracted twice with $CHCl_3$. The combined extracts were dried with $Na_2SO_4$, filtered, and evaporated to yield 620 mg of crude oil. A solution of this in EtOH was treated with concentrated HCl and evaporated to dryness. The hygroscopic product was isolated from EtOH–$Et_2O$ (1:20) by centrifuging and drying under $N_2$ to yield 524 mg of a white solid, mp 173–177 °C, after drying. Anal. ($C_9H_{16}N_2O_2 \cdot HCl$) C, H, N. Retreatment of the aqueous phase with ethyl chloroformate gave an additional 226 mg of 3·HCl (mp 179–182 °C; 31% yield).

**4-Diethylcarbamyl-1,4-diazabicyclo[3.2.1]octane (4).** To 1.0 g (0.00542 mol) of **2**·2HCl and 2.4 mL (1.75 g, 0.0173 mol) of triethylamine in 4 mL of dioxane was added 0.735 g (0.00542 mol) of diethylcarbamyl chloride. The solution was stirred overnight at room temperature. $Et_2O$ was added to precipitate fully $Et_3N \cdot HCl$, which was collected by filtration and washed with $Et_2O$. The filtrate was evaporated to dryness, and $H_2O$ was added to azeotrope off the dioxane. The residue was treated with concentrated HCl and partitioned between $H_2O$ and $CHCl_3$. The $H_2O$ layer was evaporated to dryness, and the residue was triturated in $Et_2O$–EtOH. The insoluble product was collected by centrifugation and dried under $N_2$. The yield was 582 mg of (43%) white solid, mp 195–203 °C. Anal. ($C_{11}H_{21}N_3O \cdot HCl$) C, H, N.

**1-Diethylcarbamyl-3-hydroxypyrrolidine (14).** To a cold (0 °C), stirring two-phase system of 28.9 g (0.332 mol) of 3-pyrrolidinol in 250 mL of $Et_2O$ and 17.4 g of NaOH in 217 mL of $H_2O$, 53.8 g (0.397 mol) of diethylcarbamyl chloride was added over ~15 min. The ice bath was removed, and $Et_2O$ was seen refluxing 20 min later. The reaction flask was fitted with a condenser and stirred for 18 h (refluxing during the last 10 min). The two phases were separated; the $Et_2O$ layer was dried ($Na_2SO_4$), filtered, and evaporated to yield 8.3 g of amber oil. The water layer, after extraction with $CHCl_3$, yielded an additional 29.7 g of amber oil. Distillation of the combined oils at 0.2 mmHg gave three fractions with 14 (18.5 g, 30%) collected at bp 120–130 °C (homogeneous on TLC, EtOAc).

An analytical sample was isolated from a previous reaction, bp 100–120 °C (0.075 mmHg). Anal. ($C_9H_{18}N_2O_2 \cdot 0.5H_2O$) C, H, N.

**3-(*N*-Benzyl)amino-1-diethylcarbamylpyrrolidine (15).** A solution of compound **14**, 21.0 g (0.113 mol), in $CHCl_3$ (84 mL) was brought to pH 1 by treatment with dry HCl. $SOCl_2$, 9.0 mL (0.124 mol), was added rapidly dropwise with vigorous stirring at room temperature. Heat and gas were produced. After addition was completed, the reaction was heated at reflux and an additional 1 mL of $SOCl_2$ was added after 2 h. After 0.5 h, the reaction was cooled, poured on ice, and made alkaline with solid $NaHCO_3$, and the $CHCl_3$ and $H_2O$ layers were separated. The $CHCl_3$ layer was washed once with $H_2O$, dried ($Na_2SO_4$), filtered, and evaporated to dryness to yield 25.94 g (>100%) of dark viscous oil which was distilled through a Vigreux head at 0.1 mmHg to yield four fractions; the product (15.4 g, 67%) distilled at 80–84 °C.

This intermediate, 13.96 g (0.068 mol), was refluxed at 160 °C with 34.7 mL of benzylamine (0.342 mol) for 8 h. $H_2O$, 200 mL, was added to the mixture of liquid and white solid; the solid dissolved and an oil separated. This was extracted three times with $Et_2O$, and combined extracts were washed with 50 mL of $H_2O$, dried ($Na_2So_4$), filtered, and evaporated iv to yield 23.43 g (benzylamine present) of yellow oil. This was chromatographed on a 3136-g alumina (Woelm) dry column[23] developed with $CHCl_3$. Several fractions were cut and eluted with EtOAc. In this way, 9.3 g (49%) of a still impure product was obtained. This was used directly in the next reaction.

A picrate of **15** was isolated from an initial probe, mp 71–76 °C, after recrystallization from 50% aqueous EtOH. Anal. ($C_{16}H_{25}N_3O \cdot C_6H_3N_3O_7 \cdot H_2O$) C, H, N.

**3-(*N*-Benzyl-*N*-methyl)amino-1-diethylcarbamylpyrrolidine (16).** To a stirring solution of 0.275 g (0.001 mol) of compound **15** in 3 mL of $CH_3CN$ was added 0.4 mL of 37% aqueous HCHO (0.005 mol) followed by 0.100 g of $NaBH_3CN$ (hygroscopic). The reaction was stirred 1.5 h; HOAc was added to bring to neutrality and the reaction stirred an additional 1 h. The reaction was evaporated to dryness; 10 mL of 10% aqueous NaOH was added; and the reaction was extracted three times with $Et_2O$, dried ($Na_2SO_4$), filtered, and again evaporated to dryness to give 224 mg (78%) of a yellow oily product. A solution of **16** in 50 mL of $Et_2O$ was treated with a saturated solution of maleic acid in EtOH until no increase in cloudiness was seen. Stirring in ice produced a white crystalline solid. Filtration yielded 0.192 g (47.5%) of **16**·$C_4H_4O_4$, mp 117–119 °C. Anal. ($C_{17}H_{27}N_3O \cdot C_4H_4O_4$) C, H, N.

**1-Diethylcarbamyl-3-(*N*-methyl)aminopyrrolidine (7).** A solution of compound **16**·$C_4H_4O_4$, 7.0 g (0.0173 mol), in aqueous MeOH (~100 mL of 90%) was converted to the hydrochloride by stirring with 70 g of Dowex X-4 ($Cl^-$ form) ion-exchange resin (mesh 20–50) overnight and filtering, rinsing the resin twice with MeOH. Evaporation of the filtrate to dryness gave 5.35 g (0.0164 mol) of the hydrochloride as an oil. A solution of this in 250 mL of 95% EtOH was combined with 0.5 g of 10% Pd/C and stirred under $H_2$ at room temperature in a buret. Hydrogenation was complete in 1 h. The reaction was filtered and evaporated to dryness. The oil was dissolved in a minimum amount of absolute EtOH and treated with 1.5 L of dry $Et_2O$. A very hygroscopic HCl salt precipitated. Therefore, the $Et_2O$–EtOH suspension of **7**·HCl was evaporated and the residue treated with 10% NaOH, saturated with $K_2CO_3$, and extracted three times with $CHCl_3$. The combined extracts were dried ($Na_2SO_4$), filtered, and evaporated to yield 3.073 g (94%) of oily **7**. An ethereal solution of a portion of the free base (1.248 g) was treated with 0.727 g of maleic acid, dissolved in a minimum amount of EtOH, to yield 1.5 g of white solid, mp 98–100 °C. Anal. ($C_{10}H_{21}N_3O \cdot C_4H_4O_4$) C, H, N. A picrate, mp 152.5–153 °C, was isolated from a previous reaction. Anal. ($C_{10}H_{21}N_3O \cdot C_6H_3N_3O_7$) C, H, N.

**1-Diethylcarbamyl-3-dimethylaminopyrrolidine (8).** Compound **7**, 0.308 g (0.00155 mol), was methylated as previously described for **16**. An oil (0.284 g, 86%), homogeneous on TLC, was isolated. A solution of the oil in 50 mL of $Et_2O$ was treated with 154 mg of maleic acid dissolved in a minimum volume of EtOH to yield 0.280 g (55%) of shiny plates, mp 121–123 °C. Anal. ($C_{11}H_{23}N_3O \cdot C_4H_4O_4$) C, H, N.

**1-Methyl-3-pyrrolidinol (17).**[20] While stirred and chilled in ice in a round-bottom flask, 80 g (2.58 mol) of methylamine in 260 mL of 95% EtOH was treated dropwise with 300 g (1.29 mol) of 1,4-dibromo-2-butanol. The mixture was autoclaved at 100–125 °C for 5 h. The EtOH was distilled; 1200 mL of $H_2O$ was added; and the mixture was extracted three times with $Et_2O$ and the extracts were discarded. The aqueous solution then was made very alkaline with 50% NaOH, saturated with $K_2CO_3$, and extracted two times with $Et_2O$ plus two times with $CHCl_3$. Without drying, the combined extracts were distilled at atmospheric pressure to eliminate solvents. Distillation was continued at 107 mm to yield 115.28 g of liquid, boiling range 31–66 °C. The distillation was stopped and most of the dark amber, liquid residue was decanted from the solid present in the distilling flask. The remaining pot residue was filtered, and the solid was rinsed with $CHCl_3$. The filtrate plus the decanted liquid were combined and distilled at atmospheric pressure to remove $CHCl_3$ and then at 90 mmHg to yield 51.97 g (43%) of colorless product, bp 115–120 °C.

**3-Chloro-1-methylpyrrolidine (18).**[21,22] A solution of 34.301 g of **17** (0.340 mol) in 147 mL of $CHCl_3$ was chlorinated according to the literature procedure.[22] The first step, neutralization of the $CHCl_3$ solution with dry HCl, must be monitored carefully because the end point is sudden and excess HCl results in poor yields. Distillation of the crude product yielded 19.7 g (48.5%) of colorless liquid, bp 96–139 °C (760 mm) [lit. bp 135 °C (760 mm)].

**3-(*N*-Benzyl)amino-1-methylpyrrolidine (19).** Compound **18**, 1.33 g (0.0111 mol), and 6.9 mL (6.3 g, 0.063 mol) of benzylamine were combined and gently refluxed at 150 °C for 8 h.

$Et_2O$ was added to the cooled reaction, and the white solid that formed (benzylamine hydrochloride) was filtered. The filtrate was distilled at atmospheric pressure to remove $Et_2O$, then at water aspirator vacuum to remove benzylamine (bp 78–85 °C), and then at 0.1 mmHg to yield 1.24 g (52%) of colorless liquid **19**, bp 85–88 °C. The HCl salt, mp 113–118 °C, was prepared in $Et_2O$ and analyzed as an hydrate. Anal. ($C_{12}H_{18}N_2 \cdot 2HCl \cdot H_2O$) C, H, N.

**3-(*N*-Diethylcarbamyl)amino-1-methylpyrrolidine (5).** To a solution of compound **19**, 10.0 g (0.053 mol), and triethylamine, 8.1 mL (0.058 mol), in 40 mL of dry dioxane was added 7.85 g (0.058 mol) of diethylcarbamyl chloride. A voluminous solid was present after 10 min. The reaction was stirred at room temperature for 18 h. After 2 h, 15 mL of additional dioxane was added to enable resumption of stirring. $Et_2O$ was added to precipitate all triethylamine hydrochloride, and the mixture was filtered, rinsing with $Et_2O$. The filtrate was evaporated to dryness to give a theoretical yield of a yellow oil. A solution of this crude intermediate, 14.7 g (0.051 mol), in 500 mL of EtOH and 16 mL of 6 N ethanolic HCl was hydrogenated at room temperature and atmospheric pressure in the presence of 1.6 g of 10% Pd/C for 24 h. The reaction was filtered and evaporated to dryness. The purplish solid was triturated in acetone. Filtration yielded a white solid, 7.1 g, mp 150–155 °C. Anal. ($C_{10}H_{21}N_3O \cdot HCl$) C, H, N.

**3-(*N*-Benzyl-*N*-methyl)amino-1-methylpyrrolidine (20).** Compound **19** was methylated as reported for compound **16**. A theoretical yield of the crude product was isolated as an oil and characterized as a yellow-orange picrate, mp 215–220 °C dec (trituration in hot EtOH). Anal. ($C_{13}H_{20}N_2 \cdot 2C_6H_3N_3O_7$) C, H, N.

**1-Methyl-3-(*N*-methyl)aminopyrrolidine (21).** A solution of 3.08 g of compound **20** in 150 mL of 95% EtOH and 6 mL of 6 N ethanolic HCl combined with 0.3 g of 10% Pd/C was hydrogenated at room temperature and atmospheric pressure for 21 h. The reaction was filtered and evaporated to a viscous oil which was characterized as a yellow picrate salt, mp 218–220 °C dec (trituration in hot EtOH). Anal. ($C_6H_{14}N_2 \cdot 2C_6H_3N_3O_7$) C, H, N.

A reaction run on a larger scale (16.0 g of compound **20**) required addition of fresh 10% Pd/C after 24 h to effect complete hydrogenolysis.

**3-(*N*-Carbethoxy-*N*-methyl)amino-1-methylpyrrolidine (6).** Compound **21**·2HCl, 14.8 g (0.0792 mol), as a gum, was combined with 110 mL of dioxane (**21**·2HCl initially insoluble) and 45 mL (0.324 mol) of triethylamine. This combination was stirred in the presence of Linde 3A molecular sieves for 2 h at room temperature. Then, with ice cooling, 11.4 mL (0.119 mol) of ethyl chloroformate was added rapidly from a pipet. Stirring at room temperature was resumed. Within 2–3 h, much solid $Et_3N \cdot HCl$ was present; stirring was continued for 66 h. Hot $H_2O$ (200 mL) was added and stirred 1 h to decompose excess ethyl chloroformate; the pH 7 solution, opaque due to disintegrated molecular sieves, was extracted two times with $CHCl_3$. NaOH (10%) was then added and the solution again was extracted two times with $CHCl_3$. After drying ($Na_2SO_4$), filtering, and evaporating the extracts, a total of 7.4 g of amber oil was obtained which was distilled twice at 1 mmHg to yield 1.8 g of oil, bp 81.5–95 °C, after the second distillation. This material was combined with 0.5 g of equivalent product isolated from a previous reaction and redistilled at 0.55–0.65 mmHg to yield 1.6 g of a pale yellow oil, bp 73–77 °C (9.2%). Anal. ($C_9H_{18}N_2O_2$) C, H, N.

**Acknowledgment.** We are deeply indebted to the late Dr. P. E. Thompson for his assistance during the early phases of this work. This work was supported by U.S. Public Health Service Grant AI 08622 and Contract AI 69-92 administered by the Geographic Medicine Branch, NIAID, as part of the U.S.–Japan Cooperative Medical Science Program.

## References and Notes

(1) Reference deleted on revision.
(2) P. A. Sturm, D. W. Henry, P. E. Thompson, J. B. Zeigler, and J. W. McCall, *J. Med. Chem.*, 17, 481 (1974).
(3) F. Hawking, *Pharmacol. Rev.*, 7, 279 (1955).
(4) F. Hawking in "Chemotherapy of Helminthiasis", Vol. 1, R. Cavier and F. Hawking, Ed., Pergamon Press, Oxford, 1973, pp 437–480.
(5) R. I. Hewitt, E. White, W. S. Wallace, H. W. Stewart, S. Kushner, and Y. SubbaRow, *J. Lab. Clin. Med.*, **32**, 1304 (1947).
(6) H. W. Stewart, R. J. Turner, J. J. Denton, S. Kushner, L. M. Brancone, W. L. McEwen, R. I. Hewitt, and Y. SubbaRow, *J. Org. Chem.*, **13**, 134 (1948).
(7) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *J. Am. Chem. Soc.*, **87**, 1232 (1965).
(8) J. Pecher and R. Martin, *Bull. Soc. Chim. Belg.*, **66**, 545 (1957); *Chem. Abstr.*, **53**, 583 g (1959).
(9) P. Sewell and F. Hawking, *Br. J. Pharmacol.*, **5**, 239 (1950).
(10) P. Brookes, R. Terry, and J. Walker, *J. Chem. Soc.*, 3165 (1957).
(11) M. S. Newman in "Steric Effects in Organic Chemistry", Wiley, New York, N.Y., 1956, p 5.
(12) R. Saxena, R. N. Iyer, N. Anand, R. K. Chatterjie, and A. B. Sen, *J. Pharm. Pharmacol.*, **22**, 307 (1970).
(13) R. Saxena, S. Sharma, R. N. Iyer, and N. Anand, *J. Med. Chem.*, **14**, 929 (1971).
(14) J. W. Reinertson and P. E. Thompson, *Antibiot. Chemother.*, **5**, 566 (1955).
(15) L. J. Kitchen and E. S. Hanson, *Antibiot. Chemother.*, **73**, 1838 (1951).
(16) E. F. Rogers and H. J. Becker, U.S. Patent 3 281 423 (1966).
(17) P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966).
(18) B. V. Franco and C. D. Lunsford, *J. Med. Pharm. Chem.*, **2**, 523 (1960).
(19) R. F. Borch and H. I. Hassid, *J. Org. Chem.*, **37**, 1673 (1972).
(20) C. D. Lunsford, J. W. Ward, A. J. Pallotta, T. W. Tusing, E. K. Rose, and R. S. Murphy, *J. Med. Pharm. Chem.*, 1, 73–95 (1959).
(21) C. D. Lunsford, A. D. Cole, J. W. Ward, B. V. Franco, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964).
(22) B. V. Franko and C. D. Lunsford, *J. Med. Pharm. Chem.*, **2**, 523 (1960).
(23) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

# Quinoline Derivatives as Antiallergy Agents. 2. Fused-Ring Quinaldic Acids[1]

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A series of compounds containing two or more 4-oxo-1,4-dihydropyridine-2-carboxylic acid units fused to a central aromatic nucleus was synthesized and tested in the rat passive cutaneous anaphylaxis (PCA) assay for potential antiallergy activity. Most of the compounds of this series showed significant activity in the PCA assay. Three of these compounds, **11d**, **13f**, and **21**, were more than 250 times as active as the standard drug, cromolyn sodium. The synthesis and biological activity are discussed.

Since the discovery that cromolyn sodium inhibits the release of the mediators from mast cells and that it is a useful agent in the prophylactic treatment of bronchial asthma, several other classes of compounds have been