Articles

3-Substituted Adenines. In Vitro Enzyme Inhibition and Antiviral Activity

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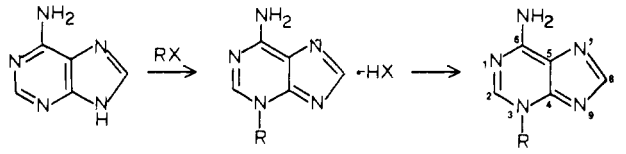
The direct alkylation of adenine at the 3 position has been extended to produce series of 3-alkyl-, 3-allyl-, and 3-(substituted benzyl)adenines. When these compounds were tested for enzyme inhibition and antiviral activity in vitro, 3-*n*-pentyladenine was found to be the most active compound in inhibiting the enzyme dopamine β-hydroxylase, and 3-(2-bromobenzyl)adenine showed the most striking inhibition of multiplication of Vaccinia virus and of Herpes simplex virus in tissue culture.

The direct alkylation of adenine at the 3 position[1-17] in the absence of base (**1** → **3**) provides the most convenient



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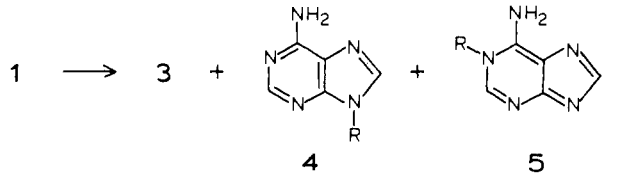
method of obtaining 3-alkyl-, allyl-, and benzyladenines. The N-3 position is also the site of methylation of adenine by *S*-adenosylmethionine and an enzyme from rabbit lung.[18] The naturally occurring 3-substituted purine derivatives presently known consist of 3-ribosyluric acid,[19] triacanthine,[20,21] which is 3-(Δ^2-isopentenyl)adenine (**3a**),[3,7,22-26] and discadenine.[27] Based on the direct alkylation of adenine, the method has been used to synthesize over 20 different 3-substituted adenines (**3**) with the purpose of testing their potential enzyme inhibition and antiviral activity.[28]

Chemistry. Treatment of adenine with Δ^2-isopentenyl bromide (γ,γ-dimethylallyl bromide) in dimethylacetamide for 30 h at room temperature furnished, after basification, 3-(Δ^2-isopentenyl)adenine (**3a**) in 66% yield, thus constituting the most direct synthesis of triacanthine.[7] The preferential 3 substitution on adenine was accompanied by formation of the corresponding 9- and 1-substituted adenines **4** and **5** in about 14 and 8% yield, respectively,



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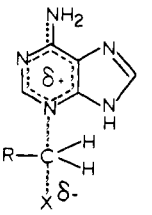
paralleling the experience of Pal[4] in ethylation and methylation under somewhat different conditions. In our earlier communication, we indicated that 3-allyladenine (**3b**) and 3-benzyladenine (**3d**) were also obtained by this method.[7] The temperatures employed in the alkylation reaction were 95 and 85 °C, respectively, and the yields were 60 and 66%. The yield of 3-benzyladenine was not improved by the use of either benzyl chloride at 150 °C or of benzyl iodide at 90 °C. The synthesis of 3-furfuryladenine (**3c**) played a role in the consideration of alternative routes for the genesis of kinetin from DNA.[26,29] Adenine must be regarded as an ambident nucleophile, with the predominant product a result of the transition state providing the best charge distribution. Delocalization of positive charge in the pyrimidine moiety is the more likely possibility (**6**), and the choice between the N-1 and



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N-3 positions may be dictated not only by this possibility but by a lower steric hindrance to reaction at the 3 position. Solvents that would favor ionic character in the transition state, such as dimethylacetamide and dimethylformamide, were most effective.

In extending the direct alkylation of adenine to other examples (**3e-x**), we found that all of the reaction mixtures showed at least two strongly UV-absorbing spots (see above) with R_f values greater than adenine in TLC on silica gel using chloroform–methanol (4:1). This system gave superior resolution to the paper chromatographic and electrophoretic techniques reported in earlier papers. Moreover, the analytically pure material obtained in previous work[9] simply by triturating the crude product (containing **2**) was possibly a mixture of at least two isomers. Our criteria of purity for the 3-substituted adenines here synthesized for biological testing included not only a correct analysis, which does not reveal the presence of isomers, but homogeneity in TLC on silica gel using chloroform–methanol (4:1) and the absence of isomers in the ^{1}H NMR spectrum. These criteria were met by repeated recrystallization, although preparative chromatography could have served equally well. The primary aim of the syntheses was to obtain the 3-substituted adenines (**3**) as pure as possible rather than to strive for maximum yield.[30]

The compounds listed in Table I were characterized as 3-substituted adenines by the determination of the dissociation constants of representative conjugate acids (**2**)[3,7] and by diagnostic ^{1}H NMR and UV characteristics. The relatively large differences in ^{1}H NMR chemical shifts, $\Delta\delta$ (Table I), between the 2- and 8-protons of the free bases in $(CD_3)_2SO$ are indicative of 3 substitution on adenine.[10]

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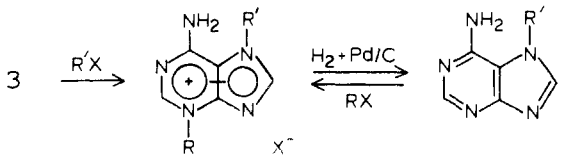
Table I. 3-Substituted Adenines. Physical and Spectral Characteristics

3	substituent	mp, °C	salt	mp, °C	formula[a]	Δδ, Hz 2- vs. 8-H	$\Delta\lambda_{min}$, nm H^+ − neutral	UV hyperchr shift in acid
a	Δ^2-isopentenyl[3,7,24]	230-231	HBr[b]	218-219	$C_{10}H_{13}N_5$	33	−6.5	+
b	allyl[7,9]	204-205	HBr[c]	207-208	$C_8H_9N_5$	30	−6	+
c	furfuryl[23,24,29]	247-248	HBr	210-213	$C_{10}H_9N_5O$	37	−8	+
d	benzyl[6,7,9]	278-280	HBr[d]	253-255	$C_{12}H_{11}N_5$	45	−7	+
e	2-chlorobenzyl	280-283	HCl	265-267	$C_{12}H_{10}ClN_5$	44	−7	+
f	3-chlorobenzyl	271-272	HBr	260-261	$C_{12}H_{10}ClN_5$	46	−8	+
g	4-chlorobenzyl	291-292	HCl	291-292	$C_{12}H_{10}ClN_5$	45	−7	+
h	2,4-dichlorobenzyl	294-296	HCl	267-269	$C_{12}H_9Cl_2N_5$	19[e]	−7	+
i	3,4-dichlorobenzyl	>300	HCl	292-295	$C_{12}H_9Cl_2N_5$	24[e]	−6	+
j	2-methylbenzyl	276-278	HBr	241-243	$C_{13}H_{13}N_5$	36	−8	+
k	3-methylbenzyl	247-248	HBr	239-240	$C_{13}H_{13}N_5$	44	−8	+
l	4-methylbenzyl[9]	281-282	HBr	262-264	$C_{13}H_{13}N_5$	44	−8	+
m	3,4-dimethylbenzyl	263-265	HCl	275-277	$C_{14}H_{15}N_5$	43	−7	+
n	2-bromobenzyl	263-265	HBr	241-242	$C_{12}H_{10}BrN_5$	41	−7	+
o	3-nitrobenzyl	>300	HBr	261-262	$C_{12}H_{10}N_6O_2$	31[e]	−8	+
p	3-(trifluoromethyl)benzyl	243-244	HCl	240-243	$C_{13}H_{10}F_3N_5$	48	−8	+
q	ethyl[4,24,31]	235-237	HBr	279-281	$C_7H_9N_5$	32	−7	+
r	propyl[9]	241-242[f]	HBr	241-244	$C_8H_{11}N_5$	32	−8	+
s	butyl	221-222	HBr	149-150	$C_9H_{13}N_5$	32	−7	+
t	pentyl	192-193			$C_{10}H_{15}N_5$	32	−7	+
u	hexyl	180-181	HBr	157-158	$C_{11}H_{17}N_5$	31	−8	+
v	isopentyl[3,32]	230-232	HBr	288-290	$C_{10}H_{15}N_5$	32	−7	+
w	cyclohexylmethyl	258-259	HBr	>300	$C_{12}H_{17}N_5$	30	−9	+
x	phytyl	153-155	HBr	172-175	$C_{25}H_{43}N_5$		−8.5	+

[a] Routine C, H, N analyses agreed with the calculated values within ±0.3% for all bases and salts. [b] HCl salt, mp 232-233 °C dec;[3] picrate, mp 257-258 °C dec. [c] HCl salt, mp 213-215 °C dec; picrate, mp 261-262 °C dec. [d] HCl salt, mp 272-273 °C dec; HI salt, mp 223-226 °C dec. [e] Bases are not soluble in $(CD_3)_2SO$; figures are given for salts. [f] Decomposition.

In addition, the appreciably negative numerical values for $\Delta\lambda_{min} = \lambda_{min}$ (acid) − λ_{min} (neutral) in the UV spectra corroborate the assignment of 3 substitution.[3] We have not obtained quantitative ultraviolet spectra in all cases, but the characteristic hyperchromic shift in acid observed in all the UV spectra was pronounced.[3,10,25a]

Further synthetic utility developed from the second stage of alkylation of the 3-substituted adenines. For example, compounds **3a,b,d,v** underwent methylation mainly at the 7 position (73–85% yield) when heated with methyl iodide in acetone or dimethylacetamide.[7] The product from **3a**, 3-(Δ^2-isopentenyl)-7-methyladenine iodide, mp 236–239 °C dec, was identical with triacanthine methiodide (**7a**, R′ = CH_3),[3] and that from **3v**, 3-isopentyl-7-methyladenine iodide (**7v**, R′ = CH_3), mp 282–284 °C dec, was identical with the methiodide of dihydrotriacanthine.[32] The iodides were readily converted to perchlorates or chlorides and, as such, had similar ultraviolet spectra, indicative of identical positional disubstitution.[33] 3-Benzyl-7-methyladenine chloride, mp 264–266 °C dec, or perchlorate, mp 288–289 °C dec, was hydrogenolyzed to 7-methyladenine (**8**, R′ = CH_3) efficiently using palladium on carbon. The synthesis of 7-methyladenine,[34-36] mp 350–351 °C dec, by benzyl blocking at the 3 position of adenine, methylation at N-7 of the free base, and hydrogenolysis is representative of a general 7-alkylation procedure. Similar blocking/deblocking has been utilized for the synthesis of the anomeric 7-D-ribofuranosyladenines.[6] Selective hydrogenolysis was also possible, as illustrated with 3,7-dibenzyladenine chloride (**7**, R = R′ = $C_6H_5CH_2$), obtained from the bromide by reaction of benzyl bromide[8] with 3-benzyladenine. The product was 7-benzyladenine (**8**, R′ = $C_6H_5CH_2$),[23,24,37] mp 236–238 °C dec, indicating that the *N*-benzyl group on the pyrimidine ring is hydrogenolyzed more readily than that on the imidazole ring. This was also recognized when a mixture of 3- and 9-benzyladenine was treated with hydrogen and palladium-on-carbon catalyst, resulting in selective cleavage of 3-benzyladenine to adenine and toluene, leaving most of the 9-benzyladenine unchanged. Resistance to catalytic hydrogenolysis by the 7- and 9-benzyl groups on purines was observed earlier by Montgomery et al.[37,38]



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The preferred site of alkylation of 7-substituted adenines was determined in the corollary experiments of heating 7-methyladenine (**8**, R′ = CH_3) with Δ^2-isopentenyl bromide, allyl bromide, and benzyl bromide in dimethylacetamide to yield (71–84%) the corresponding 3,7-disubstituted adenine bromides (**7**, R′ = CH_3; X = Br). The salts, converted to a common anion, were identical with the separate 3,7-disubstituted adenine salts produced by the first route (**3** → **7**),[7] including triacanthine methiodide.[3] The assignment of the 6-amino structure[8] for these salts is based on the ^1H NMR spectra obtained in $(CD_3)_2SO$, all of which showed a sharp signal in the region of δ 9 from Me_4Si integrating for two protons and exchangeable with D_2O. The similarity of the ultraviolet absorption spectra of 3,7-dialkyladenine salts with those of 3- and 7-alkyladenines in acidic solution is suggestive of reciprocal sites of protonation of the 3- and 7-substituted compounds in solution.[13] Subsequent to our preliminary communication,[7] the reciprocal directivity of the 3 and 7 substituents toward alkylation was reported for the methylation of 3- and 7-methyladenine,[39] the benzylation of 3- and 7-benzyladenine,[8] and additional 7-alkylation of 3-benzyladenine.[40] In addition, the synthesis of 3-substituted adenine derivatives was effected by alkylating 7-[(pivaloyloxy)methyl]adenine and then deblocking the 3,7-disubstituted intermediates with methanolic ammonia at room temperature. Pilot syntheses of 3-benzyladenine

Table II. 3-Substituted Adenines. In Vitro Activity

3	dopamine β-hydroxylase inhib: $I_{50\%}$, μg/mL	Herpes virus[a] % inhib, μg/mL 50	25	12	6	Vaccinia virus[a] % inhib, μg/mL 100	50	25	12	6	3
c		0	0	0	0	0	0	0			
d	2	0	0	0	0	3	3	0	0		
e	200	100	100	42	0	T	100	0	0	0	0
f	2	45	0	0	0	100	37	16	0	0	
g	20	15	0	0	0	T	100	70	51		
h	200	T	20	0	0	T	T	T	0	0	
i	2	T	27	0	0	T	T	T	100	87	47
j	200	30	0	0	0	T	0	0	0		
k	20	9	0	0	0	T	0	0	0		
l	20	0	0	0	0	T	10	8	0		
m	20	T	T	42	0	T	T	T	0	0	0
n	200	100	100	100	71	T	100	100	34	0	0
o	200	0	0	0	0		0	0	0		
p	20										
q	>200	0	0	0	0	0	0	0	0	0	
r	200	0	0	0	0	0	0	0	0	0	
s	20	0	0	0	0	1	0	0	0		
t	0.5	3	0	0	0	96	72	35	33		
u	1	16	0	0	0	T	100	77	27		
v	200	27	0	0	0	8	7	7	0	0	
w	2	0	0	0	0		7	0	0		

[a] T = toxic.

and 3-[(benzyloxy)methyl]adenine were followed by directed syntheses of the α and β anomers of 3-(2′-deoxy-D-ribofuranosyl)adenine[41] and of 3-β-(3′-deoxy-D-ribofuranosyl)adenine,[42] an isomer of cordycepin.

Enzyme Inhibition and Antiviral Activity. The 3-substituted adenines **3d–w** were tested in a number of enzyme systems in vitro with the purpose of detecting active compounds as candidates for subsequent selected in vivo assays. Several of the 3-substituted adenines inhibited the enzyme dopamine β-hydroxylase. A striking specificity of structure was observed in that 3-pentyladenine (**3t**) was especially active in inhibiting this enzyme system (Table II), but activity diminished when the chain was shortened to 3-butyl (**3s**) or lengthened to 3-hexyl (**3u**). The observation with 3-pentyladenine is strongly reminiscent of an homologous series of active compounds reported by Suda et al.,[43] with peak activity in the inhibition of dopamine β-hydroxylase claimed for 5-butylpicolinic acid (fusaric acid). When compound **3t** was subsequently tested in several in vivo systems, including mouse and rat behavioral assays and hypertensive rats, no activity was observed. Moreover, there was no significant reduction of norepinephrine or epinephrine levels in brain, heart, or adrenal gland when male rats were injected with 50 mg/kg 3-pentyladenine (**3t**), indicating that inhibition of dopamine β-hydroxylase had not occurred in vivo. Whether the compound is not active in vivo because it is metabolized too rapidly and fails to attain required tissue levels is not known at this time.

When the 3-substituted adenines were tested for plaque reduction in virus-infected African green monkey kidney cells, the most striking inhibition of Vaccinia virus and Herpes simplex virus was shown by 3-(2-bromobenzyl)-adenine (**3n**) (Table II). Compound **3n** was then tested against these virus infections in the mouse, but no significant protection was observed. The antiviral activity of 3-(2-bromobenzyl)adenine (**3n**) in vitro also led to the testing of the compound against transmissible gastroenteritis virus infection in piglets. However, the compound failed to show efficacy and was slightly toxic at 25 mg/pig (4–5 lb) three times a day, the lowest administered dose. The toxicity may be related to the pharmacodynamic properties that have been recorded for certain 3-substituted adenines.[17] The antiviral tissue culture activities reported here for the 3-(substituted-benzyl)adenine series are of interest with respect to the structurally related 9-(2-chloro-6-fluorobenzyl)adenine, trade name Arprinocid, which is an active coccidiostat.[44-46] The failure of compounds **3n** and **3t** to show in vivo activity remains unexplained in this study.

Experimental Section

All melting points were determined using a Thomas-Hoover capillary melting-point apparatus and are corrected. The ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or HA-100 spectrometer. Mass spectra were run on a Varian-MAT CH-5 spectrometer. Microanalyses were performed by Mr. J. Nemeth and his staff at the University of Illinois, who weighed samples for quantitative ultraviolet spectra. Routine C, H, N analyses agreed with calculated values within ±0.3% for all compounds reported herein.

General Procedure for Synthesis of 3-Substituted Adenines (3). A mixture of adenine (1) with an alkyl, allyl, or benzyl halide in about 10% molar excess in *N,N*-dimethylacetamide was heated with stirring. The optimum temperature and duration of heating varied with the halide[30] and were monitored by TLC. After removal of the solvent in vacuo, the residue was generally washed and triturated with ether and then recrystallized from ethanol or ethanol–water to TLC homogeneity. The salt of the 3-substituted adenine in $(CD_3)_2SO$ solution was examined by ^1H NMR spectrometry and was converted to the corresponding free base by dissolution in hot water, basification with concentrated aqueous ammonia, cooling and filtration, and recrystallization from ethanol.

Synthesis of 3,7-Disubstituted Adenine Salts (7). (A) From 3-Substituted Adenines (3). Representative 3-substituted adenines (e.g., **3a,b,d,v**) were heated in acetone or *N,N*-dimethylacetamide with methyl iodide or benzyl bromide.[7] After concentration and the addition of ether if necessary, the solid product was filtered and recrystallized from 70% aqueous ethanol. The structures of the products were confirmed as 3,7-disubstituted adenines by ^1H NMR and UV spectroscopic data and by hydrogenolysis in representative cases to the corresponding 7-substituted adenines.

(B) From 7-Substituted Adenines (8). 3,7-Disubstituted adenine salts were also obtained by heating 7-methyladenine, for example, with an allylic or benzylic halide in *N,N*-dimethylacetamide. The anions of the various salts were interconverted in the usual manner, and the UV spectra of compounds obtained by reciprocal routes A and B were compared for samples with common anions. The salts listed below were formed by either

Table III

hours after injection	norepinephrine, μg/g brain	norepinephrine, μg/g heart	adrenal catecholamine,[a] μg/adrenal pair
0	0.67 ± 0.02	0.55 ± 0.04	10.6 ± 0.7
3	0.65 ± 0.03	0.59 ± 0.03	14.1 ± 1.5
6	0.62 ± 0.02	0.57 ± 0.04	12.1 ± 0.3
24	0.62 ± 0.03	0.56 ± 0.06	11.3 ± 0.6

[a] Total norepinephrine plus epinephrine was measured in the adrenal glands. In these rats, epinephrine is about 90% of that total.

one or both routes and were characterized by both UV and ^{1}H NMR spectra.

3-Allyl-7-methyladenine bromide, mp 241–243 °C dec; iodide, mp 256–258 °C dec; perchlorate, mp 235–236 °C dec.

3-Benzyl-7-methyladenine bromide hemihydrate, mp 254–255 °C dec; chloride, mp 264–266 °C dec; iodide, mp 261–262 °C dec; perchlorate, mp 288–289 °C dec.

3,7-Dibenzyladenine bromide, mp 205–207 °C.

3-Isopentyl-7-methyladenine iodide, mp 282–284 °C dec; perchlorate, mp 262–264 °C dec.

3-(Δ^2-Isopentenyl)-7-methyladenine bromide, mp 230–231 °C dec; iodide, mp 236–239 °C dec; perchlorate, mp 247–248 °C dec.

In vitro enzyme inhibition studies of compounds **3c–w** (Table II) were done by Dr. Ray W. Fuller, The Lilly Research Laboratories, using a dopamine β-hydroxylase preparation which was partially purified from bovine adrenal medullae.[47]

In Vivo Testing in Rats (Courtesy of Dr. Ray W. Fuller, The Lilly Research Laboratories).[48] 3-Pentyladenine (**3t**) (Table II), as the mixed hydrochloride–hydrobromide, was injected in aqueous solution ip at a dose of 50 mg/kg into groups of male Wistar rats weighing about 150 g. Groups were killed at 3, 6, and 24 h after drug injection, and catecholamines were measured spectrofluorometrically. Values shown in Table III are the mean plus or minus standard error for five rats per group. There was no significant reduction of norepinephrine or epinephrine levels in these tissues, indicating that inhibition of dopamine β-hydroxylase had not occurred in vivo.

Plaque-Reduction Tests. African green monkey kidney cells (BSC-1) were grown in 25-cm^2 Falcon flasks at 37 °C in medium 199 with 5% inactivated fetal bovine serum (FBS), penicillin (150 units/mL), and streptomycin (150 μg/mL). When confluent monolayers were formed, one growth medium was removed and 0.3 mL of an appropriate dilution of virus was added to each flask (Vaccinia virus VI Lindeman, 152 plaque-forming units [PFU]; type I Herpes simplex virus, 268 PFU). After absorption for 1 h at room temperature, the cell sheet was overlaid with equal parts of 1% Ionagar no. 2 and 2× medium 199 (FBS, penicillin, and streptomycin) containing drug concentrations of 100, 50, 25, 12, 6, 3, and 0 μg/mL. The stock solutions of 3-substituted adenines were made up in Me_2SO at 10 000 μg/mL. All flasks were incubated for 96 h at 37 °C. A 10% formalin–2% sodium acetate solution was added to each flask to inactivate the virus and fix the cell sheet to the plastic surface. The plaques were counted after staining the surrounding cell areas with crystal violet. To facilitate the comparison of the drugs in the two virus systems, the results are recorded as percent inhibition of plaques at varying levels of drug.

In Vivo Testing in Mice and Piglets (Courtesy of Ms. Janet D. Nelson and Dr. Charles Gale, The Lilly Research Laboratories). 3-(2-Bromobenzyl)adenine (**3n**) (Table II), selected for testing against the same virus infections in the mouse, showed no significant protection. The drug did not prolong the life of piglets infected with transmissible gastroenteritis and exhibited slight toxicity at 25 mg/pig three times a day.

A Concentration of 100 mg/Pig (4–5 lb) Three Times a Day. This dose killed two of the four pigs within 24 h after the first treatment. The other two pigs died within 72 h of the first treatment.

A Concentration of 50 mg/Pig (4–5 lb) Three Times a Day. This dose killed one pig in 48 h and one pig in 72 h.

A Concentration of 25 mg/Pig (4–5 lb) Three Times a Day. Of four pigs, three lost weight 24 h after challenge. Both controls maintained their weights for 48 h. All pigs became sick and one control pig died. Of the four treated, three died. All animals treated, including control animals, were very sick and down.

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Structural Requirements for Progestational Activity. Synthesis and Properties of *rac*-8α,9β,10α,14β-Progesterone[1-3]

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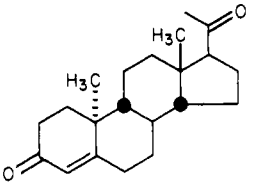
rac-8α,9β,10α,14β-Progesterone, 1, has been synthesized and subjected to X-ray crystallographic analysis which established that the ring conformations are A, 1β-sofa; B, chair; C, chair; and D, intermediate between an envelope and a half-chair. This compound is 10% as active as progesterone in the Clauberg assay and has an affinity for the uterine cytosol (rabbit) receptor for progesterone 2% as great as that of progesterone.

This work is part of a continuing investigation into the mode of binding of progesterone analogues to the uterine receptor.[4,5] Earlier, we put forward[4] an extension of Ringold's hypothesis on the mode of binding of gestogens to the uterine receptor.

In essence, the modified hypothesis[4] states that gestogens bind to the uterine receptor via their β face and that the most important binding points are the A-ring enone and the C-20 carbonyl oxygen of progesterone derivatives or the C-17β hydroxyl of 17α-ethinyltestosterone derivatives. With the molecule in the conformation which it would occupy while complexed to the receptor (with the critical A and D ring substituents in positions similar to those which the corresponding groups of progesterone or ethinyltestosterone would occupy), the bulk at C-10β must be equal to, or preferably less than, that of a methyl group, and some bulk must be present at C-13β. The hypothesis implies that the detailed stereochemistry at centers other than C-13 is unimportant, except as determinants of the β-face topography of the molecule. Kontula[6] has presented studies showing that the enone system and the acetyl side chain of progesterone each contribute approximately 3 kcal to its binding energy and an additional 6 kcal of binding energy derives from interaction of the rest of the nucleus with the receptor. The latter 6 kcal may derive, as Kontula suggests, from a loose fit between the gestogen and the receptor or it may arise from a relatively tight fit to some portion of the steroid nucleus with little or no contribution from the remaining portions.

Figure 1 depicts similar projections of the X-ray crystal structures[7] reported for progesterone and for 9β,10α-pregna-4,6-diene-3,20-dione. With the exception of the protuberance of the C-10β methyl of progesterone, the similarity of the β-face topography of these gestogens is marked. We assume that for optimal fit to the uterine receptor the β-face of a steroid must have a shape similar to these as shown in Figure 1. However, our hypothesis, in its present form, does not adequately define limits on that shape. Therefore, an extension of the hypothesis based on additional data seems to be required.

8α,9β,10α,13β,14β,17β-Progesterone (1) differs from



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progesterone in stereochemistry at four of the six chiral centers. Examination of Dreiding-type models of **1** reveal that if this structure has its C ring in a twist conformation the β-face, although slightly concave upward in contrast to the convex surfaces of the structures depicted in Figure 1, appears to meet the requirements for binding to the uterine receptor for progesterone. However, if the C ring of the model is converted to a chair form, the β face becomes strongly concave upward over the A, B, and C rings but bends sharply downward at the C/D junction. This contour is very different from that of any known gestogen and was not expected to be capable of binding to the receptor.

An X-ray crystallographic study of 3β-[(*p*-bromobenzoyl)oxy]-13α-androst-5-en-17-one, a compound having an enantiomorphic relationship to **1** at the C-8, -9, -10, -13,

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