Influence of 6-Azido and 6-Thiocyanato Substitution on Progestational and Corticoid Activities and a Structure–Activity Correlation in the Δ^6-6-Substituted Progestational Series

George Teutsch,† Lois Weber, Geoffrey Page,‡ Elliot L. Shapiro,* Hershel L. Herzog,

Natural Products Research Department

Rudolph Neri, and Elliot J. Collins

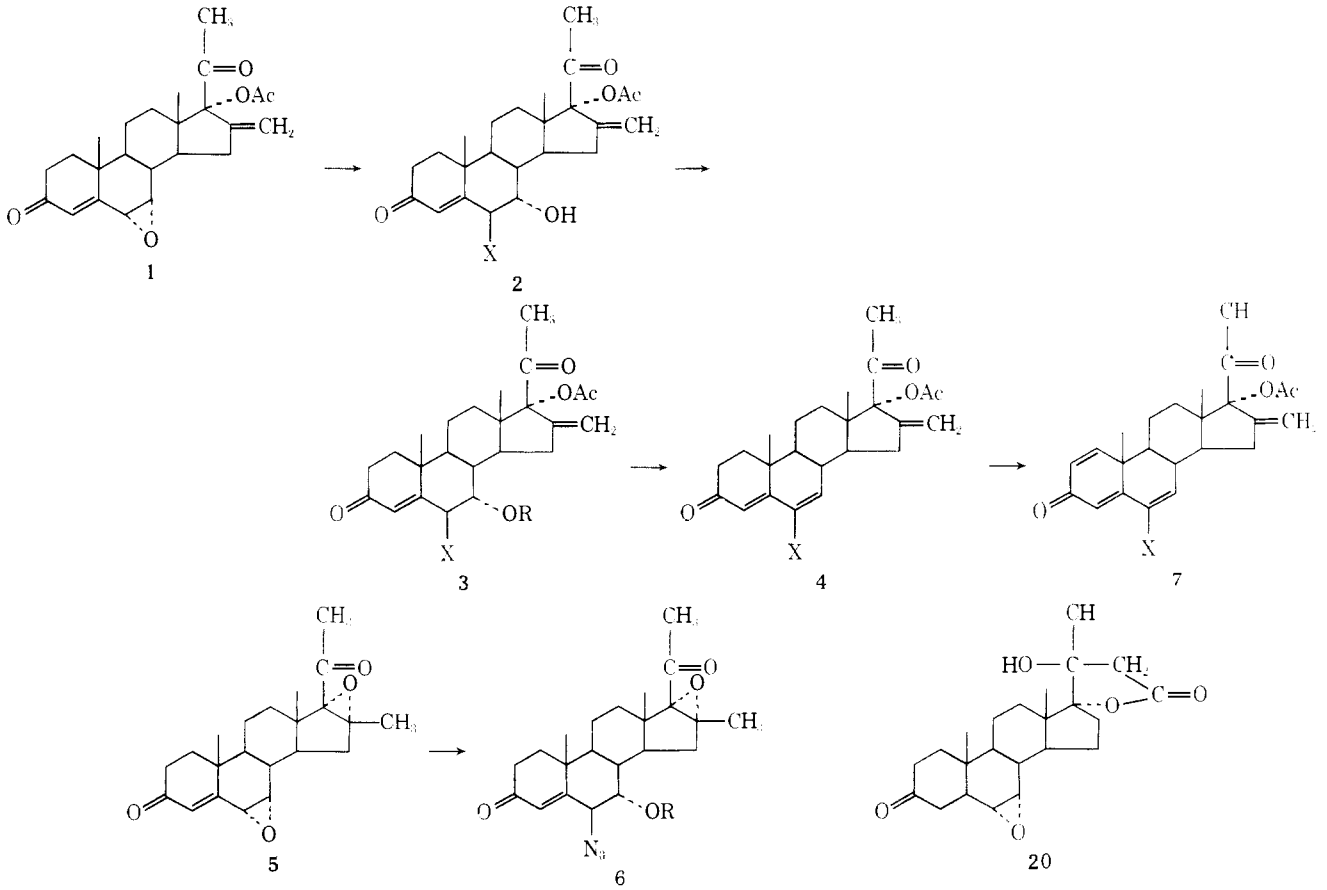
Physiology Department, Schering Corporation, Bloomfield, New Jersey 07003. *Received May 17, 1973*

The preparation and biologic (progestin, antiandrogen, and corticoid) activity of some 6-azido- and 6-thiocyanato-$\Delta^{4,6}$ steroids are described. The comparative order of activities of the 6-substituted progestins is tabulated as follows: 6-Me > 6-Cl > 6-F > 6-Br > 6-N_3 > 6-OCH_3 > 6-SCN > 6-CF_3 > 6-CN > 6-C=NOMe > 6-H, > 6-CHO, 6-OC_2H_5 > 6-$OCOCH_3$ > 6-$NHCOCH_3$; in contrast, for the described corticoids, 6-N_3 > 6-Cl. The steric and electronic influences of 6 substituents on progestational activity are discussed, with particular emphasis given to the steric influence by empirically defining their relative spacial requirements.

Substitution at the 6 position has been known to have a dominant and controlling effect on the dimensions of progestational activity among the 17α-acetoxyprogesterones and their 16-alkylated counterparts. Our own studies have centered around the 6-substituted derivatives of 6-dehydro-16-methylene-17α-acetoxyprogesterone, a series of compounds which has displayed especially pronounced potency. In this paper we bring together our biological findings and attempt to define the steric and electronic character of 6 substitution which leads to maximum progestational (Clauberg) potency within this series.

To gain a greater insight into the basis of bioactivity in this series, we have now prepared derivatives containing the pseudo-halo substituents, 6-azido and 6-thiocyanato. To accomplish this we followed the principles of the method reported from these laboratories[1-3] and also employed independently by others.[4] Reaction of the 6,7α-oxide 1[5] with NaN_3 in aqueous MeOH containing AcOH gave the 6β-azido-7α-hydroxy **2a** in 86% yield. The configurational assignment, established by nmr, was consistent with related diaxial openings of 6α,7α-oxides. In the absence of AcOH, the basic NaN_3-MeOH-H_2O reaction system caused some solvolysis of the 17-acetate group in addition to the desired opening of the 6α,7α-oxide. With this

Scheme I



a, X = N_3; b, X = SCN; c, X = Cl; d, X = H; R = H, CH_3CO, CH_3SO_2, or *p*-$CH_3C_6H_4SO_2$

† Schering Postdoctoral Fellow, 1968–1969.
‡ Schering Postdoctoral Fellow, 1970.

Table I. Progestational and Antiandrogenic Activities

Compd no.	Progestational[a,b] im	Antiandrogenic[c,d] (as % of control)[e] SV	VP	LA	Adrenals
4a	20	40	62	42	25
4b	12	61	65	84	79
4c	77[f]	36[g]	46[g]	42[g]	37
7a	10				
7c	145[h]				
4d	1	76	81	94	99

[a]Progestational activity was determined in immature rabbits by the method of M. K. McPhail, *J. Physiol. (London)*, **83,** 145 (1934), with progesterone = 1. [b]Reference 12 cites the statistical method used to obtain the results presented here. [c]In ref 3, see ref 3–5. [d]Male rats (Charles River CD strain) 21–28 days old and weighing approximately 60 g were used to assess the ability of the compounds to inhibit endogenous androgens. The compound was suspended in an aqueous suspending vehicle (0.9% NaCl, 0.5% carboxymethylcellulose, 0.4% polysorbate 80, and 0.9% benzyl alcohol) and injected sc each day at 10 mg/kg for 3 weeks. Twenty-four hours following the last drug treatment, the seminal vesicles (SV), ventral prostate (VP), levator ani (LA), and adrenals were removed and weighed. [e]With controls taken as 100, the greater the activity, the less the percentage. [f]Reference 3 and references cited therein. [g]Reference 3. [h]Reference 12.

NaN_3-MeOH-H_2O system, the bisoxide **5** afforded selective opening of the 6,7-oxide, yielding the corresponding azidohydrin **6** (R = H) (Scheme I).

We chose to study the preparation of the 6-dehydro-6-azido **4a** from **3a** (7-acetate and 7-mesylate, prepared by esterification of the 7α-hydroxyl group of **2a**) by base-catalyzed elimination of the 7 substituent. In our first base-catalyzed elimination attempts,§ treatment of the 7α-mesylate **3a** and the 7α-tosylate **6** with NaH in dioxane caused, instead, rearrangement of the 6-azide group to the 4 position,[7] accompanied by elimination of the 7 substituent. However, our goal was achieved with tetramethylammonium fluoride (TMAF),= anhydrous or hydrated,** in acetonitrile at room temperature or 60°,†† the desired elimination‡‡ being effected in good yield from the 7-acetate **3a** and the 7-mesylate **3a**, each giving the diene **4a**. The 7α,17-diacetate **3a** was readily available to us from **6a** (R = H, as well as from **2a** mentioned previously) by *p*-toluenesulfonic acid (*p*-TSA) catalyzed opening of the 16α,17α-oxide concomitant with acetylation[10] [trifluoroacetic anhydride (TFAA)-AcOH] at the 7 and 17 position.

Surprisingly, tetramethylammonium chloride (TMACl) also transformed the 7-mesylate **3a** into **4a** (58%), accompanied by about 5% of the 4-azido-$\Delta^{4,6}$ product.[7],§§ On the other hand, dehydration of **2a** to **4a** could not be effected by TMAF-CH_3CN. Apparently the success of the elimination reaction depends as much on the leaving group qualities of the 7α substituent as on the basicity of

§ Drefahl, *et al.* (ref 6), report the elimination of 7α-OH with concentrated HCl–dioxane–AcOH to afford the 6-azido-$\Delta^{4,6}$ 3-ketone in the 16-desmethylene series.

= The use of TMAF as a proton abstractor has been reported by Hajami, *et al.*, in ref 8.

** Aldrich Chemical Co., Milwaukee, Wis.

†† Prolonged heating of **1** at 60° with TMAF-CH_3CN affords the side-chain lactone **20** in 25% yield, the structure being suggested from the nmr: 1.47 (20-CH_3, geminal to hydroxyl grouping). *Cf.* ref 9 for this type of base-catalyzed cyclization using NaH and NaOH. Thus, TMAF in CH_3CN is a sufficiently strong base to catalyze Claisen condensation.

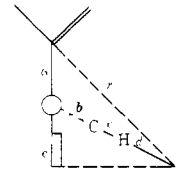
‡‡ The generality of TMAF for generation of a 6-substituted $\Delta^{4,6}$ system was demonstrated by the deacetoxylation of **3c** to give **4c** in 85% yield after 24 hr at room temperature.

§§ Hayami, *et al.*,[11] report the use of tetramethylammonium fluoride in the generation of styrene from 2-phenethyl bromide but that tetraethylammonium chloride and bromide did not generate styrene.

Table II. Correlation of Progestational Activity of Compound **4** with Steric Effects

X	Progestational act.	C_6–X bond axis[a] distance, Å	Vol, Å^3[b,d] Half-sphere	Cylinder	Circumference[c]
CH_3	91	3.00	31		8.67
Cl	77	2.71	42		6.09
F	55	1.99	17		4.27
Br	42	3.02	58		7.09
N_3	20	2.91–4.34	117	3.82	15.64
OCH_3	14	2.81	106		15.13
SCN	12	4.45	246		12.94
CF_3	11	3.55	52		11.93
CN	6	3.11		1.49–3.14	4.84
C=NOMe	2	4.31	513		28.57
OC_2H_5	1	3.60	290		23.42
H	1	1.44	6		2.32
CHO	1	3.28	48		9.92
$OC(=O)CH_3$	0.2	3.60	290		23.36
$NCOCH_3$	0.1	3.62	298		23.67

[a]In the case of the cylinder, sum of bonds along C_6–X axis, plus radius of outer atom of X (*i.e.*, for "C≡N," sum of "C_6–C," "C–N," and radius of nitrogen). For the single atom substituent, the radius of the sphere, center at C_6, was taken as projection (see footnote *b*). For the polyatom substituent the "*h*" of cone (see footnote *b*) was taken as the projection length. [b] The bond lengths, bond angles, and atomic radii used were based upon values of relevant data obtained from the following sources: (1) "Lange's Handbook of Chemistry," 9th ed, Handbook Publishers, Sandusky, Ohio, 1956, p 108; (2) "Interatomic Distances," *Chem. Soc., Spec. Publ.*, **No. 11** (1958); (3) Y. Yukawa, Ed., "Handbook of Organic Structural Analysis," W. A. Benjamin, New York, N. Y., 1965, pp 510–525. The volumes are to be considered approximations for two reasons. Firstly, the values for bond lengths and angles are taken from aliphatic and aromatic systems and not from steroidal systems. For example, the bond length of "C_6–C≡N" was derived from the values for the related bonds in vinyl cyanide (CH_2=CH-C≡N) and benzonitrile (PhCN). Similarly, for bond angles, the "C_6–O–CH_3" angle was derived from the related angle in 1,4-dimethoxybenzene. Secondly, volumes were derived by considering all the substituents, excepting CN, as describing a sphere, with center at C_6, and taking one-half the sphere volume ($^4/_3\pi r^3$) as the value. The radius (r) of the sphere was derived as follows. Single atom substituent from addition of bond length C_6 to substituent plus atomic radius of substituent. For polyatom substituent, illustrated with methoxyl, values for right triangle [*f*, *e*, (*b*, *c*, *d*)] obtained using $<eb$ as



supplementary to $<ab$ and length of hypotenuse by addition of bond lengths *b* and *c* and radius *d*. For a cylinder (*i.e.*, CN) the volume ($\pi r^2 h$) was calculated from the altitude defined by bond length of "C_6–C≡N" and atomic radius of "N," with "*r*" being atomic radius of carbon and nitrogen. [c] The radius (in $2\pi r$) was taken from "*f*" in footnote *b* above for the polyatomic substituent; for the monoatomic substituent the atom radius was used; and for "CN" the radius of carbon was used. [d] Other values for the volumes were considered (*i.e.*, using the atom attached to C_6 as the center of a sphere and also the volume generated from a cone having the elements "*f*" as radius and "*a* + *e*" as "*h*"). However, the values derived were somewhat less consistent with the ranking of biological findings.

the reaction system. Subsequently, we also observed that the 7-acetate **3a** was transformed to **4a** with NaN_3 in DMF.[7]

A progestational potency-enhancing effect has been observed with the introduction of unsaturation at position 1 (*i.e.*, Δ^1) in **4c**.[12] It therefore seemed desirable to prepare the analogous 6-azidotriene **7a**. Conventional dehydrogenation of the 6-azido **4a** with DDQ in benzene or dioxane (neat), or with benzoic acid as a catalyst, failed to afford **7a**. However, in a medium of H_2O-dioxane-HCl, DDQ effected the desired transformation to **7a** in ~20% yield.

The preparation of the 6-thiocyanato **4b**== proceeded readily by routes 1 → 2 → 4 or 1 → 2 → 3 → 4. In H_2O-MeOH-AcOH the 6α,7α-epoxide **1** was transformed into the 6β-thiocyanato-7α-hydroxy **2b** by KSCN. The linkage CS-C≡N at the 6 position was proved by the presence in the ir of a sharp band at 4.6 μ, rather than a broad, intense band expected for an isothiocyanate (CN=C=S).[14] Elimination of the 7α-hydroxyl was accomplished directly with either $HClO_4$-AcOH or MsCl-pyridine to give **4b**. Alternatively, acetylation of **2b** with Ac_2O-pyridine afforded the 7-acetate **3b** (plus 10% of **4b**), which upon treatment with *p*-TSA gave **4b**.

Biology of Progestogens. From Table I it can be seen that while the 6-azido group (in **4**) enhances progestational potency in the rabbit relative to the 6-hydrogen, it does so less efficiently than 6-chloro. The same is true for 6-thiocyanato. Introduction of a Δ^1 double bond into 6-azido **4a** to give **7a** diminishes potency, whereas the same change in 6-chloro **4c** (*i.e.*, **7c**) increases potency. Antiandrogenic activity follows progestational activity for **4a** and **4b** as contrasted with **4c**,[3] although the 6-azido compound does exhibit significant activity. Incidentally, the finding was made of a striking adrenal suppression activity in rats with **4a**. This encouraged us to begin the investigation of 6-azido substitution in corticoids, the subject of the latter portion of this paper.

From our earlier studies taken together with results reported here, we can now rank the progestational activities (listed in parentheses) of 6-substituted 6-dehydro-16-methylene-17α-acetoxyprogesterones as follows: 6-Me (91)[15] > 6-Cl (77)[3] > 6-F (55)[3] > 6-Br (42)[3] > 6-N_3 (20) > 6-OCH_3 (14)[16] > 6-SCN (12) > 6-CF_3 (11)[15] > 6-CN (6)[17] > 6-CH=NOMe (2)[17] > 6-H (1), 6-CHO (1),[17] 6-OC_2H_5 (1)*** > 6-$OCOCH_3$ (0.2)*** > 6-$NHCOCH_3$ (≤0.1).†††

We are quite aware that many different parameters may be considered in the correlation of activity with structural modification. However, we addressed ourselves to two factors, namely steric and electronic, which we felt may be contributing to modulation of progestational activity, and we chose to define the steric factor by considering the volume requirements of a 6 substituent and also its distance of extension from C_6. Table II tabulates the progestational activity and steric factors defined by the volume occupied by "X" and by its projection from C_6. The volume was derived by considering "X" as occupying either a cylinder or one-half of a sphere with the center at C_6. The projection of "X" from C_6 was considered to be along the bond axis from C_6 (Table II, footnote *a*). Although the derived values are qualitative because of the approximation used for calculating the volumes, we consider them sufficiently accurate to illuminate comparative differences.

Two generalizations may accordingly be derived. For significant activity (arbitrarily set at a value of >10 in the progestational assay), the volume should be less than 60 Å^3 but greater than the volume requirement for hydrogen as "X." The second was that for those substituents which are strongly cross-conjugated (*i.e.*, CHO, CN), steric factors are relatively unimportant, but electronic factors are critically important.

For *greatest* activity it appears that the volume should be approximately 31 ± 15 Å^3. The most active of the compounds cited has "X" as methyl. High activity in this case is achieved by a steric effect, with very little, if any, contribution from an electronic effect. From consideration of volume requirements, one would then predict high activities for halogen (F, Cl) as "X" and this is the case; yet, subtle electronic interaction must also be important since their activities are not only less than that for methyl but not equal to each other and not proportional to size. One would also expect from a consideration of only the volume factor that trifluoromethyl would have activity approximately that of bromo; yet, it does not. The steric factor would appear to be clearly manifested by the activity differences of methoxy and ethoxy, and the moderate activity of the groups N_3 and OCH_3 may be rationalized from a consideration of the steric factor, without even evaluating the importance of the electronic factor in either case. The activity of the SCN group (albeit moderate) would not have been predicted from our volume calculations.

Another parameter which may be used in conjunction with volume of the sphere is the circumference of the circle circumscribed by the substituent (Table II, circumference column). With the dimension of 4.27–8.67 Å one may group the most active substituents—F, Cl, CH_3, Br; with the dimension of 11.93–15.64 Å may be grouped the moderately active N_3, OCH_3, SCN, CF_3; and with the dimension of 23.68–28.57 Å may be grouped the least active $NCOCH_3$, OAc, OEt, and C=NOMe. This method of calculation fits the bioactivity data better for SCN and CF_3 than does the volume approach, without diminishing the reliability for calculation of effects of other substituents.

An inspection (Table II) of the influence of the length of bond projection to activity does not reveal any significant trend(s) but does point up that volume requirements are more easily related to activity.

It remains obscure why there is such a large enhancement in activity derived from change in the substituent from hydrogen to methyl or halogen. This may suggest an anchoring or fitting dependency of the 6 substituent with respect to the active site of an enzyme, for example, a 3-keto reductase or a Δ^4 reductase (assuming equal availability at the site).

In any event, for a set of 6-substituted progestational structures differing in any way from the 6-dehydro-6-substituted 16-methylene-17α-acetoxyprogesterone, the optimum substituent at the 6 position would need to be determined by experiment but would most likely come from within the group Me, Cl, Br, F, or a nonconjugated substituent which fits into the volume requirement defined by this group.

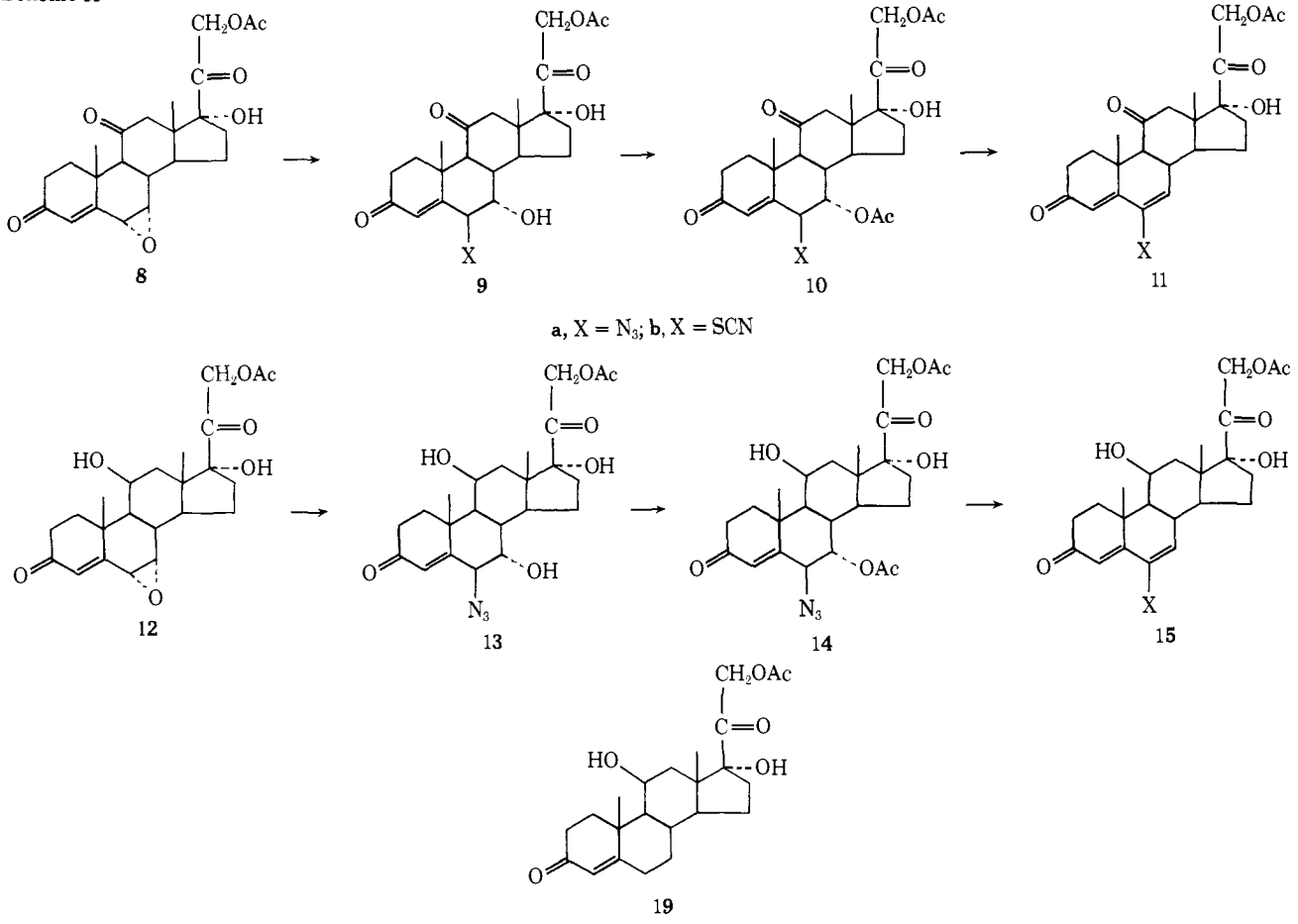
6-Azido- and 6-Thiocyanatocorticosteroids. In view of the notable adrenal-suppressing effects associated with the administration of **4a** to rats, the 6-azido-6-dehydrocortisone 21-acetate **11a** and 6-azido-6-dehydrocortisol 21-acetate **15a** were prepared. The synthetic pathway illustrated in Scheme II, which parallels that employed to prepare 6-azido-substituted progestins, was used. Opening of 6α,7α-oxidocortisone 21-acetate[1] **8** with azide ion in a weakly acid medium afforded the 6β-azide **9a** in good

== Preparation of the 16-desmethylene analog of **4b** from the related 6,7-oxido and 6-SCN, 7-OH precursors has been reported by Ponsold, *et al.*, in ref 13.

***Private communication from R. Rausser of Schering Corp.

†††Private communication from the authors of ref 5, wherein activity is only reported qualitatively.

Scheme II



a, X = N_3; b, X = SCN

a, X = N_3; b, X = Cl; c, X = H

yield. In the same way, the cortisol analog 12[18] gave 13. Acetylation of **9a** and 13 with Ac_2O-pyridine yielded the respective 7α-acetates, **10a** and 14. Elimination of the 7α position in 10a and 14 was accomplished with TMAF-CH_3CN to give the desired corticosteroids 11**a** and 15**a**, respectively. The 6-thiocyanatocorticoid 11**b** was also prepared from 8 using the route described for **4b**.

As a final demonstration of the versatility of the synthetic methodology, 6α,7α-oxido-4-androstene-3,17-dione[4,18] (16, Scheme III) was converted into the 6-azide 18**a** and 6-thiocyanate 18**b**.

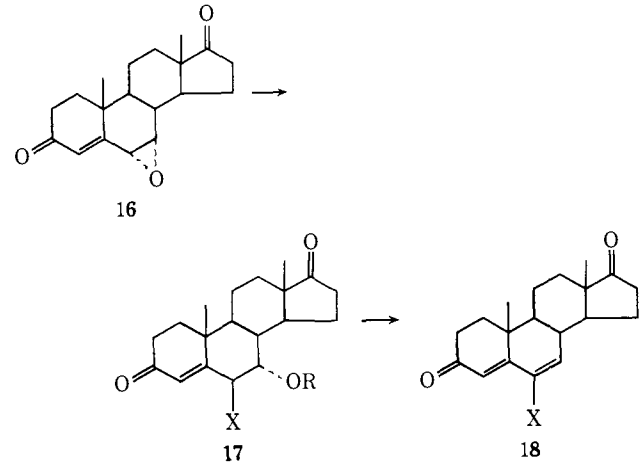
Biology of Corticoids. In the given limited corticosteroid series, it seems that somewhat different considerations govern activity enhancement achieved through 6 substitution than prevailed with the progestins. Thus, the 6-azido-6-dehydro moiety potentiates (Table III) by all indices significantly better than the 6-chloro-6-dehydro moiety, the former being 4-8 times as active as cortisol 21-acetate **19** and the latter[18] 1.5-4 times as active. Thiocyanate substitution, on the other hand, provides no measurable activity enhancement in contrast with observations in the progestin series. There are as yet insufficient data to reach conclusions other than that the 6-azido-Δ^6 system offers interesting possibilities for activity-enhance-

Table III. Rat Granuloma Pouch[a]

Compd no.	Exudate inhibition[b]	Adrenal atrophy[b]	Thymus involv[b]	Body wt	Tested at γ
15c	Inact	Inact	Inact	No effect	480–120
15b	0.3	0.8	0.7	Gain at high dose	480–120
15a	1.6	0.8	1.1	No effect	480–120
11a	1.2	*c* Active	1.3	Suppression	240–60
11b	Inact	Inact	Inact	No effect	360–90
19	0.2	0.2	0.2		960–240

[a] See E. J. Collins, J. Aschenbrenner, M. Nakahama, and I. I. A. Tabachnick, *Proc. Int. Congr. Horm. Steroids, 2nd*, 530 (1966), for the method of assay. [b] Relative potency with the standard, prednisolone acetate, assigned activity of 1. [c] Potency could not be calculated because of nonparallel slopes.

Scheme III



a, X = N_3; b, X = SCN; R = H or CH_3SO_2

Table IV

Run	Amt of 4a, mg	Solvent, ml	DDQ, mg	Time, min	Temp, °C	Yield of product, mg
a	102	8	60	30	80	57
b	507	30	320	45	80	235
c	1000	50	640	60	80	650

ment of corticosteroids. These possibilities will be explored in subsequent publications.

Experimental Section‡‡‡

6β-Azido-16-methylene-7α,17α-dihydroxy-4-pregnene-3,20-dione 17-Acetate (2a). To a solution of 6,7α-oxido 1 (4 g) in MeOH (700 ml) and AcOH (4 ml) was added a solution of NaN_3 (8 g) in 240 ml of water. The mixture was allowed to remain at room temperature for 94 hr, then diluted with water, and extracted with $CHCl_3$. Evaporation of the solvent and trituration of the residue with ether afforded 3.8 g of **2a**. Crystallization (EtOAc) gave the analytical sample: mp 229° dec; $[\alpha]D$ −92.2°; λ_{max} 238 nm (ε 13,155); λ_{max} 4.75 μ; nmr 3.74 (br, 7-H), 4.10 (d, J = 2.75 Hz, 6-H), and 5.93 (4-H). *Anal.* ($C_{24}H_{31}O_5N_3$) H, N; C: calcd, 65.28; found, 64.82.

6β-Azido-16-methylene-7α,17α-dihydroxy-4-pregnene-3,20-dione 7,17-Diacetate (3a, R = CH_3CO). A. From 2a. A mixture of 300 mg of **2a**, 0.6 ml of Ac_2O, and 4 ml of pyridine was allowed to stand at room temperature overnight. After addition to water, collection of the resulting insolubles, and crystallization from MeOH, the analytical sample (210 mg) was obtained: mp 198° dec; $[\alpha]D$ −119.3°; λ_{max} 233 nm (ε 13,000); nmr 2.05, 2.08 (7- and 17-$OCOCH_3$), 4.14 (d, J = 3 Hz, 6-H), 4.85 (d, J = 2.5 Hz, 7-H). *Anal.* ($C_{26}H_{33}O_6N_3$) C, H, N.

B. From 6 (R = H). The 6β-azido-7α-hydroxy 6 (100 mg) was dissolved in a solution of AcOH (2.5 ml), TFAA (1.25 ml), and *p*-TSA–H_2O (25 mg) and the solution was allowed to remain at room temperature for 40 min. Work-up by adding to water and collecting of the resulting precipitate gave after crystallization from CH_3OH 75 mg (38.7%) of **3a** (R = CH_3CO).

6β-Azido-16β-methyl-16,17α-oxido-7α-hydroxy-4-pregnene-3,20-dione 6 (R = H). A solution of NaN_3 (20 g) in water (100 ml) was added to a solution of the bisoxide **5** (8 g) in MeOH (1 l.). After standing at room temperature for 17 hr, the mixture was added to water and then extracted with $CHCl_3$. Work-up gave, after crystallization from EtOAc, 3.48 g (38.8%) of **6** (R = H); mp 217° dec; $[\alpha]D$ +53.5°; λ_{max} 235 nm (ε 13,200); λ_{max} 4.76 μ; nmr 1.45 (16-CH_3), 2.20 (20-CH_3), 3.67 (br, 7-H), 4.10 (d, J = 3 Hz, 6-H), 5.90 (4-H). *Anal.* ($C_{22}H_{29}O_4N_3$) H, N; C: calcd, 66.14; found, 65.54; *m/e* 339.

6β-Azido-16-methylene-7α,17α-dihydroxy-4-pregnene-3,20-dione 7-Mesylate 17-Acetate (3a, R = CH_3SO_2). The 7α-hydroxy **2a** (3 g) was dissolved in pyridine (30 ml) and CH_3SO_2Cl (1.2 ml) was added. The reaction mixture was maintained at room temperature for 7 hr, at which time an additional 0.3 ml of CH_3SO_2Cl was added and the reaction maintained at room temperature for an additional 17 hr. Work-up by water precipitation and collection of insolubles, followed by crystallization (Et_2O), gave 3.1 g (87%): mp 200° dec; $[\alpha]D$ −111°; λ_{max} 234 nm (ε 13,377); nmr 3.08 (OSO_2CH_3), 4.44 (d, J = 3 Hz, 6-H), 4.73 (d, J = 3 Hz, 7-H). *Anal.* ($C_{25}H_{33}O_7N_3S$) C, H, N.

6-Azido-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (4a). A. From 7-Mesylate. A solution of TMAF-$5H_2O$ (1.53 g) in CH_3CN (150 ml) was evaporated to dryness *in vacuo*, and this process was repeated two times. CH_3CN (150 ml) was added to the residue of TMAF, followed by 7α-mesyloxy **3a** (1.5 g). The reaction mixture was heated at 60° for 35 min. Water was then added and the volume was reduced under vacuum to about 100 ml. The residual liquid was extracted with $CHCl_3$ and the $CHCl_3$ extracts were evaporated, the 6-azidodiene residue being obtained in about 90% purity (tlc). Purification was effected by thick-layer chromatography (silica gel, $CHCl_3$–EtOAc, 9:1) to give 1.1 g of **4a** which was crystallized from MeOH, affording 0.71 g of purified **4a**: mp 190° dec; $[\alpha]D$ −63°; λ_{max} 252 nm (ε 14,616), 298 (14,616); λ_{max} ($CHCl_3$) 4.75, 5.76, 5.86, 6.00, 6.21, 6.31 μ; nmr 0.80 (13-CH_3), 1.15 (10-CH_3), 2.06 (17-$OCOCH_3$), 5.53, 5.64 (C=CH_2), 5.78 (d, J = 1.5 Hz), 6.17 (4-H). *Anal.* ($C_{24}H_{29}O_4N_3$) C, H, N.

B. From 7-Acetate (3a). A suspension of TMAF-$5H_2O$ (2 g) in CH_3CN (200 ml) was heated with stirring until the solid was liquified. After cooling under N_2(g) to ambient temperature, 2 g of **3a** (R = CH_3CO) was added and the reaction mixture stirred at room temperature for 3 hr. The solvent was evaporated under N_2(g) *in vacuo* to about 100 ml, and then the mixture was added to water and extracted with CH_2Cl_2. After work-up, the residue was trituated with boiling ether (25 ml), cooled to −20°, and filtered to obtain 1.11 g of **4a** (63.5%).

C. From 3a (R = CH_3SO_2) with DMF. To a suspension of TMAF (from 200 mg of TMAF-$5H_2O$ by evaporation three times of 150-ml portions of CH_3CN) in DMF was added 100 mg of 7-mesylate **3a**. After remaining at room temperature for 19 hr, tlc indicated complete transformation of starting material. The reaction mixture was added to water (175 ml), NaCl (5 g) was added, and the insolubles were collected by filtration. The filtrate was extracted with CH_2Cl_2 and the residue from the CH_2Cl_2 evaporation was combined with the collected precipitate. Preparative silica gel tlc ($CHCl_3$–EtOAc, 9:1) afforded 30 mg (37.5%) of **4a**.

D. From 3a (R = CH_3SO_2) with TMACl. Mesylate **3a** (130 mg) was added to a suspension of TMACl (160 mg) and CH_3CN (15 ml); the mixture was maintained at 60° for 26 hr and then added to water. The resulting precipitate (three components by tlc) was collected by filtration and separated by preparative plate chromatography ($CHCl_3$–EtOAc, 9:1) to yield 60 mg (58%) of **4a**, 12 mg (9.2%) of starting material, and 5.5 mg (5.3%) of the 4-azido-$\Delta^{4,6}$ product.[7]

E. From 3a (R = CH_3CO) with NaN_3–DMF. A mixture of 100 mg of **3a** and 150 mg of NaN_3 in 10 ml of DMF was stirred at 25° for 3 hr, after which time it was poured into water. The precipitate was isolated by filtration to yield 88 mg; extraction of the water layer with CH_2Cl_2 yielded an additional 8 mg. Tlc (silica gel) of the two samples indicated them to be the same material; uv indicated *ca.* 10% of the $\Delta^{4,6}$ **4a** present. A recycle of 50 mg of the product with 75 mg of NaN_3 in 5 ml of DMF for 90 hr yielded, by filtration of the water precipitate, 35 mg of **4a**, by uv and ir. Extraction of the water phase with CH_2Cl_2 gave an additional 5 mg, which by tlc appeared to be mainly **4a**.

6-Azido-17α-hydroxy-16-methylene-1,4,6-pregnatriene-3,20-dione 17-Acetate (7a). The dehydrogenation of **4a** was carried out in three similar experiments (see Table IV) (with only the length of reaction time being different), using a stock solution of the solvent mixture consisting of 49.5 ml of dioxane, 0.5 ml of concentrated HCl, and 5 ml of water.

Work-up was by addition to water and extraction with CH_2Cl_2 and EtOAc. The products from the three runs were combined and purified by silica gel preparative tlc plate ($CHCl_3$–EtOAc, 9:1). Crystallization from Et_2O gave *ca.* 265 mg of **7a** of approximately 70–80% purity as evaluated by visualization of the tlc which exhibited two minor impurities of very similar R_f, although by nmr, the impurities were not detectable. The analytical data of this material were mp 140–160° dec; $[\alpha]D$ −131.6°; λ_{max} 250 nm (ε 15,475), 310 (6925); λ_{max} 4.75, 5.70, 5.80, 5.95, 6.11 μ; nmr 0.85 (13-CH_3), 1.23 (10-CH_3), 2.03 (17-$OCOCH_3$), 2.17 (20-CH_3), 5.52 and 5.65 (16=CH_2), 5.65 (7-H), 6.29 (d of d, $J_{1,2}$ = 10 and $J_{2,4}$ = 2 Hz, 2-H), 6.42 (smeared, 4-H), 7.07 (d, $J_{1,2}$ = 10 Hz, 1-H). *Anal.* ($C_{24}H_{27}O_4N_3$) C, H, N; *m/e* 421.

6β-Thiocyanato-16-methylene-7α,17α-dihydroxy-4-pregnene-3,20-dione 17-Acetate (2b). To a solution of the 6,7α-oxide 1 (1.0 g) in MeOH (160 ml) was added a solution of KSCN (6 g) in water (40 ml) and AcOH (1 ml). After remaining at room temperature for 48 hr, the reaction mixture was added to water (800 ml), and the resulting mixture was extracted with $CHCl_3$. Work-up of the extracts gave a residue which was crystallized from EtOAc, yielding 815 mg (71%) of **2b**. The analytical sample (EtOAc) gave mp 232° dec; $[\alpha]D$ 230°; λ_{max} 241 nm (ε 13,637); λ_{max} 2.98, 4.58, 5.74, 5.97, 6.17 μ; nmr 2.08 (17-$OCOCH_3$), 3.38 (7-OH), 4.02 (7-H), 4.28 (d, J = 2 Hz, 6-H), 6.01 (4-H). *Anal.* ($C_{25}H_{31}O_5NS$) C, H, N, S.

6-Thiocyanato-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (4b). A. From 2b with CH_3SO_2Cl. To an ice-cooled solution of **2b** (700 mg) in pyridine (20 ml) was added 2 ml of CH_3SO_2Cl. After remaining at room temperature for 20 hr,

‡‡‡All melting points were determined on a Kofler hot-stage microscope and are uncorrected. Optical rotations are in dioxane at 25° at about 1% concn. uv spectra are in MeOH solution, ir spectra are in Nujol, and nmr chemical shifts are given in parts per million on the δ scale (TMS = 0) using a Varian A-60A spectrometer and $CDCl_3$, unless otherwise stated. Mass spectra were determined on a Varian-Mat CH5 spectrometer using an electron impact source at 70 eV and at 250°. Analyses were determined by the Physical Organic Chemistry Department of Schering Corp. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

the reaction mixture was added to ice-water (150 ml), and the resulting insolubles were collected and dried to give 616 mg of **4b** (crystallized from MeOH): mp 218–220°; $[\alpha]D$ −123°; λ_{max} 274 nm (ϵ 19,920); λ_{max} 4.63, 5.74, 5.83, 5.96, 6.25 μ; nmr 0.80 (13-CH_3), 1.16 (10-CH_3), 2.03 (17-$OCOCH_3$), 2.16 (20-CH_3), 5.51 and 5.63 (16=CH_2), 6.25 (4-H), 6.78 (7-H). *Anal.* ($C_{25}H_{29}O_4NS$) H, N; C: calcd, 68.32; found, 67.64; S: calcd, 7.30; found, 7.98; *m/e* 439.

B. From 2b with $HClO_4$. A solution of 77 mg of **2b** in AcOH (5 ml) and $HClO_4$ (0.7 ml of a 70% solution) was allowed to remain at room temperature for 45 hr. Usual work-up and preparative tlc plate (silica gel, $CHCl_3$–EtOAc, 9:1) gave 17 mg of **4b**.

C. From 3b (R = CH_3CO). To an ice-cooled solution of **2b** (574 mg) in pyridine (8 ml) was added Ac_2O (0.5 ml). The reaction mixture was allowed to remain at room temperature for 6 hr and then at 5° for 42 hr, with an additional 2 ml of Ac_2O being added after 24 hr. After the usual work-up, 480 mg of principally the 7-acetate **3b** but containing about 10% (or less) of the $\Delta^{4,6}$-diene **4b** was obtained: nmr 2.03, 2.10 (7- and 17-$OCOCH_3$), 2.16 (20-CH_3), 4.28 (d, J = 2.5 Hz, 6-H), 5.05 (7-H), 5.95 (4-H). A solution of 50 mg of **3** thus obtained in $CHCl_3$, containing 12 mg of *p*-TSA–H_2O, was allowed to remain at room temperature for 30 days, and following the usual work-up and preparative silica gel tlc ($CHCl_3$–EtOAc, 9:1), 28 mg of **4b** was obtained.

6β-Azido-7α,17α,21-trihydroxy-4-pregnene-3,11,20-trione 21-Acetate (9a). A solution of 1.4 g of 6,7α-oxido **8** containing MeOH (200 ml), dioxane (90 ml), water (60 ml), AcOH (3 ml), and NaN_3 (4.6 g) was allowed to remain at room temperature overnight. After adding to water, extraction with $CHCl_3$, and evaporation, a solid was obtained which was crystallized from CH_2Cl_2, giving 550 mg of the azide **9a**: mp 200° dec; $[\alpha]D$ +123°; λ_{max} 231 nm (ϵ 12,975); λ_{max} 4.75 μ; nmr (DMSO-d_6) 3.58 (br, J = 10 Hz, 7-H), 4.29 (d, J = 2.5 Hz, 6-H), 5.99 (4-H), and 5.60 (d, J = 4.5 Hz, 7-OH), 5.77 (17-OH). *Anal.* ($C_{23}H_{29}O_7N_3$) C, H, N.

6β-Azido-7α,17α,21-trihydroxy-4-pregnene-3,11,20-trione 7,21-Diacetate (10a). Ac_2O (1.4 ml) was added to a solution of **9a** (317 mg) in pyridine (6 ml). After 3 days at room temperature the usual work-up afforded 278 mg of **10a** (crystallized from EtOAc): mp 175° dec; $[\alpha]D$ +89.4°; λ_{max} 230 nm (ϵ 12,977): nmr 2.12, 2.15 (7- and 21-$OCOCH_3$), 4.11 (d, J = 3 Hz, 6-H), 4.93 (d, J = 3 Hz, 7-H), 5.82 (4-H). *Anal.* ($C_{25}H_{31}O_8N_3$) C, H, N.

6-Azido-17α,21-dihydroxy-4,6-pregnadiene-3,11,20-trione 21-Acetate (11a). Using the procedure for the preparation of **4a** from the 6-azido 7-mesylate **3**, exposure of 1 g of the azido-7-acetoxy **10a** to TMAF in CH_3CN gave a residue which was crystallized from MeOH, affording 468 g of **11a** solvated with 1 mol equiv of water: mp dec over 350°; $[\alpha]D$ +300.7°; λ_{max} 250 nm (ϵ 13,176) and 294 (12,274); λ_{max} 2.94, 4.73, 5.73, 5.86, 6.00, 6.20, 6.30 μ; nmr 0.71 (13-CH_3), 1.31 (10-CH_3), 2.16 (21-$OCOCH_3$), 3.82 (H_2O), 4.66 and 5.13 (d, J = 17.5 Hz, 20-CH_2), 5.76 (7-H), 6.12 (4-H). *Anal.* ($C_{23}H_{27}O_6N_3 \cdot H_2O$) C, H, N; *m/e* 441 and also 413 (−28) and 415 (−26 from −28 + 2).

6β-Azido-7α,11β,17α,21-tetrahydroxy-4-pregnene-3,20-dione 21-Acetate (13). A mixture consisting of 1.0 g of the 6,7-oxide **12**, 40 ml of MeOH, 20 ml of dioxane, 10 ml of water, 3.0 g of NaN_3, and 20 ml of AcOH was allowed to remain at room temperature for 4 days. Then 600 ml of water containing NaCl was added and the resulting mixture was extracted with CH_2Cl_2. After water washing, the organic phase afforded 1.0 g. Crystallization of 874 mg from Et_2O gave 658 mg of **13a**, solvated with water: mp initial melt at 120°, resolidify to 180° dec; $[\alpha]D$ +90.5°; λ_{max} 236 nm (ϵ 12,650); λ_{max} ($CHCl_3$) 4.75 μ; nmr (DMSO-d_6) 3.61 (multiplet, 7-H), 4.22 (d, J = 2.5 Hz, 6-H), 4.27 (11-H), 4.28 (7-OH), 5.85 (4-H). *Anal.* ($C_{23}H_{32}O_7N_3$) *m/e* 461.

6β-Azido-7α,11β,17α,21-tetrahydroxy-4-pregnene-3,20-dione 7,21-Diacetate (14). A mixture of the 7-hydroxy **13** (640 mg), pyridine (4.6 ml), and Ac_2O (3.2 ml) after 17 hr at room temperature gave after the usual work-up 550 mg of the 7-acetate **14a**: mp 140° dec; $[\alpha]D$ +63°; λ_{max} 233 nm (ϵ 12,186); nmr (DMSO-d_6) 2.04 (7-$OCOCH_3$), 2.11 (21-$OCOCH_3$), 4.34 (7- and 11-H), 4.41 (d, J = 2.5 Hz, 6-H), 5.93 (4-H). *Anal.* ($C_{25}H_{33}O_8N_3$) *m/e* 503.

6-Azido-11β,17α,21-trihydroxy-4,6-pregnadiene-3,20-dione 21-Acetate (15a). TMAF-5H_2O (350 mg) was suspended in 35 ml of CH_3CN; the mixture was warmed to give solution and then allowed to cool to room temperature. The 7-acetoxy **14** (350 mg) was added and the mixture allowed to remain at room temperature for 24 hr. After addition to water and CH_2Cl_2 extraction, a solid residue of 276 mg was obtained, which was purified by preparative tlc plate (silica gel, $CHCl_3$–EtOAc, 1:1) giving 201 mg of the azido **15a**. An analytical sample from Me_2CO gave mp indeterminate, 130–190° dec; $[\alpha]D$ +204.9°; λ_{max} 250 nm (ϵ 21,750) and 298 (12,600); λ_{max} 2.88, 2.92, 4.71, 4.70, 5.77, 5.89 (Me_2CO), 6.02, 6.19, 6.29 μ; nmr 1.01 (13-CH_3), 1.37 (10-CH_3), 2.12 [$CO(CH_3)_2$ as solvate], 2.17 (21-$OCOCH_3$), 2.80 (17-OH), 4.48 (multiplet, 11-H), 4.93 (d, J = 1.5 Hz, 11-OH), 5.87 (d, J = 2 Hz), 6.06 (4-H). *Anal.* ($C_{23}H_{29}O_6N_3$) C, H, N; *m/e* 417 (loss of N_2 plus 2 by disproportionation).

6β-Thiocyanato-7α,17α,21-trihydroxy-4-pregnene-3,11,20-trione 21-Acetate (9b). A suspension of 6,7-oxido **8** (830 mg) and 6 g of KSCN in 60 ml of MeOH, 40 ml of water, and 1 ml of AcOH was stirred at room temperature for approximately 2 days, then added to 1.5 l. of water, and extracted with $CHCl_3$ to obtain after work-up 740 mg of the thiocyanate. An analytical sample from Me_2CO–C_6H_{14} gave mp 238–241°; $[\alpha]D$ +178.7°; λ_{max} 240 (ϵ 13,700); λ_{max} 4.62 μ; nmr 3.87 (7-H), 4.46 (d, J = 2 Hz, 6-H), 5.97 (4-H), 6.10 (d, J = 5 Hz, 7-OH). *Anal.* ($C_{24}H_{29}O_7NS$) C, H, N, S.

6-Thiocyanato-17α,21-dihydroxy-4,6-pregnadiene-3,11,20-trione 21-Acetate (11b). To a solution of pyridine (20 ml) and CH_3SO_2Cl (1 ml), at *ca.* 10°, was added 6β-thiocyanato-7α-hydroxy **9b**. The mixture was allowed to remain at room temperature for 2 hr and then at 5° for 17 hr. After the usual work-up and silica gel chromatography ($CHCl_3$–EtOAc, 1:1), 225 mg of the 6-thiocyanato **11b** was obtained and crystallized from CH_2Cl_2–Et_2O, giving 160 mg: mp 204–206°; $[\alpha]D$ +252.5°; λ_{max} 274 nm (ϵ 17,900); λ_{max} 2.93, 4.69, 5.73, 5.78, 5.83, 6.02, 6.23, 6.31 μ; nmr 0.73 (13-CH_3), 1.32 (10-CH_3), 2.16 (21-$OCOCH_3$), 4.48 (d, J = 18 Hz) and 5.10 (d, J = 18 Hz, 20-CH_2), 6.25 (4-H), 6.83 (7-H). *Anal.* ($C_{24}H_{27}O_6NS$) C, H, N, S.

6β-Azido-7α-hydroxy-4-androstene-3,17-dione (17a, R = H). In a similar manner to that used for the preparation of **3a** (R = H), 1.9 g of the 6,7-oxide **16** gave 1.98 g of **17a** (R = H). An analytical sample (CH_2Cl_2–EtOAc) gave mp indeterminate from 170° dec; $[\alpha]D$ +95.3°; λ_{max} 236 nm (ϵ 12,219); λ_{max} 2.95, 4.75 μ. *Anal.* ($C_{19}H_{25}O_3N_3$) C, H, N.

6β-Azido-7α-hydroxy-4-androstene-3,17-dione 7-Mesylate (17a, R = CH_3SO_2). A solution of the 7-hydroxy **17a** (785 mg), CH_3SO_2Cl (0.6 ml), and pyridine (6.5 ml) was allowed to stand at room temperature for 18 hr. After the usual work-up, 700 mg was obtained, predominantly the mesylate **17a**, which after purification by preparative plate chromatography (silica gel, $CHCl_3$–EtOAc, 9:1) and crystallization from CH_2Cl_2–Et_2O gave the analytical sample: mp 148° dec; $[\alpha]D$ +38.2°; λ_{max} 234 nm (ϵ 12,456); nmr 3.02 (SO_2CH_3), 4.48 (d, J = 3 Hz, 6-H), 4.83 (multiplet, 7-H), 5.97 (4-H). *Anal.* ($C_{20}H_{27}O_5N_3S$) C, H, N, S.

6-Azido-4,6-androstadiene-3,17-dione (18a). To a mixture of TMAF (500 mg) and CH_3CN (50 ml) (prepared as in the preparation of **4a** at room temperature) was added the 7-mesyloxy **17a** (500 mg). After 1 hr at room temperature and then 15 min at 60°, and the usual work-up followed by silica gel preparative plate chromatography and crystallization from MeOH, 220 mg of **18a** was obtained: mp 136–138° dec; $[\alpha]D$ 206.6°; λ_{max} 253 nm (ϵ 13,285), 299 (12,930); λ_{max} 4.74, 5.76, 6.00, 6.17, 6.27 μ; nmr 1.0 (13-CH_3), 1.18 (10-CH_3), 5.88 (d, J = 2.5 Hz, 7-H), 6.16 (4-H). *Anal.* ($C_{19}H_{23}O_2N_3$) C, H, N.

6β-Thiocyanato-7α-hydroxy-4-androstene-3,17-dione (17b, R = H). A solution of 6,7α-oxido **16** (1.6 g), MeOH (160 ml), water (35 ml), AcOH (5 ml), and KSCN (7.8 g) was allowed to remain at room temperature for 17 hr. Evaporation of the solvent to one-half the volume gave 1.2 g of **17b** (R = H), with an additional 248 mg obtained from the filtrate by extraction. An analytical sample (CH_2Cl_2–EtOAc) gave mp 185–188°; $[\alpha]D$ +188°; λ_{max} 242 nm (ϵ 13,200); λ_{max} 2.97, 4.62 μ; nmr (I MSO-d_6) 3.92 (multiplet, 7-H), 4.45 (d, J = 2.2 Hz, 6-H), 5.98 (4-H). *Anal.* ($C_{20}H_{25}O_3NS$) C, H, N, S.

6-Thiocyanato-4,6-androstadiene-3,17-dione (18b). A solution of the 6-thiocyanato **17b** (R = H) (500 mg) was stirred at room temperature for 5 hr in pyridine (5 ml) containing CH_3SO_2Cl (1.5 ml). After the usual work-up and purification by preparative plate chromatography (silica gel, $CHCl_3$–EtOAc, 9:1), followed by crystallization (MeOH), 182 mg of 4,6-thiocyanato **18b** was obtained: mp 176–177°; $[\alpha]D$ +119.1°; λ_{max} 274 nm (ϵ 19,142); λ_{max} 4.60, 5.71, 5.97 (sh), 6.00, 6.21 μ; nmr 0.98 (13-CH_3), 1.18 (10-CH_3), 6.28 (4-H), 6.93 (d, J = 2.5 Hz, 7-H). *Anal.* ($C_{20}H_{23}O_2NS$) C, H, N, S.

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N-Alkylnorketobemidones with Strong Agonist and Weak Antagonist Properties

Tokuro Oh-ishi† and Everette L. May*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014. *Received July 2, 1973*

Replacement of the *N*-methyl group of ketobemidone (1) with propyl, cyclopropylmethyl, or allyl (*cf.* 6, 11, and 13) does not produce antagonists but weak to medium strength analgesics with high physical dependence capacity (Rhesus monkeys). When the N-substituent is amyl (8) strong analgesic and atypical properties of antagonism are exhibited. *N*-Hexyl- and -heptylnorketobemidones (9 and 10) are between morphine and pethidine in analgesic potency, and both are weak, long-acting, nalorphine-like antagonists in monkey and guinea-pig ileum experiments. *N*-Ethylnorketobemidone (5) is a weak agonist, but the *N*-butyl homolog 7 is as potent as morphine with low physical dependence capacity.

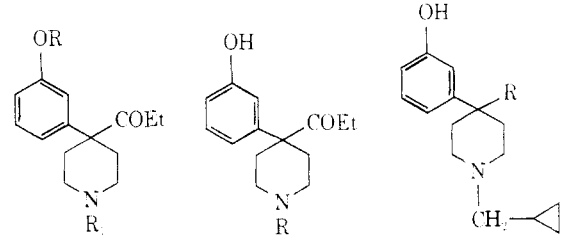
It is well known that strong analgesics of fused tricyclic to hexacyclic systems (benzomorphans to *endo*-ethenooripavines) can be converted to potent antagonists by replacement of methyl on the nitrogen with allyl, propyl, or cyclopropylmethyl. More recently it was demonstrated that the strong analgesic, 5-*m*-hydroxyphenyl-2-methylmorphan,[1] bicyclic in character, gave only weak antagonists by this simple change despite a favorable location of the phenolic hydroxyl. We now wish to report complete failure to obtain antagonists from the powerful analgesic, ketobemidone (monocyclic), with these three N-substitutions and the preparation of strong analgesics containing properties of antagonism by higher *N*-alkyl substitution.

Chemistry. The starting material, **2**, for the preparations described herein was obtained in double the yield and one-fifteenth the time reported by Avison, *et al.*,[2] in the reaction of EtMgI with 4-cyano-4-*m*-methoxyphenyl-1-methylpiperidine, simply by very efficient stirring. Conversion of **2** to **3** was effected by the ethyl chloroformate method.[3]

Reaction of **3**·HCl with alkyl bromides or iodides in boiling 2-butanone or DMF at 90° (K_2CO_3) followed by treatment of the resultant *N*-alkyl methyl ethers with boiling 48% HBr gave phenols **5**–**10**. Compound **11** was similarly obtained using allyl bromide.

The cyclopropylmethyl analog, **13**, was synthesized by a less direct route. Phenol **4**, prepared from **3** with boiling 48% HBr, and cyclopropylcarbonyl chloride gave the *O*,*N*-diacyl derivative which was reduced to carbinol **12** with $LiAlH_4$. Oxidation of **12** to **13** was effected with DMSO-Ac_2O[4] or by the Oppenauer method.

† Visiting Associate from Tokyo, Japan. On leave from Tanabe Seiyaku Co., Ltd. Saitama, Japan.



1, R = H; R_1 = Me
2, R = R_1 = Me
3, R = Me; R_1 = H
4, R = H
5, R = Et
6, R = Pr
7, R = Bu
8, R = Am
9, R = Hex
10, R = Hept
11, R = allyl
12, R = CHOHEt
13, R = COEt

Pharmacology. In Table I are given analgesic activities (hot-plate and Nilsen),[5] physical dependence capacities (PDC),[6] and properties of narcotic antagonism for ketobemidone (**1**) and pentazocine (standards) and analogs of **1**. Predictably, a change from methyl to ethyl with respect to the N-substituent (**1** *vs.* **5**) nearly abolishes the CNS effects seen in the strongly active **1**, partially restored in the *N*-propyl homolog **6** and its *O*-acetyl derivative. *N*-Butyl homolog **4** is half as potent (as an analgesic) as **1** but is more toxic and has little PDC. The *N*-amyl derivative **8** is nearly three times stronger than **1** but will not sustain morphine dependence in monkeys; in fact, it displays some (atypical) properties of antagonism. The hexyl and heptyl homologs **9** and **10** are typical nalorphine-like antagonists with a longer duration of action, a steeper