Chemotherapeutic Nitroheterocycles. Nitropyrrole-2-carboxaldehyde Derivatives[1]

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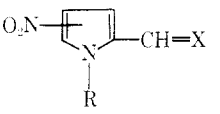
A series of 4- or 5-nitropyrrole-2-carboxaldehydes, either unsubstituted or bearing alkyl or phenyl substituents in the 1 position, have been synthesized by straightforward methods. A series of simple carbonyl derivatives prepared from them was evaluated as antimalarial and antibacterial agents. Only a slight positive effect was noted in either type of assay.

The association of useful chemotherapeutic properties with five-membered heterocyclic rings bearing a nitro group began with the discovery of the antibacterial properties of 5-nitrofurfural derivatives in 1944.[2] Since that time, investigations of this and various related nitro heterocyclic systems have revealed valuable inhibitory activities against many pathogenic organisms infecting man and animals. The nitrofurans, for example, possess not only antibacterial action but also antifungal properties and are effective against various protozoan parasites such as coccidia and trichomonads.[3] Various derivatives of 2-amino-5-nitrothiazole are used for treatment of the protozoan disease of turkeys, enterohepatitis,[4] as is a 5-nitroimidazole (dimetridazole).[5] Another 2-amino-5-nitrothiazole derivative has been recently found highly efficacious in the treatment of human schistosomiasis[6,7] and amebiasis.[8] Metronidazole, a nitroimidazole, is the drug of choice for the cure of human trichomoniasis.[9,10] In experimental animal systems or *in vitro*, other nitro-bearing heterocyclic rings such as pyrrole (mono[11,12] or dinitro[13]) and thiophene[12,14] have demonstrated interesting antibacterial, antitrichomonal, or anthelmintic activities.

As part of a systematic survey of new types of five-membered nitroheterocycles, we have prepared a series of 4- and 5-nitropyrrole-2-carboxaldehyde derivatives (**1**) for evaluation as antimalarial agents. In addition, the *in vitro* antibacterial properties of some of these compounds seemed desirable because of the isosteric relationship of 5-nitropyrrole-2-carboxaldehyde with 5-nitrofurfural and because an additional structural parameter, the N-substituent, is available for manipulation in the pyrrole ring. The structural similarity of this series to 1-hydroxyethyl-5-nitropyrrole-2-carboxamide (**2**), a compound reported during the course of this study to possess *in vivo* antitrichomonal activity,[11] provided further interest in the series.



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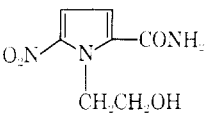


2

Chemistry.—The compounds prepared and tested in this series are listed in Table I. 4-Nitro- and 5-nitropyrrole-2-carboxaldehyde, required for the synthesis of many of the structures, were prepared from pyrrole-2-carboxaldehyde by a minor variation of the procedure of Fournari and Tirouflet.[15] The N-methyl derivatives of these aldehydes (*e.g.*, **15**) were obtained by a modification of the alkylation procedure of these same authors.[15] More vigorous conditions were required for the synthesis of the N-isoamyl and N-benzyl analogs. Prolonged heating of 5-nitropyrrole-2-carboxaldehyde sodium salt with isoamyl bromide or benzyl chloride in dimethylformamide solution was necessary to provide these compounds.

Preparation of the 1-phenyl derivatives in this series was only partially successful. The 4-nitro isomer, 1-phenyl-4-nitropyrrole-2-carboxaldehyde, was obtained in moderate yield by the direct nitration of 1-phenylpyrrole-2-carboxaldehyde. A number of approaches to the corresponding 5-nitro system were unsuccessful; the direct nitration procedure gave none of this isomer. Nitration of 1-phenyl 2-methylpyrrole, potentially capable of conversion to a pyrrole-2-aldehyde, gave an inseparable mixture of at least three different nitro isomers according to pmr spectroscopy. Formylation of 1-phenyl-2-nitropyrrole did not occur even under forcing conditions.

Several procedures for the direct introduction of a 1-aryl group into 5-nitropyrrole-2-carboxaldehyde were also investigated without success. Reaction of the sodium salt of 5-nitropyrrole-2-carboxaldehyde with diphenyliodonium iodide, various "benzyne" reagents, and 4-fluoronitrobenzene provided no 1-arylpyrroles. Attempts to obtain this system *via* aromatization of 1-cyclohexyl derivatives have also failed to give the desired 1-aryl compound.

Carbonyl derivatives were prepared by standard techniques or according to references given in the Experimental Section.

Biological Activity.—These compounds were assayed against lethal, blood-induced, *Plasmodium berghei* in-

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is Contribution No. 253 from the Army Research Program on Malaria.

(2) M. Dodd and W. Stillman, *J. Pharmacol. Exptl. Therap.*, **82**, 11 (1944).

(3) H. E. Paul and M. F. Paul in "Experimental Chemotherapy," Vol. II, Part I, R. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1964, pp 307–370.

(4) L. Joyner, S. Davies, and S. Kendall in "Experimental Chemotherapy," Vol. I, R. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1963, pp 341–343.

(5) A. Flowers, C. Hall, and L. Grumbles, *Avian Diseases*, **9**, 394 (1965), and references cited therein.

(6) Coded as Ciba 32644Ba. P. Schmidt and M. Wilhelm, *Angew. Chem. Intern. Ed. Engl.*, **5**, 857 (1966).

(7) P. Jordan, *Brit. Med. J.*, 276 (1966), and references cited therein.

(8) S. J. Powell, I. MacLeod, A. J. Wilmot, and R. Elsdon-Dew, *Lancet*, 20 (July 2, 1966).

(9) R. Schnitzer, ref 3, Vol. IV, 1966, p 423, and references cited therein.

(10) R. Sands, *Am. J. Obstet. Gynecol.*, **94**, 350 (1966).

(11) F. Benazet, C. Cosar, P. Ganter, L. Julou, P. Populaire, and L. Guillaume, *Compt. Rend.*, **263**, 609 (1966).

(12) G. Gunn, P. Actor, and V. DiPasquo, *J. Med. Chem.*, **9**, 751 (1966).

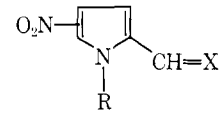
(13) G. W. Brown, R. Wellerson, and A. B. Kupferberg, *J. Pharm. Pharmacol.*, **17**, 747 (1965).

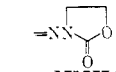
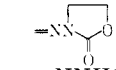
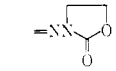
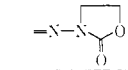
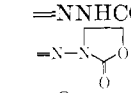
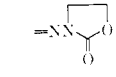
(14) F. Kametani, O. Umezawa, M. Soto, and F. Kobayashi, *J. Pharm. Soc. Japan*, **83**, 174 (1963).

(15) P. Fournari and J. Tirouflet, *Bull. Soc. Chim. France*, 484 (1963).

TABLE I

NITROPYRROLE-2-CARBOXALDEHYDE DERIVATIVES



No.	Nitro isomer	R	X	Mp, °C	Yield, %	Analyses[a]	Antimalarial act.[b] Survival time, T/C, at 40 mg/kg	160 mg/kg	640 mg/kg
3	4	H		266 dec	50	C, H, N	0.2	0.2	0.2
4	4	CH_3	$=NNHCH_2CONH_2$	139–153	21	C, H, N	0.1	0.1	0.1
5	4	CH_3	$=NNHCOCH_3$	266	69	C, H, N	0.6	0.6	1.8
6	4	CH_3	$=NNHCO(CH_2)_3CH_3$	152–153	66	C, H, N	0.1	0.1	0.1
7	4	CH_3		248	95	C, H, N	1.0	1.4	1.8
8	4	C_6H_5	$=NNHCONH_2$	247–250	88	C, H, N	0.1	0.1	0.3
9	4	C_6H_5	$=NNHCOCH_3$	252–254	73	C, H, N	0.1	0.1	0.1
10	4	C_6H_5	$=NNHCO(CH_2)_3CH_3$	155–158	67	C, H, N	0.5	0.7	0.7
11	5	H	$=O$[c]				1.0	1.0	... (5/5)
12	5	H	$=NNHCOCH_3$	248 dec	83	C, H, N	0.5	2.1	... (5/5)
13	5	H	$=NNHCO(CH_2)_3CH_3$	170–171	57	C, H, N	0.7	0.9	1.7 (1/5)
14	5	H		228 dec	85	C, H, N	0.8	0.8	1.0
15	5	CH_3	$=O$[c]				0.9	1.3	... (5/5)
16	5	CH_3	$=NOH$[c]				0.9	1.2 (1/5)	... (5/5)
17	5	CH_3	$=NNHCONH_2$	235 dec	97	C, H, N	1.1	1.3	1.5
18	5	CH_3	$=NNHCOCH_3$	201–202	97	C, H, N	1.4	1.4	1.8
19	5	CH_3	$=NNHCO(CH_2)_3CH_3$	160–162	77	C, H, N	1.1	1.1	2.5
20	5	CH_3		233–235	64	C, H, N	0.2	0.2	0.6
21	5	CH_3	$=NNHCH_2CONH_2$ $COCH_3$	190–192 dec	77	C, H, N	0.3	0.3	0.3
22	5	CH_3	$=NNCH_2CONH_2$	230–234	37	C, H, N	0.9	1.1	1.2 (1/5)
23	5	$CH_2CH_2CH(CH_3)_2$	$=NOH$	100–104	66	C, H, N	0.4	0.4	0.4
24	5	$CH_2CH_2CH(CH_3)_2$	$=NNHCONH_2$	205–210	85	C, H, N	0.3	0.3	0.5
25	5	$CH_2CH_2CH(CH_3)_2$	$=NNHCOCH_3$	136–137	91	C, H, N	0.1	0.3	0.5
26	5	$CH_2CH_2CH(CH_3)_2$	$=NNHCO(CH_2)_3CH_3$	118–120	31	C, H, N	0.0	0.0	0.4
27	5	$CH_2CH_2CH(CH_3)_2$		91.5–92	64	C, H, N	0.0	0.0	0.0
28	5	$CH_2C_6H_5$	$=O$	40–42	70	C, H, N	0.0	0.0	0.0
29	5	$CH_2C_6H_5$	$=NOH$	140–145	39	C, H, N	0.2	0.2	0.2
30	5	$CH_2C_6H_5$	$=NNHCONH_2$	186–190	58	C, H, N	0.0	0.0	0.0
31	5	$CH_2C_6H_5$	$=NNHCOCH_3$	157–158	87	C, H, N	0.2	0.2	... (5/5)
32	5	$CH_2C_6H_5$	$=NNHCO(CH_2)_3CH_3$	123–128	54	C, H, N	0.0	0.2	0.2
33	5	$CH_2C_6H_5$		157–162	45	C, H, N	0.0	0.2	0.2
Chloroquine							4.6	10.0	... (5/5)
Quinine							1.0	2.0	5.4

[a] Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. [b] Mice were treated 3 days postinfection with a single subcutaneous drug dose of 40, 160, and 640 mg/kg; the therapeutic criterion is the prolongation of survival time of treated animals over controls. Controls normally live 6–7 days. Drug toxicity is considered the cause of death when treated mice die before controls and fractions in parentheses represent toxicity deaths over total mice in treated group. See also T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). [c] Known compounds.[15]

fections in mice,[16] as part of the Walter Reed Army Institute of Research malaria program. The antimalarial screening results are presented in Table I. Chloroquine and quinine are included for comparison purposes. The majority of the compounds were essentially without a positive effect. Derivatives **7**, **12**, and **19** prolonged survival times of treated mice by about 2 days at the higher doses, but this must be regarded as marginal protection at best. Insofar as generalizations can be made on the basis of the borderline activity found, it would appear that either a 4- or 5-nitro group is acceptable and that a small substituent (hydrogen or methyl) on the 1 position is desirable. Compounds containing the phenyl, isoamyl, and benzyl substituents in the 1 position were uniformly without any effect. Little specificity as to favorable carbonyl derivatives is apparent.

Some of the nitropyrroles prepared in this study were also assayed *in vitro* against a few other microorganisms. Both a paper disk–agar plate diffusion method and a tube dilution method were employed. None of the compounds was appreciably inhibitory to *Staphylococcus albus*, *Escherichia coli*, *Serratia marcescens*, *Klebsiella aerobacter*, *Saccharomyces cerevisiae*, *Penicillium notatum*, or *Sporobolomyces salmoncolor* in the diffusion test. Against these same organisms in the tube dilution test, however, some compounds did display low-level broad spectrum activity. Compounds **20** and **27**, for ex-

(16) Performed by Dr. Leo Rane of the University of Miami, Miami, Fla.

ample, were inhibitory at the 1000- or 100-μg/ml level against all of them.

Experimental Section

Pmr spectra were obtained on a Varian Model A-60 spectrometer. Melting points are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.3\%$ of the theoretical values.

5-Nitropyrrole-2-carboxaldehyde and 4-nitropyrrole-2-carboxaldehyde were prepared using a convenient modification of the procedure of Fournari and Tirouflet,[15] *i.e.*, the nitration reagent used was that of Bordwell[17] and it was added at 0° to the reaction at −30°. Somewhat improved yields of each isomer (*ca.* 20%) were routinely obtained; ir spectra, λ^{Nujol} 6.0 (C=O) for the 4-NO_2 compound, 5.91 μ (C=O) for the 5-NO_2 compound; thin layer chromatography (silica gel, $CHCl_3$), R_f 0.15 (4-NO_2), R_f 0.27 (5-NO_2).

1-Methyl-5-nitropyrrole-2-carboxaldehyde and 1-methyl-4-nitropyrrole-2-carboxaldehyde were prepared in considerably higher yield by modification of the procedure of Fournari.[18] The nitropyrrole-2-carboxaldehyde (0.0321 mole) was dissolved, under N_2, in 150 ml of dry THF. Sodium ethoxide solution, prepared from the reaction of 0.034 g-atom of Na in 25 ml of EtOH, was added all at once to the stirred pyrrole solution at room temperature. After 15 min, Me_2SO_4 (0.035 mole) in 10 ml of THF was added over 10 min, and the resultant reaction mixture was refluxed for 4 hr. The cooled solution was acidic to litmus paper. The solvent was removed *in vacuo*. The resultant solid was crushed thoroughly in the presence of H_2O, filtered, and washed with additional H_2O. This procedure yielded 92% of pure 4-nitro isomer: mp 156–158° (lit.[18] mp 158°); thin layer chromatography (silica gel F, $CHCl_3$), R_f 0.4; ir spectrum, λ^{Nujol} 6.0 μ (C=O, strong); pmr spectrum ($CDCl_3$), τ 0.37 (singlet, 1 H, C*H*O), 2.34 (broad singlet, 1 H Ar*H*), 2.62 (doublet, 1 H, J = 2 cps, Ar*H*), 6.01 (singlet, 3 H, CH_3).

The 5-nitro isomer was obtained in 84% yield: mp 70–71° (lit.[18] mp 70°); ir spectrum, λ^{Nujol} 6.0 μ (C=O, weak); pmr spectrum ($CDCl_3$), τ 0.35 (singlet, 1 H, C*H*O), 2.95 (doublet, 1 H, J = 5 cps, Ar*H*), 3.20 (doublet, 1 H, J = 5 cps, Ar*H*), 5.78 (singlet 3 H, CH_3).

1-(3-Methylbutyl)-5-nitropyrrole-2-carboxaldehyde.—The sodium salt of 5-nitropyrrole-2-carboxaldehyde was prepared from 0.073 mole of NaOEt (from 1.68 g of Na and 75 ml of EtOH) and 10 g (0.0715 mole) of 5-nitropyrrole-2-carboxaldehyde in 125 ml of dry THF. The reaction was allowed to proceed for 20 min at room temperature, and the dry sodium salt was isolated by removal of the solvent at 65° *in vacuo*. It was dissolved in 175 ml of DMF and treated at room temperature with 12.1 g (0.08 mole) of isoamyl bromide dissolved in 30 ml of DMF. The resulting mixture was heated under N_2 to 80–90° for 40 hr. The reaction mixture was cooled and poured into 600 ml of H_2O. The resulting oil was extracted into two 100-ml portions of $CHCl_3$ and the combined extracts were filtered and washed twice (H_2O). The $CHCl_3$ solution was dried (Na_2SO_4) and the $CHCl_3$ was removed *in vacuo* to yield 13.9 g of crude product (dark oil). Purification was effected by chromatography on a 13 × 7 cm column of silica gel using $CHCl_3$ elution. A small amount of rapidly eluted material was discarded, and the pure product was collected in the next liter of eluate as a clear yellow oil, 6.1 g (41%). *Anal.* ($C_{10}H_{14}N_2O_3$) C, H, N. Thin layer chromatography showed only one component, R_f 0.58 (silica gel F, $CHCl_3$); ir spectrum, λ^{Nujol} 5.91 μ (C=O); pmr spectrum ($CDCl_3$), τ 0.42 (singlet, 1 H, C*H*O), 2.98 (doublet, 1 H, J = 5 cps, Ar*H*), 3.22 (doublet, 1 H, J = 5 cps, Ar*H*), 5.28 (triplet, 2 H, J = 8 cps, NCH_2), 8.38 (multiplet, 3 H, CH_2C*H*), 9.09 (doublet, 6 H, CH_3).

1-Benzyl-5-nitropyrrole-2-carboxaldehyde (28).—Sodium salt of 5-nitropyrrole-2-carboxaldehyde was prepared as with 1-(3-methylbutyl)-5-nitropyrrole-2-carboxaldehyde. The salt (0.0143 mole) in 35 ml of DMF was treated rapidly with 2.03 g (0.016 mole) of benzyl chloride in 10 ml of DMF. The mixture was heated under N_2 for 21 hr at 90°. NaCl started to precipitate from the reaction mixture after about 1 hr. The reaction mixture was cooled and poured into 200 ml of H_2O. The crude product (3.39 g, dark oil) was isolated by $CHCl_3$ extraction. This material decomposed upon attempted distillation and it was necessary to purify the product by chromatography. The oil was chromatographed on a 17 × 4.5 cm column of silica gel using $CHCl_3$ elution. The first 750 ml of eluate contained small quantities of by-products; the product (2.4 g, 70%) was collected in the next liter of eluate. It was pure by thin layer chromatography, R_f 0.42–0.57 ($CHCl_3$, silica gel F); ir spectrum, λ^{Nujol} 5.90 μ (C=O); pmr spectrum ($CDCl_3$), τ 0.30 (singlet, 1 H, C*H*O), 2.7–3.2 (multiplet, 7 H, Ar*H*), 3.93 (singlet, 2 H, CH_2). In a later preparation, the chromatographically pure material crystallized. The original analytical sample was seeded to induce crystallization; it melted at 40–42°. Recrystallization from ether–pentane did not alter the melting point.

1-Phenyl-4-nitropyrrole-2-carboxaldehyde.—1-Phenylpyrrole-2-carboxaldehyde[19] was nitrated according to the nitration procedure used for pyrrole-2-carboxaldehyde. The Dry Ice–acetone bath was kept between −10 and −20° during the addition of the HNO_3–Ac_2O mixture. A solid began to form when half had been added. At the end of the addition, the reaction mixture was poured on ice and the gummy solid which formed was filtered off. Crystallization from EtOH gave a 20% yield of a single isomer, mp 169–174°. *Anal.* ($C_{11}H_8N_2O_3$) C, H, N. Investigation of the filtrate and reaction mixture (by chromatography, thin layer chromatography, and melting point) did not show the presence of other isomers.

The product was identified as the 4-nitro isomer by the splitting of the pyrrole ring protons in the pmr spectrum. This and previous 1-substituted 4-nitro isomers have 3,5 proton splittings of *ca.* 2–3 cps. The 1-substituted 5-nitropyrrole-2-carboxaldehydes display 3,4 proton splittings of 5 cycles; ir spectrum, λ^{Nujol} 5.95 μ (C=O); pmr spectrum ($CDCl_3$), τ 0.50 (singlet, 1 H, C*H*O), 1.54 (doublet, 1 H, J = 2 cps, Ar*H*), 2.36 (doublet, 1 H, J = 2 cps, Ar*H*), 2.50 (singlet, 5 H, C_6H_5).

2-(1-Methyl-5-nitro-2-pyrrylmethylidenehydrazino)acetamide (21).—The procedure utilized was identical with that given by Ebetino, *et al.*, for a nitrofuran analog.[20] The product was obtained as an orange solid: mp 192–194° dec; 77% yield; ir spectrum, λ^{Nujol} 3.0, 3.1 (NH_2), 6.0 (C=O), 6.25 μ (C=N).

2-[1-Acetyl-2-(1-methyl-5-nitro-2-pyrrylmethylidene)hydrazino]acetamide (22).—A mixture of 25 ml of Ac_2O and 2.82 g (0.0125 mole) of 2-(1-methyl-5-nitro-2-pyrrylmethylidenehydrazino)acetamide was heated to reflux for 2 hr. Solid was present through the reaction, but the color changed from orange to yellow, indicating conversion of starting material to product. The reaction mixture was cooled to room temperature and the precipitated solid was collected by filtration and washed with Et_2O to yield 1.27 g (38%) of product as yellow crystals: mp 230–234° (sublimation at ~220°); ir spectrum, λ^{Nujol} 2.95, 3.15 (NH_2), 5.88, 5.92 (C=O), 6.15 μ (C=N).

Additional solids recovered from the reaction mixture proved to be a mixture of starting material, product, and (mainly) a diacetylated product (mp 215–225°).

3-Amino-2-oxazolidinone,[21] methyl hydrazinoacetate hydrochloride,[22] and *n*-valerhydrazide[23] were prepared according to the cited procedures.

In Vitro **Antimicrobial Assays.**—The agar plate diffusion assay employed 6.0-mm paper disks impregnated with 0.5 mg of test compound and pressed onto sensitivity agar plates streaked with dilute cultures of test organism. A ring of inhibited growth around the disk after a 24-hr incubation indicated antimicrobial activity.

For bacteria, in the tube dilution assay, a solution of test compound in an inert organic solvent was injected into a series of 2-ml portions of sensitivity broth so as to give concentrations ranging from 1000 to 0.1 μg/ml and differing by factors of 10. The test solutions were inoculated with test organism and incubated for 24 hr. A yellow color upon adding a drop of brom thymol blue solution indicated bacterial growth, a blue color,

(17) F. Bordwell and E. Garbisch, *J. Am. Chem. Soc.*, **82**, 3588 (1960).
(18) P. Fournari, *Bull. Soc. Chim. France*, 488 (1963).
(19) N. Elming and N. Kass, *Acta Chem. Scand.*, **6**, 867 (1952).
(20) F. Ebetino, W. Carey, and B. Stevenson, *J. Med. Chem.*, **6**, 633 (1963).
(21) Norwich Pharmacal Co., British Patent 735,169 (1955); *Chem. Abstr.*, **50**, 7874g (1956).
(22) A. Darapsky and M. Prabhakar, *Chem. Ber.*, **45**, 1660 (1912).
(23) N. Makhnenko and T. Sysoeva, *Zh. Prikl. Khim.*, **32**, 449 (1959); *Chem. Abstr.*, **53**, 13084c (1959).

lack of growth. The yeast and fungus tube-dilution assays were performed by incorporating the compound and inoculum into sensitivity agar instead of broth. Visible inhibition of growth on the surface of the agar after 24 hr was the criterion of activity in these cases.

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Synthesis and Activity of Some Nitro Steroids[1]

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The synthesis of several 3- and 20-nitro-5α-androstane and -pregnene derivatives was undertaken by oxidation of the corresponding oximes. Improved conditions (irradiation and oxygenation) were developed for this technique. Biological evaluation of the final derivatives for anabolic and progestational activities indicated that the replacement of a carbonyl oxygen by a nitro group in these compounds leads to weakly active or inactive products.

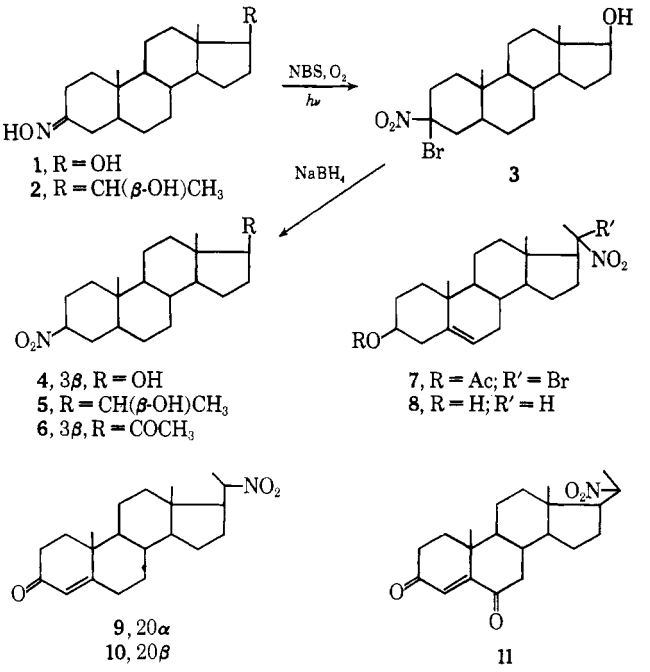
All steroid hormones except estradiol and testosterone possess a carbonyl group at C-20 and all but estradiol have a keto group at C-3. In work directed at defining the function of this moiety in eliciting biological responses,[2] we speculated that a combination of high electron density and hydrogen-bond acceptance might be key factors in the importance of these ketones. In the present work, we have examined this possibility by determining if a nitro group can be substituted in the region of a carbonyl function with retention of activity.

Nitro steroids have been prepared by nitration of unsaturated steroids with nitric acid[3a-c] or nitrogen tetroxide,[3d] by condensation of steroidal aldehydes with nitromethane,[3e] by nitration of oximes,[3f] by oxidation of oximes with a peracid,[3g] from reactions of steroids with nitrosyl chloride,[3h] and by displacement of alkyl nitrates,[3i] but these methods appeared too drastic or otherwise unsuitable for unsaturated steroids. Attempts to displace steroidal 3-tosylates with sodium nitrite[4] failed. Finally we employed and modified the mild oxidation of oximes[5] which had been used for the preparation of 17-nitro steroids.[6]

Treatment of **1** with N-bromosuccinimide (NBS) in dioxane–water solution, followed by stirring and exposure to air for 48 hr and final $NaBH_4$ reduction gave a mixture of the nitro compound **4** (27%) and androstane-3β,17β-diol (Scheme I). It was thus apparent that two competing reaction sequences occur during the NBS reaction: (a) formation of a *gem*-bromonitroso compound followed by air oxidation to a *gem*-bromonitro compound, and (b) hydrolysis of the oxime to the parent ketone, and subsequent reduction to the corresponding alcohol by the borohydride. It was clear that b could be minimized by accelerating the steps in a. This was done by bubbling oxygen through the mixture rather than relying on atmospheric air, and by irradiating with ultraviolet light. We reasoned that the irradiation would generate bromine radicals, thus facilitating the bromination and, second, would convert molecular oxygen, a sluggish oxidizing agent, to atomic oxygen, a much better oxidizing agent. As a result of these modifications, the yield was increased to about 50%. The assignment of the configuration of the nitro group in **4** was based on the broad multiplet exhibited in the nmr spectrum of the 3α-proton; this is due to axial–axial splittings and is compatible only with an axial proton at C-3.

In extending the method to C-20 oximes, a complex mixture of epimeric C-20 nitro compounds and alcohols was obtained, as shown by glpc. Therefore, the intermediate bromonitro compound **7** was isolated and freed

SCHEME I



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