The hydrogen bonds between O(3) and O(19) and O(17) and O(19) are within the range normally observed, 2.828 and 2.926 Å, respectively. A third possible hydrogen bond involves O(3) and O(17) with a separation of 3.114 Å. The fourth short contact (3.318 Å) involves O(3) and C(18).

Conclusions

These results also indicate that the conformation with the methyl group over the B ring should also be the preferred conformation in most solvents. Any change in the B-ring conformation or the conformation of the C-(19)-methyl substituent would result in shortening of the nonbonded contacts and a corresponding increase in energy.

The isolation of the 19*R* configuration as the minor product and conformation of the bulky C(19)-methyl substituent both indicate that the mechanism of Wicha and Caspi is incorrect. Furthermore, a 19*S* configuration for the major product[8] would require approach of C(19) by the methyllithium from over the less sterically hindered B ring. Since the mechanism of tritium addition and the configurational assignment of Skinner and Akhtar are dependent on the correctness of the methyllithium reaction, it also seems likely that these are also incorrect.

Acknowledgment. The authors wish to express their gratitude to Miss M. Tugac for her assistance in the preparation of the illustrations. This work has been supported by Grant No. CA-10906 awarded by the National Cancer Institute and Grant No. HD-04945 awarded by the National Institute of Child Health and Human Development of DHEW. The authors also gratefully acknowledge Dr. K. Shibata for the synthesis of this compound.

Supplementary Material Available: listing of the structure factor amplitudes (9 pages). Ordering information is given on any current masthead page.

References and Notes

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(8) A recent investigation of the major product revealed that C(19) has a 19*S* configuration.

Contraceptive Agents from Cycloaddition Reactions of Diarylcyclopropenones and Diarylthiirene 1,1-Dioxides

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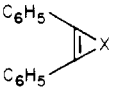
The potential for compounds with antifertility activity from the reactions of diphenylcyclopropenone (1) and 2,3-diphenylthiirene 1,1-dioxide (2) with enamines is described. In certain instances, a marked dissociation of antifertility from estrogenic activity was possible. Two series were studied extensively, one was stilbene amides (7) and the other stilbene amino ketones (8). The latter series (8) afforded several materials from which, on further biological work-up, was singled out compound 21 as a potent antifertility agent in rats and hamsters.

The synthesis of triarylethylenes,[1] diaryldihydronaphthalenes,[2] diarylindenes,[3] and diaryl heterocycles[4] and the antifertility activity of these compounds in rodents have been described.[5] Most of the compounds described have marked estrogenic or antiestrogenic activity. It was our intention to investigate compounds which were structurally very different from the above and whose antifertility activity was evident in doses far lower than those required to exert estrogenic activity. Some of the compounds screened in the present study did indeed demonstrate enhanced antifertility and reduced estrogenic activity.

At the beginning of this study, diphenylcyclopropenone (1)[6] and 2,3-diphenylthiirene 1,1-dioxide (2)[7] had been recently described and only the former had been utilized in cycloaddition reactions.[8] We recognized that these molecules contained a stilbene pharmacophoric group which could be incorporated into novel structures. We

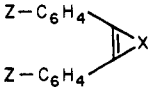


1, X = C=O
2, X = SO_2

report here materials from such a study which exert marked antifertility activity in laboratory rodents.

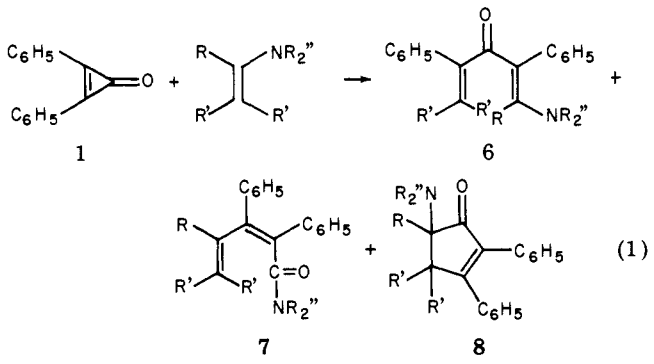
Chemistry. The preparation of 1 and 2 and their derivatives (3, 4, and 5, respectively) was by literature methods (Table I).[6,9,10] Cycloadditions of 1 with acyclic and cyclic enamines were investigated (eq 1). Treatment of 1 with an equimolar amount of enamine according to ref 8 afforded their reported substance which the authors incorrectly assigned as 6 and a new substance whose analytical properties better fit this structural type. Further investigation showed the reported material in ref 8 to be amide 7 and the new substance, 6.[11] Certain structural

Table I. Starting Materials[a]



Compd	Z	X
1	H	C=O
3	4-OCH_3	C=O
4	4-Cl	C=O
2	H	SO_2
5	4-Cl	SO_2

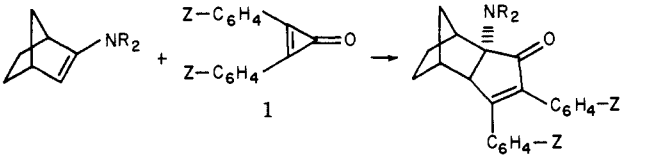
[a] None of these compounds exerted antifertility activity when administered orally to rats at a dose of 25 mg/kg on days 1–9 of pregnancy.



1 6 7 8 (1)

modifications in the enamines led to amino ketone 8.[11]

The antifertility activities of **9**, **15**, and **19** encouraged synthesis of a number of derivatives shown in Tables II and III. The novelty of structure **19** for such an activity[12] led us to utilize bicyclic enamines which would be expected to have a propensity for the formation of amino ketones **8** (eq 2).[13]



1 **20** (2)

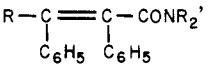
The antifertility activity of **20**, a substance derived from that study, warranted the need for a detailed structure–activity study (Table III). The cis,exo geometry is assigned for amino ketones **8** and is based on literature precedence.[10,13] In some instances, derivatives of structural type **7** were obtained as well as those related to **8**.

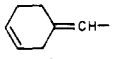
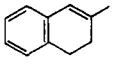
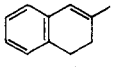
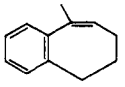
When thiirene 1,1-dioxide **2** was employed in a similar transformation, amino sulfone **38** was obtained; its activity was altered by the indicated modifications in Table IV.[14]

Antifertility Activity and Other Biological Properties. All compounds in Table I were inactive. In all of our studies only one compound with the structural type **6** was isolated and it was inactive (R' = CH_3; R = H; R'' = Pyrr).[11]

Of the compounds listed in Table II, **9**, **15**, and **16** showed very marked antifertility activity, completely preventing maintenance of pregnancy when administered orally at a daily dose of 25 mg/kg on days 1–9 of pregnancy in rats. None were active at lower doses.

Table II. Physical Properties and Antifertility Activity



Compd	R	NR_2'	Mp, °C	Yield, %	Formula[a]	Antifertility act.[b]
9	$(CH_3)_2C{=}CH-$	1-Pyrr[c]	*k*			+4
10	$C_6H_{10}{=}CH-$	1-Pyrr	143[d]	40	$C_{26}H_{29}NO$	A
11		1-Pyrr	134–135[d]	24	$C_{26}H_{27}NO$	A
12		1-Pip[c]	178–180[e]	10[f]	$C_{28}H_{31}NO$	A
13		1-Pyrr	145–146[g]	41[h]	$C_{27}H_{29}NO$	A
14		1-Pip	182–184[d]	16[i]	$C_{28}H_{31}NO$	A
15		1-Pyrr	*l*			+4, 50 mg/kg
16		1-Pip	120–122[d]	27	$C_{30}H_{29}NO$	+4
17		1-Pyrr	*l*			A
18		1-Pyrr	258–260 dec[j]	52	$C_{30}H_{29}NO$	A

[a] The compounds were analyzed for C, H, and N. [b] Dose of 25 mg/kg unless otherwise stated. Scoring system is as follows: A = possibly active but not sufficiently potent for biological interest (0–24% change); +1 = 25–49% reduction in litter size of treated animals; +2 = 50–74% reduction in litter size; +3 = 75–99% reduction in litter size; +4 = 100% reduction in litter size. [c] Pyrr is pyrrolidine and Pip is piperidine. [d] From ether. [e] From ether–hexane. [f] Obtained from a mixture with **29** and isolated by fractional crystallization. [g] From tetrahydrofuran–ether. [h] Obtained from a mixture with **32** and isolated by fractional crystallization. [i] Obtained from a mixture with **31** by chromatographing on neutral Woelm alumina (activity 1) and eluting with ether–chloroform (80:20). [j] From ethyl acetate. [k] See ref 11b. [l] See ref 11c.

Table III. Physical Properties and Antifertility Activity of Amino Ketones

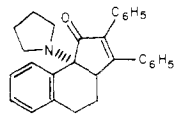
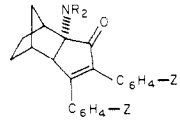
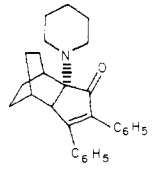
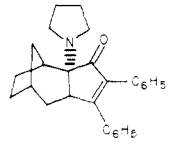
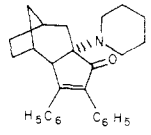
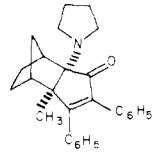
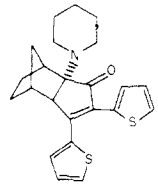
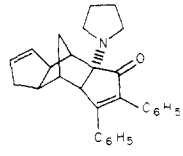
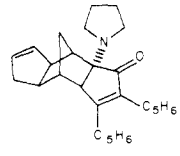
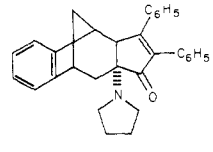
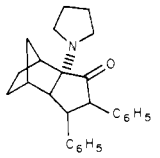
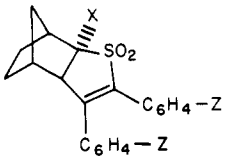
Compd	Structure		Mp, °C	Yield, %	Formula[a]	Antifertility act.[b]
19			*o*			+2
						
	NR_2	Z				
20	1-Pyrr[c]	H	197-198[d]	68	$C_{26}H_{27}NO$	+4 (hamster, A at 50 mg/kg)
21	1-Pip[c]	H	159.5-160[e]	50	$C_{27}H_{29}NO$	+4 (hamster, +4 at 50, +1 at 10 mg/kg)
22	1-Morp[c]	H	217-218[e]	38	$C_{26}H_{27}NO_2$	A
23	1-Homopip	H	172-173.5[f]	53.5	$C_{28}H_{31}NO$	+4 (hamster, A at 50)
24	4-Me-1-piperazine	H	110-112	10	$C_{27}H_{30}N_2O$	+3, 5 mg/kg
25	$N(CH_3)_2$	H	151-153[d]	36	$C_{24}H_{25}NO$	A
26	1-Pyrr	4-Cl	209-210[f]	42	$C_{26}H_{25}Cl_2NO$	A
27	1-Pyrr	4-OCH_3	147-149[f]	37.5	$C_{28}H_{31}NO_3$	A
28	1-Pip	4-Cl	166-168 dec[g]	21.5	$C_{27}H_{27}Cl_2NO$	A
29			176-178[e]	35.5[h]	$C_{28}H_{31}NO$	+4
30			174-176[d]	89	$C_{27}H_{29}NO$	A
31			147-149[i]	16[j]	$C_{28}H_{31}NO$	+4
32			148-149[f]	41[k]	$C_{27}H_{29}NO$	A, 5 mg/kg
33			170-171.5[f]	28[l]	$C_{23}H_{25}NOS_2$	A
34			205-207[f]	73	$C_{29}H_{29}NO$	A
35			182-183[e]	56.5	$C_{29}H_{31}NO$	A
36			169-170	21.5	$C_{31}H_{29}NO$	+4 (hamster, +1 at 50 mg/kg)

Table III (*Continued*)

Compd	Structure	Mp, °C	Yield, %	Formula[a]	Antifertility act.[b]
37		148–150[m]	50[n]	$C_{26}H_{29}NO$	+1

[a] The compounds were analyzed for C, H, and N. [b] See footnote *b*, Table II. [c] Pyrr is pyrrolidine, Pip is piperidine, and Morp is morpholine. [d] From 95% ethanol. [e] From ethyl acetate. [f] From tetrahydrofuran–ether. [g] From tetrahydrofuran–hexane. [h] Obtained from a mixture with 12 and isolated by fractional crystallization. [i] From ether. [j] Obtained from a mixture with 14 (Table II, footnote *i*, elution with hexane). [k] Obtained from a mixture with 13 and isolated by fractional crystallization. [l] The reaction was done with impure cyclopropenone prepared by methods described in ref 9. [m] From ethyl acetate–ethanol. [n] Obtained by hydrogenation of 20 in ethyl acetate–tetrahydrofuran with platinum oxide in a Parr apparatus at 50°: γ^{CHCl_3} 1715 cm^{-1} (strong) [compares with a diphenylcyclopentanone from the literature, γ^{CHCl_3} 1724 cm^{-1}: P. Yates, N. Yoda, W. Brown, and B. Mann, *J. Am. Chem. Soc.*, **80**, 202 (1958)]. [o] See ref 11c.

Table IV. Physical Properties and Antifertility Activity (in Rats)



Compd	X	Z	Mp, °C	Yield, %	Formula[a]	Antifertility act.[b]
38	1-Pyrrolidinyl	H	*f*			+3
39	1-Piperidinyl	H	180–181[c]	66[d]	$C_{26}H_{29}NO_2S$	+4
40	1-Pyrrolidinyl	4-Cl	201–203[e]	57[d]	$C_{25}H_{25}Cl_2NO_2S$	A

[a] The compounds were analyzed for C, H, and N. [b] See footnote *b*, Table II. [c] From ethyl acetate–hexane. [d] Prepared according to the general procedure in ref 10. [e] From tetrahydrofuran–hexane. [f] See ref 10 and 14.

Of the compounds listed in Table III, **20**, **21**, **23**, **24**, **29**, **31**, and **36** induced virtually complete inhibition of implantation and/or abortion of implanted embryos at a daily oral dose of 25 mg/kg for 9 days. Compounds **38** and **39** (Table IV) were similarly effective.

Of the above compounds, **9**, **15**, **16**, **20**, **21**, **23**, **24**, **29**, **31**, **36**, and **39** were screened at a lower dose (5 mg/kg for 9 days of pregnancy). The results are shown in Table V.

Compound **21** was selected for further studies, the complete results of which will be reported elsewhere.

Compound **21** exerted moderate estrogenic activity in immature and adult ovariectomized rats. Thus, compound **21** induced vaginal opening and cornification and stimulated uterine growth in the absence of the ovaries. Compound **21** had no antiestrogenic activity in rats. Based on our experience, the estrogenic potency was not sufficient to fully account for the antifertility activity.

Compound **21** was an effective contraceptive agent in hamsters at an oral daily dose of 50 mg/kg. The substance also exerted uterotrophic activity in this species. The ratio of the daily doses necessary for 100% effective contraception in hamsters/rats was 10. This was the smallest ratio we have observed with either steroidal or nonsteroidal agents, many of which are essentially inactive in hamsters.[15] The relatively high potency in hamsters supports the view that the antifertility effects of compound **21** are not due primarily to estrogenicity as the hamster is highly resistant to estrogens.[15]

Compound **21** had antideciduomal properties in pseudopregnant rats and was fully active as a contraceptive when administered once weekly to female rats permanently caged with male partners. Compound **21** was weakly estrogenic in rats (stimulating uterine weight increase and vaginal opening in immature animals) but was not sufficiently estrogenic to prime the immature rabbit uterus for a Clauberg progestational response. It was not antiprogestational in the rabbit. Compound **21** had no effect on mating behavior in spayed dogs but did induce withdrawal bleeding in ovariectomized or immature rhesus monkeys at doses of 25–50 mg/kg. The compound was not toxic to a rhesus monkey at doses up to 800 mg/kg po.

Table V. Effect of Compounds on Fertility in Rats[c]

Compd	No. of rats	Av. no. of living fetuses	Av. no. of resorptions	Av. no. of total implants
9	5	5.4	2.6	8.0
15	5	7.2	3.0	10.2
16	5	15.8	0	15.8
20	5	11.4	0	11.4
21	5	0	0	0
23	5	0	2.2	2.2
24	5	1.0	4.6	5.6
29	5	6.8	0.4	7.2
31	5	6.6	5.2	11.8
36	5	0	0	0
39	5	11.6	2.6	14.2
Standard Diethylstilbestrol[a]	5	11.4	0	11.4
Diethylstilbestrol[b]	5	0	2.2	2.2
Controls	26	10.6	0	10.6

[a] 2.5 μg/kg po. [b] 25 μg/kg po. [c] 5 mg/kg po on days 1–9 of pregnancy.

Compound **21** was proposed for antifertility trials in rhesus monkeys and baboons. The results of these studies will be reported elsewhere.

Experimental Section

General Comments. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 21 or 521 grating spectrophotometer and performed in Nujol; ultraviolet spectra were recorded on a Cary 14 and performed in methanol. The nuclear magnetic resonance spectra were determined in deuterated

Table VI. Analytical Properties for Representative Amides (7) and Amino Ketones (8)

Compd	ν^{Nujol}, cm^{-1}	$Uv_{max}^{CH_3OH}$, nm	$\delta_{Me_4Si}^{CDCl_3}$
4-Cyclohexylidene-2,3-diphenyl-1-pyrrolidino-2-buten-1-one (10)	1611	205 (29 400), 234 (20 200), 295 (14 400)	5.71[a,b]
3-(Bicyclo[2.2.2]oct-2-en-2-yl)-2,3-diphenyl-1-pyrrolidino-2-propen-1-one (12)	1621	231 (18 600), 290 (12 300)	6.33[a] (doublet of doublets)
3-(Bicyclo[3.2.1]oct-2-en-3-yl)-2,3-diphenyl-1-pyrrolidino-2-propen-1-one (14)	1616	228 (19 100), 283 (10 700)	6.10[a,b]
3-(3,4-Dihydro-2-naphthyl)-2,3-diphenyl-1-pyrrolidino-2-propen-1-one (16)	1628	226 sh (24 000), 277 (15 700), 312 (17 500)	6.68[a,b]
4,5-Diphenyl-2-pyrrolidino-2,6-*cis*-tricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-one (20)	1674	226 (17 300), 298 (12 600)	[c]
6-Methyl-4,5-diphenyl-2-pyrrolidino-2,6-*cis*-tricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-one (32)	1702	219 sh (15 100), 294 (13 400)	[c]
3a,4,9,10-Tetrahydro-2,3-diphenyl-10a-pyrrolidino-4,9-methanobenz[*f*]azulen-1-one (36)	1691	220 sh (22 700), 268 (7810), 274 (8690), 298 (10 900)	[c]
4,5-Diphenyl-2-piperidino-3-thiatricyclo[5.2.1.$0^{2,6}$]-dec-4-ene 3,3-dioxide (39)	1620[d]	220 (19 600), 256 (9610)	[c]

[a] Vinyl proton. [b] Multiplet. [c] Compatible with the assigned structure. [d] Weak intensity double bond stretch.

chloroform and performed on a Varian A-60. Absorptions are quoted in δ values against tetramethylsilane as internal standard. Mass spectra were recorded for most of the materials and were obtained on an AEI MS-902 spectrometer (70 eV). Elemental analyses were done on a Perkin-Elmer 240 C, H, N analyzer.

Biology Methods. Antifertility Assays in Rats and Hamsters. Adult female rats (Charles River CD strain) and hamsters (Lakeview LAK/LVG-SVR) were housed in a day–night reversed room (dark 6 a.m.–6 p.m.; light 6 p.m.–6 a.m.). At 9:00 a.m. the animals were caged with males of proven fertility. At 3:00 p.m. the females were examined and those exhibiting copulation plugs or sperm in their vaginal smears were deemed pregnant (day 0). The pregnant females were isolated and test compounds were administered orally, generally for 9 days to groups of five animals each. The animals were then killed on day 11 of pregnancy and living fetuses, resorptions, and total implantation sites were counted. The uterine contents of treated animals were compared with those of controls. Several known steroidal and nonsteroidal contraceptives are run periodically in our laboratory as standards.[15] In mechanism of action studies, test compounds were administered before (day 3) or just after (day 5) implantation as single oral doses. All compounds were screened in the rat test while only those active at low doses in rats were tested in hamsters. Activity was evaluated by the percentage reduction in the number of viable fetuses: A = possibly active but less than 24% reduction; +1 = 25–49% reduction; +2 = 50–74% reduction; +3 = 75–99% reduction; +4 = no living fetuses.

There was a tendency for individual pregnant animals to respond to active drugs in an all-or-none fashion (i.e., the entire litter either lived or died). Thus, the standard error about the mean value was generally greatest around the 50% reduction mark (±20–30%) and lowest (±5–10%) at threshold or completely effective doses. A reduction of 50% or more in the number of viable fetuses was almost always statistically significant ($p < 0.05$). Lesser reductions were biologically meaningful, especially when the total number of implantation sites was similar to control but the number of resorptions increased. No compounds were evaluated beyond the original screen in rats unless a 3 or 4+ response was obtained at the 25 mg/kg dose and at least a 3+ at 5 mg/kg.

Starting Materials. The starting materials were prepared according to the literature (ref 10 and those cited therein). The unknown materials had the following physical properties: 1-(cyclohexylidenemethyl)pyrrolidine, bp 55–57° (0.27 mm); 1-[(3-cyclohexenylidene)methyl]pyrrolidine, bp 57–58° (0.25 mm); 1-(bicyclo[2.2.1]hept-2-en-2-yl)hexahydroazepine, bp 70° (0.20 mm); 1-(bicyclo[2.2.1]hept-2-en-2-yl)-4-methylpiperazine, bp 110° (12 mm); 1-(bicyclo[3.2.1]oct-2-en-2-yl)pyrrolidine, bp 90° (0.28 mm); 1-(bicyclo[3.2.1]oct-2-en-3-yl)pyrrolidine, bp 75° (0.18 mm); 1-(3-methylbicyclo[2.2.1]hept-2-en-2-yl)pyrrolidine, bp 63° (0.18 mm); 1-(bicyclo[2.2.2]-oct-2-en-2-yl)piperidine, bp 75° (0.40 mm); 1-(tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-8-yl)pyrrolidine, bp 70° (0.20 mm); 1-(tricyclo[5.2.1.$0^{2,6}$]dec-8-en-8-yl)pyrrolidine, bp 90° (0.18 mm); 1-(6,9-dihydro-5,9-methano-5*H*-benzocyclohept-6-en-7-yl)pyrrolidine, mp 65–68°.

General Procedure for the Reaction of Diarylcyclopropenones with Enamines. A stirred solution of the diarylcyclopropenone in dry benzene was treated dropwise under nitrogen beginning at 20° with a solution of the enamine in the same solvent. The reaction mixture was not allowed to go above 50° during the addition period. The reaction mixture was heated at 65° to reflux for 1–8 h and left overnight at 20°. Concentration of the deep red solution in vacuo and trituration of the resultant oil with ether–hexane or cold ether afforded full crystallization. The materials were filtered and recrystallized from the indicated solvents (see Tables II–IV). Table VI contains the infrared (ν cm^{-1}), ultraviolet (uv max), and NMR (δ_{Me_4Si}) spectral data for representative amides (7) and amino ketones (8).

Typical Procedure. 4,5-Diphenyl-2-piperidino-2,6-*cis*-tricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-one (21). A stirred solution of 3.0 g (0.015 mol) of diphenylcyclopropenone in 10 ml of dry benzene was treated dropwise under nitrogen in 5 min, beginning at 20°, with a solution of the enamine in 10 ml of the same solvent. The reaction mixture turned green and then black, and the temperature rose to 50°. When the temperature began to fall, the mixture was heated at reflux for 1 h and allowed to cool to ambient temperature (20°) and left overnight. Concentration of the dark red solution in vacuo gave a brown oily liquid which crystallized on trituration with ether–hexane. Filtering and washing with ether afforded 2.5 g (43.5%, not optimized) of 21, mp 159–160°. Recrystallization from ethyl acetate yielded an analytical sample, mp 159.5–160°, which was true yellow in color.

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Synthesis of Some 1,8- and 2,8-Disubstituted Derivatives of Adenosine Cyclic 3',5'-Phosphate and Their Interaction with Some Enzymes of cAMP Metabolism

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1,8-Disubstituted derivatives of adenosine cyclic 3',5'-phosphate (cAMP) were synthesized by N-oxidation or N-methylation of previously reported 8-substituted cAMP derivatives to yield 8-bromoadenosine cyclic 3',5'-phosphate 1-oxide and 8-(benzylthio)-1-methyladenosine cyclic 3',5'-phosphate. Substituents were introduced into the 8 position of 2-methyladenosine cyclic 3',5'-phosphate and 2-butyladenosine cyclic 3',5'-phosphate by bromination, followed by treatment with sodium benzylmercaptide, sodium *p*-chlorothiophenolate, or, in the former case, sodium azide. Each of the 1,8- and 2,8-disubstituted derivatives of cAMP was tested as activators of cAMP-dependent protein kinase and as substrates for and inhibitors of cyclic nucleotide phosphodiesterases. Depending on the substitutions, examples were found where the disubstituted derivatives were either more active, equally as active, or less active than the monosubstituted parent compounds as protein kinase activators. For the compounds reported, 8-substitution completely or substantially eliminated the ability of 1- or 2-substituted derivatives of cAMP to serve as substrates for phosphodiesterase and diminished the ability of these latter derivatives to inhibit cAMP hydrolysis.

The synthesis and biological evaluation of analogs of adenosine cyclic 3',5'-phosphate (cAMP) have for the most part been directed toward singly modified derivatives.[1,2] To date, virtually all accessible positions of the cAMP molecule have been modified (the 1, 2, 6, 8, 2', 3', 4', and 5' positions and the phosphorus atom). We have now undertaken a systematic investigation of the effects of multiple substitutions of cAMP on its biological activity. We have previously reported on the synthesis and enzymic activity of 5',6- and 2',8-disubstituted derivatives of cAMP and 2,6-disubstituted derivatives of 9-β-D-ribofuranosylpurine cyclic 3',5'-phosphate (cNMP)[3-5] and on the synthesis of N^6,8-disubstituted derivatives of cAMP and 6,8-disubstituted derivatives of cNMP.[6]

As cAMP-dependent protein kinase activators, the 5',6-, 2',8-, and 2,6-disubstituted analogs were found to be less active than either of the singly modified parent compounds from which they were derived,[3-5] while the 6,8-disubstituted derivatives demonstrated activities intermediate between those of the singly modified parent compounds.[7] As substrates for cyclic nucleotide phosphodiesterase, the 5',6-, 2',8-, and 6,8-disubstituted analogs were resistant to hydrolysis,[3,4,7] while the 2,6-disubstituted derivatives were hydrolyzed at rates which approached those of the singly modified parent compounds.[5]

As a logical next step from our reports on the synthesis and enzymic activities of 1-,[8] 2-,[9,10] and 8-monosubstituted[11-13] cAMP derivatives, we here report the synthesis and enzymic properties of some representative 1,8- and 2,8-disubstituted cAMP derivatives and compare them to the singly modified parent compounds.

Synthesis. 2-Methyl- (**1**) and 2-butyladenosine cyclic 3',5'-phosphate[9] (**2**) were treated with aqueous sodium acetate buffer (pH 4) saturated with bromine, in a manner analogous to the preparation of 8Br-cAMP from cAMP,[11] to give 8-bromo-2-methyladenosine cyclic 3',5'-phosphate (**3**) and 8-bromo-2-butyladenosine cyclic 3',5'-phosphate (**4**), respectively. These 8-bromo nucleotides provided convenient intermediates for the preparation of the additional 2,8-disubstituted derivatives by treatment with nucleophiles in the manner previously described.[11] Thus, treatment of **3** with sodium benzylmercaptide, sodium *p*-chlorothiophenolate, and sodium azide gave, respectively, 8-(benzylthio)-2-methyladenosine cyclic 3',5'-phosphate (**5**), 8-(*p*-chlorophenylthio)-2-methyladenosine cyclic 3',5'-phosphate (**6**), and 8-azido-2-methyladenosine cyclic 3',5'-phosphate (**7**). Likewise, 8-(benzylthio)-2-butyladenosine cyclic 3',5'-phosphate (**8**) and 2-butyl-8-(*p*-chlorophenylthio)adenosine cyclic 3',5'-phosphate (**9**) were prepared from **4**.