Studies in Potential Filaricides. 6. Synthesis of 3,8-Disubstituted 1,3,8-Triazabicyclo[4.4.0]decan-2-ones and -thiones†

Satyavan Sharma, R. Bindra, R. N. Iyer, and Nitya Anand*

Central Drug Research Institute, Lucknow, India. *Received October 2, 1974*

1,3,8-Triazabicyclo[4.4.0]decan-2-ones and -thiones having varying substituents at positions 3 and 8 have been synthesized. When tested in cotton rats for their antifilarial activity against *Litomosoides carinii*, some of the compounds showed moderate microfilaricidal activity.

3-Ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**28**), synthesized earlier in this laboratory as an analog of diethylcarbamazine (DEC) having greatly reduced conformational mobility, was found to possess marked microfilaricidal activity.[1] In a structure–activity relationship study, analogs of **28** with variations at positions 2, 3, and 8 have been prepared and screened for their biological activity and the results are reported in this communication.

In the earlier synthesis[2] of **28**, the substituents which were to appear at positions 3 and 8 were present in the synthetic units (synthons) right from the initial step of the synthesis and, thus, the method was not suitable for carrying out variations at these positions. Therefore, alternative routes for the synthesis of compounds of the type **28** were investigated and the method described below provides the needed flexibility for carrying out these variations.

Chemistry. Condensation of *N*-alkylethylenediamines **1–4**[3] with *N*-alkylmaleamic acids **5–7**[4] gave *N*-alkyl-2-(1-alkyl-2-oxo-3-piperazinyl)acetamides **8–13** (Table I). It is noteworthy that in these condensations, of the two possible position isomers, mainly **8–13** are formed, obviously due to lesser steric hindrance offered by the primary amines over the secondary amines in the Michael addition. The structures of the amides **8–13** were confirmed by an alternative synthesis of **13**. Thus, treatment of *N*-benzylethylenediamine (**4**) with diethyl maleate or fumarate (**62**) gave 4-benzyl-2-carbethoxymethylpiperazin-3-one (**63**) which on reaction with ethylamine yielded **13**.

The amides **8–13** were reduced with $LiAlH_4$ to 1-alkyl-3-(2-alkylamino)ethylpiperazines **14–19** (Table II). The amines **14–19**, on treatment with ethyl chloroformate yielded the corresponding ethoxycarbonyl derivatives **20–24**‡ (Table II) which were conveniently cyclized with NaOEt to 3,8-disubstituted 1,3,8-triazabicyclo[4.4.0]decan-2-ones **25–30**.[2] Reaction of **17–19** with $COCl_2$ gave **28–30** in one step but in lower yields.

Catalytic hydrogenation of **30** using Pd/C as catalyst yielded 3-ethyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**36**) which proved to be a very useful intermediate for preparing **28** as also its other 8-substituted analogs **37–61** (Table III). Methylation of **36** with HCOOH–HCHO gave **28** while treatment with various alkyl or aralkyl halides, epoxides, alkyl and aryl isocyanates, and isothiocyanates gave other 8-substituted derivatives (see Scheme I).

Reaction of **16**, **17**, and **19** with thiophosgene yielded 3,8-disubstituted 1,3,8-triazabicyclo[4.4.0]decane-2-thiones **33–35**. 1-Benzyl-3-(2-benzylamino)ethylpiperazine (**16**) failed to react with ethyl chloroformate which is very likely due to steric hindrance offered by the bulky benzyl group at 3′-N position which hinders the approach of ethyl chloroformate to the secondary nitrogen of the piperazine ring. However, **16** on reaction with $COCl_2$ furnished the required 3,8-dibenzyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**27**).

Catalytic hydrogenation of **27** using Pd/C or treatment with ethyl chloroformate followed by the hydrolysis of the resulting ethoxycarbonyl derivative **32** with HBr[5] removed only the 8-benzyl protection giving **31**. This 8-debenzylation was confirmed by the NMR studies of **27**, **31**, and **32**. In the NMR spectrum of **27**, the signal at δ 3.41 has been assigned to NCH_2Ph and the signal at δ 4.43 for the more deshielded $CONCH_2Ph$ protons. Debenzylation of **27**, either with Pd/C or the ClCOOEt–HBr method, gives **31** and **32**, respectively, both of which do not show absorption corresponding to NCH_2Ph at δ 3.41, while the signal for $CONCH_2Ph$ around δ 4.43 is retained in both the compounds, thus indicating the preferential removal of 8-benzyl group.

Biological Activity. All the compounds synthesized were evaluated for their in vivo antifilarial activity in cotton rats infected with *Litomosoides carinii* by the technique of Hawking and Sewell[6] in the division of chemotherapy of this Institute. The compounds were administered intraperitoneally daily for 6 days at dosages of 30 and 10 mg/kg using three animals per experimental group. In this test only **25**, **26**, **36**, and **48** showed 80–90% reduction of blood microfilarial count at a dose of 30 mg/kg in comparison with the same order of activity exhibited by **28** and DEC at 1 and 6 mg/kg, respectively.[1] Other compounds were inactive at 30 mg/kg. None of the compounds possessed any action on adult worms.

The results thus show that (1) substitution of the 3-ethyl group by methyl as in **25** results in reduction of activity; (2) removal of the 8-methyl group as in **36** or increasing the size of the alkyl group also brings about either lowering or loss of activity; (3) substitution of C=O by C=S (**34**) causes complete disappearance of activity in **28**.

The above data suggest that in addition to the electron density on the three-component nitrogen atoms and the geometry of the molecule, the bulk of the groups around those atoms and the associated steric factors are also important in determining the antifilarial activity in this class of compounds.

Some of the compounds were also subjected to pharmacological screening, but the only noteworthy activity shown was the antiinflammatory activity. When tested in mice according to the method of Winter et al.[7] at a dose of 40 mg/kg po, **48** caused 32% inhibition of carrageenin-induced edema as compared to 31% inhibition by phenylbutazone at 25 mg/kg.

Experimental Section

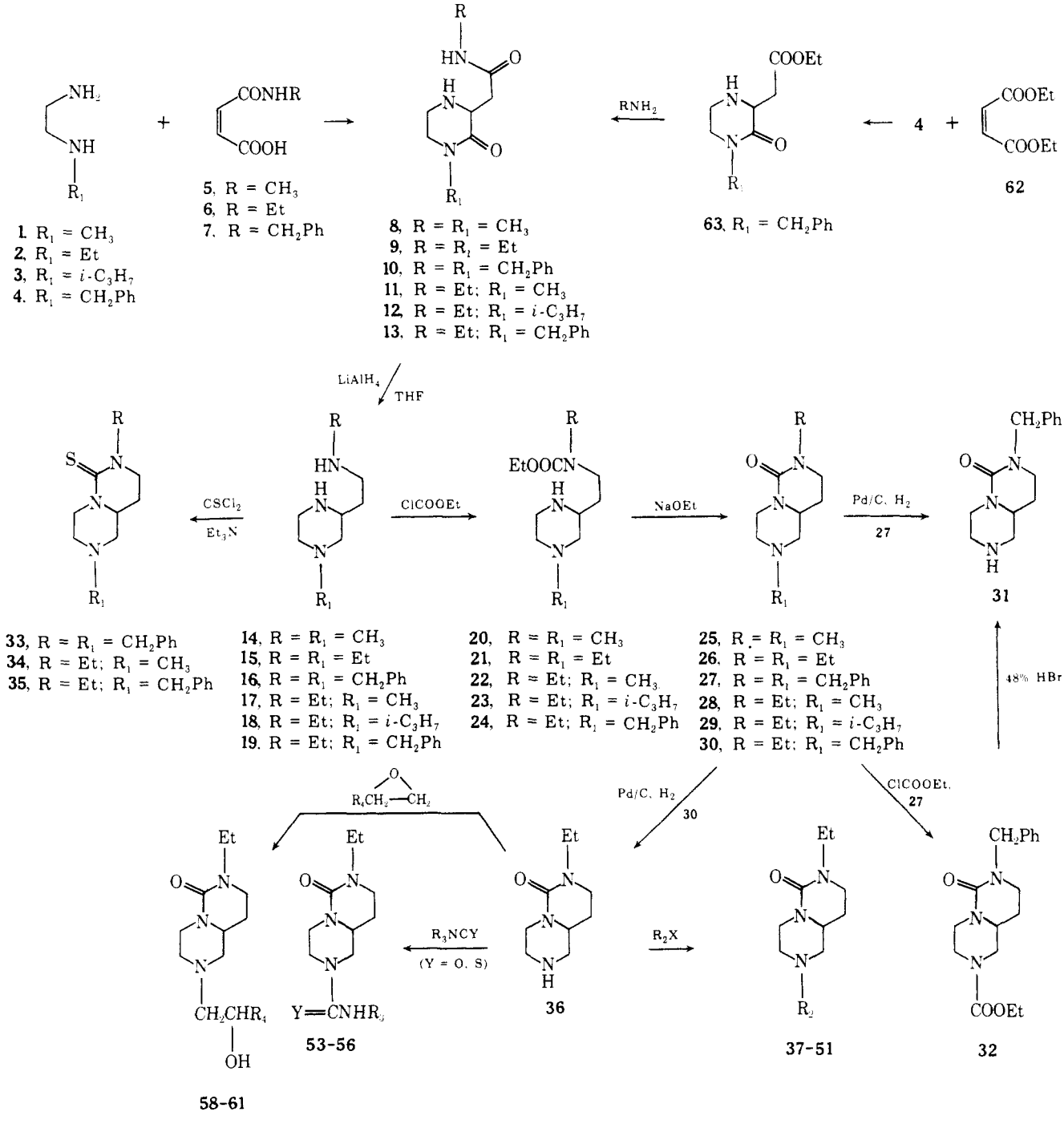
Melting and boiling points are uncorrected; melting points were taken in a sulfuric acid bath. Ir spectra were recorded on 137 and 337 Perkin-Elmer infracord spectrophotometers, while NMR spectra were taken on a Varian A-60-D spectrometer. The mass spectra were determined with a Hitachi RMU-6E single focusing spectrometer. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

Synthesis of N-Substituted 2-(1-Substituted-2-oxo-3-piperazinyl)acetamides. Method A. *N*-Ethyl-2-(1-methyl-2-oxo-3-

†Communication No. 2001 from Central Drug Research Institute, Lucknow, India.

‡The exact location of the -COOEt group has not been assigned. Its position has been given arbitrarily.

Scheme I



piperazinyl)acetamide (11). A solution of 1 (10 g, 0.135 mol) in dioxane (50 ml) was added dropwise to a stirred solution of 6 (19.3 g, 0.135 mol) in dioxane (100 ml). The reaction mixture was refluxed for 12 hr and cooled to room temperature, the clear solution was decanted off from a small amount of oil, and the solvent was removed to give the product as a thick oil. Compounds **8–10** and **12** were also made by the same method.

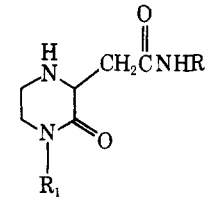
Method B. *N*-Ethyl-2-(1-benzyl-2-oxo-3-piperazinyl)acetamide (13). A solution of 4 (15.0 g, 0.1 mol) in dry ether (75 ml) was added dropwise to a stirred solution of diethyl fumarate **62** (17.2 g, 0.1 mol) in dry ether (75 ml) kept at room temperature and the reaction mixture stirred at the same temperature for 4 hr. The solvent was removed to get 4-benzyl-2-carbethoxymethylpiperazin-3-one (**63**) as a thick oil: yield 26.0 g (94%). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

A mixture of **63** (20 g, 0.07 mol), $EtNH_2$ (10 ml), and absolute EtOH (25 ml) was heated at 140° in a sealed tube for 72 hr. The solvent was removed in vacuo and the residue crystallized from benzene to give 13 as colorless flakes.

1-Benzyl-3-(2-ethylamino)ethylpiperazine (19). 13 (50 g, 0.18 mol) was added in portions to a slurry of $LiAlH_4$ (35 g, 0.9 mol) in dry THF (400 ml) kept in an ice bath and the reaction mixture refluxed for 18 hr. Solvent was removed; the residual mixture was cooled in ice and then suspended in ether. Excess of $LiAlH_4$ was decomposed by 10% NaOH solution, the thick colorless mass filtered off, solvent removed from filtrate, and the residue distilled under reduced pressure. Compounds **14–18** were also made by a similar procedure.

***N*-Ethoxycarbonyl-1-benzyl-3-(2-ethylamino)ethylpiperazine (24).** To a stirred solution of **19** (72 g, 0.29 mol) in H_2O (175 ml), cooled to 0°, HCl was added to bring the pH of the solution to 3–3.5 and to this solution ethyl chloroformate (35 ml, 0.36 mol) was added dropwise maintaining the pH between 3 and 3.5. This range of pH was kept constant by the addition of an aqueous solution of CH_3COONa from time to time. Stirring was continued for an additional 1 hr and then the reaction mixture was kept in refrigerator overnight. The solution was washed with ether (100 ml), the aqueous layer was saturated with K_2CO_3, the oil which sepa-

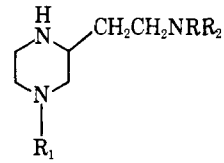
Table I. N-Substituted 2-(1-Substituted-2-oxo-3-piperazinyl)acetamides



No.	R	R_1	Mp or bp (mm), °C	Yield, %	Formula	Analyses
8	CH_3	CH_3	180–185 (2×10^{-3})	41	$C_8H_{15}N_3O_2$	C, H, N
9	C_2H_5	C_2H_5	Oil[a]	45	$C_{10}H_{19}N_3O_2$	C, H
10	$C_6H_5CH_2$	$C_6H_5CH_2$	95	52	$C_{20}H_{23}N_3O_2$	C, H, N
11	C_2H_5	CH_3	180 (5×10^{-3})	41	$C_9H_{17}N_3O_2$	C, H
12	C_2H_5	i-C_3H_7	155–157 (2×10^{-2})	21	$C_{11}H_{21}N_3O_2$	C, H, N
13	C_2H_5	$C_6H_5CH_2$	112	80	$C_{15}H_{21}N_3O_2$	C, H, N

[a]Purified by chromatography over a basic alumina column using C_6H_6 as eluent.

Table II. 1,3-Disubstituted Piperazines



No.	R	R_1	R_2	Bp (mm), °C	Yield, %	Formula	Analyses
14	CH_3	CH_3	H	130–135 (6)	72	$C_8H_{19}N_3$	C, H, N
15	C_2H_5	C_2H_5	H	130 (17)	76	$C_{10}H_{23}N_3$	C, H
16	$C_6H_5CH_2$	$C_6H_5CH_2$	H	168–170 (1×10^{-2})	96	$C_{20}H_{27}N_3$	C, H
17	C_2H_5	CH_3	H	110–112 (8)	80	$C_9H_{21}N_3$	C, H
18	C_2H_5	i-C_3H_7	H	118–122 (20)	57	$C_{11}H_{25}N_3$	C, H, N
19	C_2H_5	$C_6H_5CH_2$	H	175–180 (8)	90	$C_{15}H_{25}N_3$	C, H, N
20	CH_3	CH_3	$CO_2C_2H_5$	100–103 (2×10^{-3})	70	$C_{11}H_{23}N_3O_2$	C, H, N
21	C_2H_5	C_2H_5	$CO_2C_2H_5$	110–115 (2×10^{-3})	90	$C_{13}H_{27}N_3O_2$	C, H, N
22	C_2H_5	CH_3	$CO_2C_2H_5$	Oil[a]	82	$C_{12}H_{25}N_3O_2$	C, H, N
23	C_2H_5	i-C_3H_7	$CO_2C_2H_5$	110–111 (2×10^{-3})	76	$C_{14}H_{29}N_3O_2$	C, H
24	C_2H_5	$C_6H_5CH_2$	$CO_2C_2H_5$	140–145 (1×10^{-2})	86	$C_{18}H_{29}N_3O_2$	C, H, N

[a]Purified by chromatography over a basic alumina column using $CHCl_3$ as eluent.

rated was extracted with ether (3 × 200 ml), combined extracts were dried (Na_2SO_4), and solvent was removed to get the product as an oil. Compounds **20–23** were prepared using the same method.

3-Ethyl-8-benzyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (30). A solution of **24** (80 g, 0.25 mol) and NaOEt (Na, 7.0 g, 0.3 mol, and absolute EtOH, 250 ml) in absolute EtOH (100 ml) was refluxed for 36 hr. Solvent was removed thoroughly from the reaction mixture, the residue treated with 50% NaOH solution, and the aqueous phase extracted with CH_2Cl_2 (3 × 200 ml). The combined extracts were dried (Na_2SO_4) and solvent was removed to get the product as an oil. Compounds **25, 26, 28,** and **29** were also obtained by the similar manner.

3-Ethyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (36). A solution of **30** (78 g, 0.28 mol) in glacial AcOH (100 ml) was added to a suspension of 5% Pd/C (31.2 g) in glacial AcOH (200 ml) and hydrogenated in a Parr hydrogenator at 3.50 kg/cm^2 for 24 hr. The catalyst was removed by filtration and solvent removed under reduced pressure. The free base was obtained from the residue either by passing dry NH_3 in the $CHCl_3$ solution of the residue and filtering the separated CH_3COONH_4 or by treating the ice-cooled C_6H_6 solution of the residue with 50% NaOH and extracting the aqueous phase with C_6H_6 (3 × 150 ml). The solvent was removed and the product obtained as an oil. **27** was also debenzylated in a similar manner to give **31**.

3-Ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (28). HCHO (25 ml, 40%) was added dropwise to a solution of **36** (5.0 g, 0.027 mol) in 85% HCOOH (7.5 ml) kept at 80° and the mixture heated at the same temperature for 8 hr. Excess of HCOOH and HCHO were removed under reduced pressure and the residue was treated with 50% NaOH solution (25 ml). The separated oil was extracted with CH_2Cl_2 (4 × 30 ml), the combined extracts were dried (Na_2SO_4), and the solvent was removed to get the product as an oil.

3-Ethyl-8-substituted 1,3,8-Triazabicyclo[4.4.0]decan-2-ones (37–61). Starting with **36**, various 8-substituted compounds were prepared by one of the following methods.

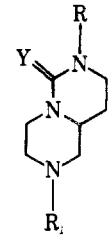
Method C. A mixture of **36** (2 g, 0.011 mol), n-butyl iodide (1.3 ml, 0.011 mol), anhydrous K_2CO_3 (3 g), and dry acetone (50 ml) was refluxed for 24 hr, the inorganic salts were filtered off, and the solvent was removed from the filtrate to give 3-ethyl-8-n-butyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**38**) as an oil. By a similar method compounds **39–51** were also prepared.

Method D. PhNCO (0.81 ml, 0.008 mol) in dry C_6H_6 (10 ml) was added dropwise to an ice-cold solution of **36** (1.5 g, 0.008 mol) in dry C_6H_6 (25 ml); the mixture was kept for 12 hr at room temperature and finally refluxed for 1 hr. The residue, obtained on removal of the solvent, was crystallized from C_6H_6–petroleum ether to get 3-ethyl-8-phenylcarbamoyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**54**). Compounds **53, 55,** and **56** were made in a similar manner.

Method E. A mixture of **36** (1 g, 0.0054 mol) and 1,2-epoxy-3-phenoxypropane (0.81 g, 0.0054 mol) in EtOH (30 ml) was refluxed for 6 hr. Removal of solvent from the reaction mixture gave 3-ethyl-8-(3-phenoxy-2-hydroxypropyl)-1,3,8-triazabicyclo[4.4.0]decan-2-one (**60**) as an oil which was purified by chromatography over a basic alumina column using C_6H_6 as eluent. Compounds **58, 59,** and **61** were also prepared by this method.

3-Ethyl-8-guanyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (52).

Table III. 3,8-Disubstituted 1,3,8-Triazabicyclo[4.4.0]decan-2-ones and -thiones



No.	R	R_1	Y	Method	Mp or bp (mm), °C	Yield, %	Formula	Analyses	MED[c] × 6 days ip, mg/kg
DEC									6
25	CH_3	CH_3	O	A[e]	95–98 (2×10^{-3})	70	$C_9H_{17}N_3O$	C, H, N	30, 10 (inactive)
26	C_2H_5	C_2H_5	O	A	140–145 (2×10^{-2})	81	$C_{11}H_{21}N_3O$	C, H	30, 10 (inactive)
27	$C_6H_5CH_2$	$C_6H_5CH_2$	O	A	180–185 (2×10^{-2})	27	$C_{21}H_{25}N_3O$	C, H, N	i[d]
28	C_2H_5	CH_3	O	B[f]	130–132 (5×10^{-2})[a]	90	$C_{10}H_{19}N_3O$	C, H	1
29	C_2H_5	i-C_3H_7	O	A	115–120 (2×10^{-2})	50	$C_{12}H_{23}N_3O$	C, H, N	i
30	C_2H_5	$C_6H_5CH_2$	O	B	165 (5×10^{-3})	90	$C_{16}H_{23}N_3O$	C, H	i
31	$C_6H_5CH_2$	H	O	A	Oil	64	$C_{14}H_{19}N_3O$	C, H, N	i
32	$C_6H_5CH_2$	$CO_2C_2H_5$	O	A	Oil	61	$C_{17}H_{23}N_3O_3$	C, H	i
33	$C_6H_5CH_2$	$C_6H_5CH_2$	S	A	Oil	54	$C_{21}H_{25}N_3S$	C, H, N	i
34	C_2H_5	CH_3	S	A	130–133 (5×10^{-3})	75	$C_{10}H_{19}N_3S$	C, H, N	i
35	C_2H_5	$C_6H_5CH_2$	S	B	210–215 (5×10^{-3})	43	$C_{16}H_{23}N_3S$	C, H, N	i
36	C_2H_5	H	O	B	125–128 (2×10^{-2})	80	$C_9H_{17}N_3O$	C, H	30, 10 (inactive)
37	C_2H_5	$CH_2CH_2CH_3$	O	C	130 (5×10^{-3})	83	$C_{12}H_{23}N_3O$	C, H	i
38	C_2H_5	$CH_2(CH_2)_2CH_3$	O	C	145 (5×10^{-3})	76	$C_{13}H_{25}N_3O$	C, H, N	i
39	C_2H_5	$CH_2(CH_2)_3CH_3$	O	C	Oil	76	$C_{14}H_{27}N_3O$	C, H, N	i
40	C_2H_5	$CH_2CH_2CH(CH_3)_2$	O	C	116 (2×10^{-2})	38	$C_{14}H_{27}N_3O$	C, H, N	i
41	C_2H_5	$CH_2(CH_2)_4CH_3$	O	C	Oil	78	$C_{15}H_{29}N_3O$	C, H, N	i
42	C_2H_5	$CH_2(CH_2)_5CH_3$	O	C	142 (4×10^{-2})	64	$C_{16}H_{31}N_3O$	C, H, N	i
43	C_2H_5	$CH_2(CH_2)_6CH_3$	O	C	165–170 (2×10^{-2})	94	$C_{17}H_{33}N_3O$	C, H, N	i
44	C_2H_5	$CH_2(CH_2)_8CH_3$	O	C	Oil	58	$C_{19}H_{37}N_3O$	C, H	i
45	C_2H_5	$COOC_2H_5$	O	C	Oil	76	$C_{12}H_{21}N_3O_3$	C, H	i
46	C_2H_5	$CH_2COOC_2H_5$	O	C	150 (2×10^{-2})	32	$C_{13}H_{23}N_3O_3$	C, H, N	i
47	C_2H_5	$CON(C_2H_5)_2$	O	C	162 (5×10^{-2})	93	$C_{14}H_{26}N_4O_2$	C, H, N	i
48	C_2H_5	$CH_2CH_2C_6H_5$	O	C	180 (4×10^{-2})	80	$C_{17}H_{25}N_3O$	C, H, N	30, 10 (inactive)
49	C_2H_5	$CH_2CH_2N(C_2H_5)_2$	O	C	138–140 (5×10^{-3})	53	$C_{15}H_{30}N_4O$	C, H, N	i
50	C_2H_5	$CH_2CH_2N(CH_3)_2$	O	C	Oil	70	$C_{13}H_{26}N_4O$	C, H	i
51	C_2H_5	$CH_2(CH_2)_2N(CH_3)_2$	O	C	148–150 (5×10^{-2})	70	$C_{14}H_{28}N_4O$	C, H, N	i
52	C_2H_5	$HN{=}CNH_2$	O	F[g]	Oil	83	$C_{10}H_{19}N_5O$	C, H	i
53	C_2H_5	$CONHC_2H_5$	O	D	151–153	92	$C_{12}H_{22}N_4O_2$	C, H	i
54	C_2H_5	$CONHC_6H_5$	O	D	90–92	50	$C_{16}H_{22}N_4O_2$	C, H, N	i
55	C_2H_5	$CSNHC_2H_5$	O	D	140–142	81	$C_{12}H_{22}N_4OS$	C, H	i
56	C_2H_5	$CSNHC_6H_5$	O	D	195–196	38	$C_{16}H_{22}N_4OS$	C, H	i
57	C_2H_5	CH_3[b]	O	F	143–145	47	$C_{10}H_{19}N_3O_2$	C, H, N	i
58	C_2H_5	$CH_2CH(OH)C_6H_5$	O	E	Oil[h]	84	$C_{17}H_{25}N_3O_2$	C, H	i
59	C_2H_5	$CH_2CH(OH)CH_2O$-p-$ClC_6H_4CH_2$	O	E	Oil	75	$C_{18}H_{26}ClN_3O_3$	C, H, N	i
60	C_2H_5	$CH_2CH(OH)CH_2OPh$	O	E	Oil	83	$C_{18}H_{27}N_3O_3 \cdot H_2O$	C, H	i
61	C_2H_5	$CH_2CH(OH)CH_2O$-$CH(CH_3)_2$	O	E	Oil	62	$C_{15}H_{29}N_3O_3$	C, H	i

[a] Lit.[2] bp 130–132° (5×10^{-2}). [b] N-Oxide. [c] Minimum effective dose to clear 90% of the pretreatment circulating microfilariae. [d] Inactive at 30 mg/kg. [e] Refers to N-alkylethylenediamine and N-alkylmaleamic acid route. [f] Refers to N-benzylethylenediamine and diethyl fumarate route. [g] Method described in the Experimental Section. [h] All the compounds, obtained as oils, were purified by chromatography over a basic alumina column using benzene as eluent.

A mixture of **36** (1 g, 0.0054 mol) and *S*-methylthiourea sulfate (1.01 g, 0.0054 mol) in 65% EtOH (30 ml) was refluxed for 24 hr until no more methyl mercaptan was evolved. The solvent was removed from the reaction mixture and the residue treated with 50% NaOH solution (25 ml). The separated oil was extracted with C_6H_6 (3 × 50 ml), the combined extracts were dried (Na_2SO_4), and solvent was removed to get the product as a thick oil.

3-Ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one 8-Oxide (57). A solution of **28** (1.5 g, 0.007 mol) in H_2O (2 ml) was treated with 30% H_2O_2 (2 ml) and the reaction mixture stirred for 1 hr at 60°. Excess of H_2O_2 was decomposed by adding $KMnO_4$ solution to the reaction mixture and concentrated under reduced pressure, and the residue was extracted with hot C_6H_6 (3 × 50 ml). The combined extracts were dried (Na_2SO_4), the solvent was removed, and the residue was crystallized from C_6H_6–petroleum ether.

3,8-Dibenzyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (27). A mixture of **16** (20 g, 0.06 mol) and Et_3N (18 ml, 0.128 mol) in dry $CHCl_3$ (200 ml) was added dropwise with stirring to $COCl_2$ (15 ml) kept below −20° when a vigorous exothermic reaction took place and a thick mass of Et_3N·HCl separated out. After the addition was over, the reaction mixture was stirred for an additional 12 hr at room temperature and solvent removed in vacuo. The residue was taken up in dry C_6H_6 (200 ml), the insoluble Et_3N·HCl filtered off, and the solvent removed from the filtrate to get the product as an oil.

3-Ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decane-2-thione (34). A solution of $CSCl_2$ (3.1 ml, 0.035 mol) in dry $CHCl_3$ (25 ml) was added dropwise under stirring to an ice-cold mixture of **17** (6 g, 0.035 mol) and Et_3N (9.8 ml, 0.07 mol) in dry $CHCl_3$ (100 ml) and the reaction mixture stirred for 1 hr at room temperature and then refluxed for 1 hr. Solvent was removed in vacuo and the residue taken up in dry C_6H_6 (100 ml). The insoluble Et_3N·HCl was filtered off, the solvent removed from filtrate, and the residue distilled under reduced pressure. Using this procedure compounds **33** and **35** were also made.

3-Benzyl-8-carbethoxy-1,3,8-triazabicyclo[4.4.0]decan-2-one (32). A solution of ethyl chloroformate (2 ml, 0.02 mol) in C_6H_6 (10 ml) was added dropwise to a cold solution of **27** (1.4 g, 0.004 mol) in C_6H_6 (40 ml) and the reaction mixture refluxed for 24 hr. The solvent was removed in vacuo, the residue cooled in ice and treated with 50% NaOH solution (10 ml), and the separated oil extracted with C_6H_6 (3 × 25 ml). Removal of the solvent from combined extracts yielded the product as an oil.

3-Benzyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (31). A mixture of **32** (1 g, 0.003 mol) and 48% HBr solution (20 ml) in glacial AcOH (20 ml) was refluxed for 24 hr. The solvent was removed from the reaction mixture, the residue treated with 50% NaOH solution (25 ml), and the separated oil extracted with C_6H_6 (3 × 20 ml). The combined extracts were dried (Na_2SO_4) and solvent was removed to get the product as an oil.

Acknowledgments. The authors thank Drs. A. B. Sen and R. K. Chatterjee of the division of chemotherapy of this Institute for providing the antifilarial screening results, Dr. B. N. Dhawan and his associates for antiinflammatory data, and the staff of our Instrumentation Services for various spectroscopic and analytical data. One of us (S.S.) thanks CSIR, New Delhi, for the award of a junior research fellowship.

References and Notes

(1) R. Saxena, R. N. Iyer, N. Anand, R. K. Chatterjee, and A. B. Sen, *J. Pharm. Pharmacol.*, **22**, 307 (1970).
(2) R. Saxena, S. Sharma, R. N. Iyer, and N. Anand, *J. Med. Chem.*, **14**, 929 (1971).
(3) D. K. Yung, L. G. Chatten, and D. P. MacLeod, *J. Pharm. Sci.*, **57**, 2073 (1968).
(4) N. B. Mehta, A. P. Phillips, F. Fu Lui, and R. E. Brooks, *J. Org. Chem.*, **25**, 1012 (1960).
(5) W. B. Wright, Jr., and H. J. Brabander, *J. Org. Chem.*, **26**, 4057 (1961).
(6) F. Hawking and P. Sewell, *Br. J. Pharmacol. Chemother.*, **3**, 285 (1948).
(7) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

Potential Bioreductive Alkylating Agents. 5. Antineoplastic Activity of Quinoline-5,8-diones, Naphthazarins, and Naphthoquinones

Ai Jeng Lin,* Brian J. Lillis, and Alan C. Sartorelli

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510. *Received February 12, 1975*

A number of 2-chloromethyl and 2-bromomethyl derivatives of naphthoquinones, quinolinediones, and naphthazarins were designed and synthesized as potential bioreductive alkylating agents, and the antitumor activity of these compounds was assessed in mice bearing Sarcoma 180 ascites cells. The results indicated that, with the exception of 3-benzamido-2-chloromethyl-1,4-naphthoquinone, which was inactive, all newly synthesized naphthoquinones possessed strong antitumor activity against this neoplasm. 6,7-Bis(bromomethyl)quinoline-5,8-dione had moderate inhibitory activity against Sarcoma 180 at its optimal daily dosage level of 15 mg/kg. 3-Bromo-2-bromomethyl- and 3-bromo-2-chloromethylnaphthazarin produced a moderate extension of the life span of tumor-bearing mice; whereas, in contrast, 6,7-dimethyl analogs of these agents were inactive when employed in daily doses up to 40 mg/kg of body weight.

The synthesis of a series of benzo- and naphthoquinone derivatives with common structural features (**1**), which were designed to generate a reactive species in cells, have been reported previously.[1-5] These agents were found to be potent inhibitors of (a) the growth of rodent tumors,[1-3] (b) the synthesis of DNA and RNA in these neoplastic cells in vitro,[1,2] and (c) the coenzyme Q-mediated beef heart mitochondrial enzymes, NADH-oxidase and succinoxidase.[2,4] The mechanism by which these compounds exert their cytotoxicity has been postulated[6] to involve the enzymatic reduction of the quinone ring in vivo, presumably by an NADPH-dependent quinone reducing system analogous to that acting on mitomycin C,[7-9] to form a dihydroquinone, which spontaneously generates the reactive species, an *o*-quinone methide (**2**); this reactive intermediate may then act to alkylate cellular components. Chemical evidence[10] has been obtained to substantiate the existence of an *o*-quinone methide from 2,3-dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone (**3**).

As part of a study to develop new antineoplastic agents of this class with (a) greater therapeutic potency and (b) better water solubility (in salt form), the synthesis of a