equation as described above, K_i values were calculated, using for pepsin: $E_t = 1.2 \times 10^{-8}$ M, $S_0 = 1.0 \times 10^{-4}$ M, and $K_m = 1.25 \times 10^{-5}$ M. Values for rhizopuspepsin were $E_t = 6.0 \times 10^{-8}$ M, $S_0 = 1.0 \times 10^{-4}$ M, and $K_m = 5.0 \times 10^{-5}$ M. Values of K_m were determined under the conditions of the assay. Rabbit liver cathepsin D was purified, and compounds were assayed for inhibition as described previously,[26] using [^{14}C-methyl]-glycinated hemoglobin substrate, pH 4.0 (citrate), 37 °C, giving K_i values from Dixon plots.[43] Porcine plasma angiotensin converting enzyme was assayed at pH 7.65 (Tris-HCl), 30 °C, as described previously, with (benzyloxycarbonyl)-Phe-His-Leu as substrate.[27]

In Vivo Renin Inhibition. The relative effects of 1 and 3 on blood pressure was determined in four conscious, sodium-deficient dogs. The dogs were prepared essentially as described previously.[36] Sodium deficiency was established with use of a low-sodium diet and furosemide as described. The compounds were administered intravenously through an indwelling venous catheter by peristaltic pump to trained beagles in a Pavlov sling. Compounds were administered at various infusion rates as solutions in 5% dextrose, containing up to 0.1% acetic acid. No effect of vehicle was noted (results not shown). Each dose was preceded by a bolus injection of 4 times the per minute infusion rate to hasten the attainment of equilibrium, and each infusion was continued for 45 min. Two dogs received increasing doses of 1 first, followed by the doses of 3, and the order was reversed for the other two dogs. Full blood pressure recovery was attained prior to infusion of the other compounds. Blood pressure and heart rate were measured by tail cuff and recorded as an average of six readings, 1 min apart at post 45 min.

Acknowledgment. We thank Dr. A. A. Seymour, S. G. Smith, Dr. G. M. Fanelli, I. I. Stabilito, S. L. Fitzpatrick, C. F. Homnick, J. S. Murphy, J.-P. Moreau, and Dr. D. W. Cochran for analytical support, Dr. Roger M. Freidinger for helpful discussions, Professor Erwin Haas for a gift of human kidney renin standard, Dr. Eve E. Slater for the gift of fully purified human kidney renin, Dr. David Davies for the gift of rhizopuspepsin, and Dr. Richard Bott and Dr. David Davies for provision of the X-ray coordinates for rhizopuspepsin. We acknowledge gratefully the support and encouragement of Drs. Paul S. Anderson and Ralph F. Hirschmann.

Registry No. 1, 86153-45-9; 1·2$C_2H_4O_2$, 98168-92-4; 2, 98105-33-0; 3, 98105-34-1; 3·$C_2H_4O_2$, 98168-93-5; 4, 87063-27-2; 5, 98105-35-2; 6, 98105-36-3; 7, 98105-37-4; 8, 98126-19-3; 9, 87063-45-4; 10, 98105-38-5; 11, 98105-39-6; 12, 93962-09-5; 13, 98105-40-9; 14, 93961-79-6; 16, 51987-73-6; 17, 98105-41-0; 18, 98105-42-1; 19 (isomer 1), 98105-43-2; 19 (isomer 2), 98105-44-3; 20, 98105-45-4; 21, 72155-48-7; CH_3I, 74-88-4; Boc-Phe-OH, 13734-34-4; His-Sta-Leu-Phe-NH_2·2HCl, 98168-94-6; Boc-Sta-OEt, 67010-43-9; Sta-OEt·HCl, 84851-46-7; Boc-His(DNP)-OH, 25024-53-7; Boc-His-Sta-OEt, 98105-46-5; Boc-His-Sta, 92608-47-4; Boc-Leu-OH, 13139-15-6; Phe-NH_2, 5241-58-7; Boc-Leu-Phe-NH_2, 33900-15-1; Leu-Phe-NH_2·HCl, 74214-38-3; Boc-His-Sta-Leu-Phe-NH_2, 93962-08-4; Boc-Phe-His-ACHPA-Leu-Phe-OCH_3, 98105-47-6; [(isopropyloxy)carbonyl]-Phe-His-ACHPA-Leu-OCH_3, 98126-20-6; [(isopropyloxy)carbonyl]-Phe-His-ACHPA-Leu-$NHNH_2$, 98105-48-7; Phe-NH_2·HCl, 65864-22-4; Phe-His-ACHPA-Leu-Phe-NH_2·2HCl, 98105-49-8; Ac-Phe, 2018-61-3; Ac-Phe-His-ACHPA-Leu-Phe-OCH_3, 98105-50-1; Boc-Sta-OH, 58521-49-6; Boc-Pro-OH, 15761-39-4; Boc-His(DNP)-Sta-OEt, 98105-51-2; 3,3-dimethylacrylic acid, 541-47-9; ethyl acetate, 141-78-6; phenoxyacetic acid, 122-59-8; isovaleric acid, 503-74-2; isopropyl *p*-nitrophenyl carbonate, 90923-15-2; renin, 9015-94-5; ethyl chloroformate, 541-41-3.

(43) Dixon, M. *Biochem. J.* **1953**, *55*, 170.

1,2-Dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxylic Acid, Analogues, and Derivatives. A New Class of Oral Hypoglycemic Agents

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Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001. *Received April 22, 1985*

1,2-Dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarboxylic acid was found to be a hypoglycemic agent but not to have the undesirable mechanism of action possessed by nicotinic acid. A series of 1,2-dihydro-2-oxo-3-pyridinecarboxylic acids with a substituent primarily at the 6-position was prepared by hydrolysis of the corresponding nitriles. The nitriles were prepared by reaction of the sodium enolate of the appropriate 3-substituted 3-oxopropionaldehyde with cyanoacetamide. The sodium enolates were synthesized from ethyl formate and the appropriate ketone and sodium or sodium hydride. The active 1,2-dihydro-2-oxo-3-pyridinecarboxylic acids, listed in order of decreasing hypoglycemic potency, had the following substituents: 6-(2,2-dimethylpropyl), 6-(2,2-dimethylbutyl), 6-(1,1-dimethylethyl), 6-(2-methylpropyl), 6-(1,1-dimethylpropyl), 1-methyl-6-(2-methylpropyl), 6-hydrogen. The inactive compounds were those with 6-methyl, 6-(1-methylethyl), 6-pentyl, 4-(2,2-dimethylpropyl), 6-(3-methylbutyl), 6-(1,1-dimethylheptyl), 6-(2,2-dimethyloctyl), 6-(1-cyclobutylmethyl), and 1-methyl-6-(2,2-dimethylpropyl) substituents. The corresponding alcohol, aldehyde, tetrazole, sodium salt, and ethyl ester of the most potent acid were also active compounds. The corresponding amide, decarboxyl compound, and 2-deoxo compound were inactive.

During the course of screening for oral hypoglycemic agents in the 18-h fasted normal rat,[1] 1,2-dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarboxylic acid[2] (**13**) was found to be active. A search of the literature disclosed only two 1,2-dihydro-2-oxo-3-pyridinecarboxylic acids which are reported to be associated with hypoglycemic activity. Fang[3] reported that 1,2-dihydro-2-oxo-6-methyl-3-pyridinecarboxylic acid[4] (**10**) was inactive and that 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid[5] (**9**) was active in the diabetic rat. Fang[6] concluded that the hypoglycemic action of **9** was achieved through the suppression of the release of free fatty acids from the adipose tissues. Since nicotinic acid[7] also displays this activity and nicotinic acid has been reported to be ineffective as a hypoglycemic agent in man,[8,9] this mechanism of action for hypoglycemic ac-

(1) See the Experimental Section and: Schmidt, F. L.; Squiers, G. J.; McElheny, A. *Adv. Autom. Anal. Technicon Int. Cong.* **1972**, *9*, 107.
(2) Mariella, R. P. *J. Am. Chem. Soc.* **1947**, *69*, 2670.
(3) Fang, V. S. *Arch. Int. Pharmacodyn.* **1976**, *176*, 193.
(4) Available from the Aldrich Chemical Co.
(5) Cativiela, C.; Fernandez, J.; Melendez, E. *J. Heterocycl. Chem.* **1982**, *19*, 1093.
(6) Fang, V.; Foye, W. O.; Robinson, S. M.; Jenkins, H. *J. Pharm. Sci.* **1968**, *57*, 2111.
(7) Carlson, L. A.; Orö, L. *Acta Med. Scand.* **1962**, *172*, 641.
(8) Carlson, L. A.; Östman, J. *Acta Med. Scand.* **1965**, *177*, 71.

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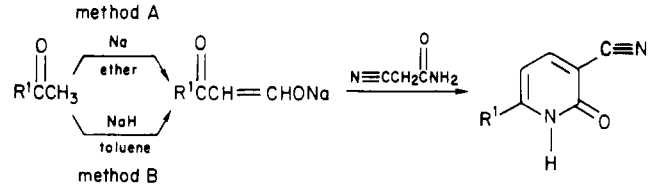
Scheme I

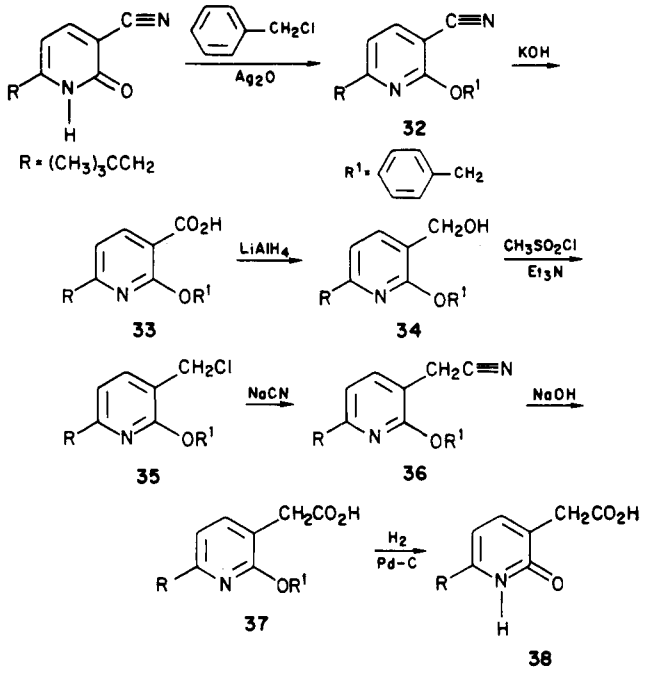


tivity is considered undesirable. To determine whether **13** had this undesirable mechanism of action, **13** and also **9** were tested in the fasted–refed normal rat[10] in which nicotinic acid has been shown to be inactive as a hypoglycemic agent.[11] Compound **13** was found to be active while compound **9** was found to be inactive. This result was the stimulus for the synthesis of compounds and the determination of their hypoglycemic activity in order to find a more potent analogue of **13**. The bulk of the work was centered on novel compounds containing an alkyl group at position 6 of the pyridine ring. The syntheses of some analogues, 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxylic acid[12] (**14**) and 1,2-dihydro-2-oxo-6-(2,2-dimethylbutyl)-3-pyridinecarboxylic acid[13] (**19**), and derivatives, 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxylic acid ethyl ester[12] (**27**), 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxaldehyde[14] (**29**), and 3-(1*H*-tetrazol-5-yl)-6-(2,2-dimethylpropyl)-2(1*H*)-pyridinone[14] (**31**), have been described previously by one of us. In addition to **9**, **10**, and **13**, the hypoglycemic activity of the literature compounds 1,2-dihydro-2-oxo-6-(1-methylethyl)-3-pyridinecarboxylic acid[15] (**11**) and 1,2-dihydro-2-oxo-6-pentyl-3-pyridinecarboxylic acid[15] (**18**) was determined in order to complete the structure–activity relationship investigation.

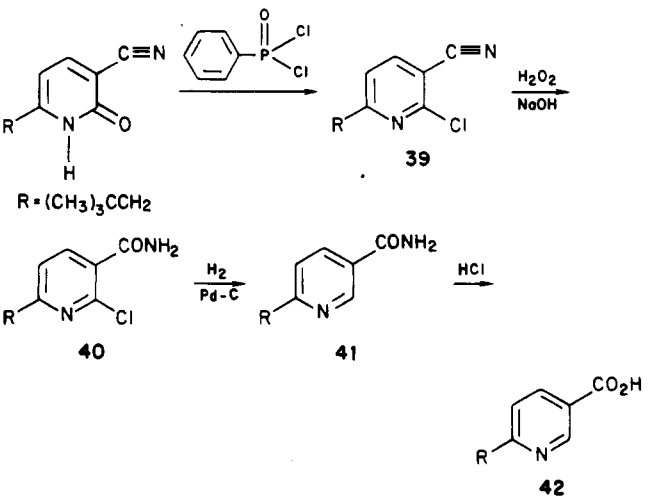
Chemistry. The novel 1,2-dihydro-2-oxo-6-alkyl-3-pyridinecarbonitriles (Table I) used to prepare the corresponding acids were synthesized by method A or B (Scheme I). A mixture of the ketone and ethyl formate was added to sodium in ether, which is the procedure of Mariella[2] (method A). More conveniently the mixture of the ketone and ethyl formate was added to sodium hydride in toluene (method B). The resulting sodium enolate was reacted with cyanoacetamide, producing the nitrile. The preparation of the 4-alkyl compound **6** was modeled after the procedure of Powers and Ponticello.[16] Sodium 3-oxo-5,5-dimethylhexanal[12] was treated with ammonium hydroxide, and the resulting enamino ketone was reacted with ethyl cyanoacetate to produce **6**. The *N*-methyl compound **7** was prepared by alkylating 1,2-dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarbonitrile[2] with dimethyl sulfate. The *N*-methyl compound **8** was made by alkylating 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] with methyl iodide.

Hydrolysis of the nitriles to the novel acids (Table II) could not be accomplished by a single procedure. The various procedures used are described in the Experimental Section under the individual compounds.

Scheme II



Scheme III



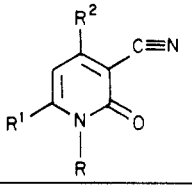
Since **14** was the most potent hypoglycemic agent of the compounds in Table II, compounds were synthesized in which the 6-(2,2-dimethylpropyl) group was retained but the other substituents on the pyridine ring were modified (Table III). As mentioned before, the syntheses of the ethyl ester **27**,[12] the aldehyde **29**,[14] and the tetrazole **31**[14] modifications have been described previously by one of us.

Refluxing a mixture of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] and 50% H_2SO_4 gave the decarboxylated compound **25**. Treatment of **14** with slightly less than 1 equiv of NaOH gave the sodium salt **26** as a hydrate. Hydrolysis of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] in concentrated H_2SO_4 at ambient temperature produced the amide **28**. Catalytic hydrogenation of **29** afforded the alcohol **30**.

1,2-Dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridineacetic acid (**38**) was prepared by the sequence outlined in Scheme II. Reaction of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] with benzyl chloride in the presence of Ag_2O produced the 2-phenylmethoxy compound **32** which upon hydrolysis with KOH gave the acid **33**. The reduction of **33** with $LiAlH_4$ afforded the

(9) Carlson, L. A. "Diabetes", Proceedings of the Sixth Congress of the International Diabetes Federation; Östman, J., Ed.; Excerpta Medica Foundation: Amsterdam, 1969; p 343.
(10) The test system is the same as described in ref 1 except that after the 18-h fast the rats were given by stomach tube 2 mL of liquid diet that has been described by: Miller, W. L.; Krake, J. J. *Proc. Soc. Exp. Biol. Med.* **1962**, *109*, 215. Rats were then dosed immediately with compound being tested.
(11) Gerritsen, G. C., unpublished observation.
(12) Youngdale, G. A. U.S. Patent 4 220 648, 1980.
(13) Youngdale, G. A. U.S. Patent 4 275 069, 1981.
(14) Youngdale, G. A. U.S. Patent 4 288 440, 1981.
(15) Kochetkov, N. K. *Dokl. Akad. Nauk. S.S.S.R.* **1952**, *84*, 289; *Chem. Abstr.* **1953**, *47*, 3309.
(16) Powers, J. C.; Ponticello, I. *J. Am. Chem. Soc.* **1968**, *90*, 7102.

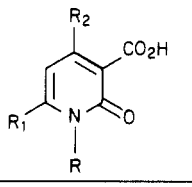
Table I. 1,2-Dihydro-2-oxo-3-pyridinecarbonitriles



no.	method	R	R^1	R^2	mp, °C	recryst solvent[a]	% yield[b]	formula[c]
1	A	H	$(CH_3)_2CHCH_2CH_2$	H	135–136	A–H	60	$C_{11}H_{14}N_2O$
2	B	H	$C_2H_5C(CH_3)_2$	H	148–150	C–E	40	$C_{11}H_{14}N_2O$[d]
3	B	H	$CH_3(CH_2)_5C(CH_3)_2$	H	80–83	C–H	15	$C_{15}H_{22}N_2O$
4	B	H	$CH_3(CH_2)_5C(CH_3)_2CH_2$	H	114–116	N	4	$C_{16}H_{24}N_2O$
5	B	H		H	184–187	C–S	24	$C_{11}H_{12}N_2O$
6		H	H	$(CH_3)_3CCH_2$	267–269	A	22	$C_{11}H_{14}N_2O$
7		CH_3	$(CH_3)_2CHCH_2$	H	97.5–99.5	A–H	48	$C_{11}H_{14}N_2O$
8		CH_3	$(CH_3)_3CCH_2$	H	88–89	A–H	13	$C_{12}H_{16}N_2O$

[a] Code: A, acetone; C, methylene chloride; E, ether; H, hexane; N, none (combined column fractions); S, Skellysolve B (a saturated hydrocarbon fraction, bp 60–70 °C). [b] Yield is from the ketone. [c] Analyzed for C, H, and N; analytical results were within ±0.4% of theoretical unless otherwise noted. [d] C: calcd. 69.44; found, 68.93.

Table II. 1,2-Dihydro-2-oxo-3-pyridinecarboxylic Acids



				hypoglycemic act.				
				18-h fasted rat			fasted-refed rat: % change in blood glucose[b] at 2 h	
					% change in blood glucose[b] at 2 h			
no.	R	R^1	R^2	rel[a] potency	treated[c]	pos control[d]	treated	pos control[e]
9	H	H	H	0.25	−26	−33	−4[f]	−55
10	H	CH_3	H	inact	+1	−34		
11	H	$(CH_3)_2CH$	H	inact[g]	−23	−26		
12	H	$(CH_3)_3C$	H	1.0	−69	−39	−58[h]	−40
13	H	$(CH_3)_2CHCH_2$	H	1.0	−61	−34	−54[h]	−48
14	H	$(CH_3)_3CCH_2$	H	13.0	−59	−39	−60[i]	−40
15	H	H	$(CH_3)_3CCH_2$	inact	−9	−34		
16	H	$(CH_3)_2CHCH_2CH_2$	H	inact	−4	−28		
17	H	$C_2H_5C(CH_3)_2$	H	0.9	−67	−32		
18	H	$CH_3(CH_2)_4$	H	inact	−2	−25		
19	H	$C_2H_5C(CH_3)_2CH_2$	H	3.8	−54	−38		
20	H	$CH_3(CH_2)_5C(CH_3)_2$	H	inact	+5	−37		
21	H	$CH_3(CH_2)_5C(CH_3)_2CH_2$	H	inact	+8	−37		
22	H		H	inact	−14	−37		
23	CH_3	$(CH_3)_2CHCH_2$	H	0.6	−36	−22		
24	CH_3	$(CH_3)_3CCH_2$	H	inact	−3	−34		

[a] Potency was determined by a parallel line assay compared with 1-butyl-3-(*p*-tolylsulfonyl)urea (Orinase). [b] A decrease of less than 19% from the control blood glucose was considered inactive. [c] 100 mg/kg. [d] 25 mg/kg of 1-butyl-3-(*p*-tolylsulfonyl)urea. [e] 100 mg/kg of 1-butyl-3-(*p*-tolylsulfonyl)urea. [f] 200 mg/kg. [g] Inactive at 100 mg/kg at the second stage of testing. [h] 100 mg/kg. [i] 25 mg/kg.

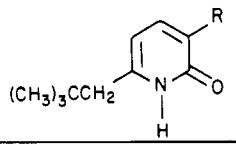
alcohol **34**. Reaction of **34** with methanesulfonyl chloride in the presence of triethylamine produced the chloromethyl compound **35** which was treated with NaCN, giving the acetonitrile **36**. Hydrolysis of **36** with NaOH produced the acetic acid **37** which was debenzylated by catalytic hydrogenation to afford the acetic acid **38**.

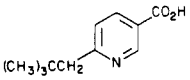
6-(2,2-Dimethylpropyl)-3-pyridineacetic acid **42** was prepared by the sequence outlined in Scheme III. Reaction of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] with phenylphosphonic dichloride produced the 2-chloro compound **39** which was hydrolyzed by a NaOH and H_2O_2 mixture to give the amide **40**. Catalytic hydrogenation of **40** removed the chlorine, affording the amide **41** which was hydrolyzed in hydrochloric acid to give the acid **42**.

Hypoglycemic Activity. Hypoglycemic activity in the 18-h fasted normal rat[1] was evaluated for all the compounds in Tables II and III. Hypoglycemic activity in the fasted–refed normal rat[10] was evaluated for selected compounds in Table II.

Structure–Activity Relationships. Structure–activity relationships can be deduced by examination of the hypoglycemic activity data presented in Tables II and III. Since the unsubstituted acid **9** had activity in the 18-h fasted normal rat but was inactive in the fasted–refed normal rat, it was of no further interest. The methyl compound **10** and the 1-methylethyl compound **11** had no activity. The 1,1-dimethylethyl compound **12** and the 2-methylpropyl compound **13** were equally potent. Addition of another methylene group to **13** to give the 3-

Table III. Modifications of 1,2-Dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxylic Acid



		hypoglycemic act. in 18-h fasted rat		
			% change in blood glucose at 2 h[b]	
no.	R	rel[a] potency	treated[c]	pos control[d]
25	H	inact	−1	−36
26	CO_2Na	7.9	−56	−26
27	$CO_2C_2H_5$	7.4	−54	−42
28	$CONH_2$	inact	+30	−25
29		5.9	−47	−47
30	CH_2OH	5.3	−40	−26
31		1.6	−37	−34
38	CH_2CO_2H	0.25	−25	−25
42		inact	−4	−31

[a] Potency was determined by a parallel line assay compared with 1-butyl-3-(*p*-tolylsulfonyl)urea. [b] A decrease of less than 19% from the control blood glucose was considered inactive. [c] 100 mg/kg. [d] 25 mg/kg of 1-butyl-3-(*p*-tolylsulfonyl)urea.

methylbutyl compound **16** resulted in the loss of activity. Substitution of the methyl group in **12** with the ethyl group to give the 1,1-dimethylpropyl compound **17** did not change the potency while the hexyl group substituent compound **20** was inactive. The 2,2-dimethylpropyl compound **14** was the most potent compound while its 4-isomer **15** was inactive. Substitution of the methyl group in **14** with the ethyl group to give the 2,2-dimethylbutyl compound **19** resulted in slightly lower potency while the hexyl group substituent compound **21** was inactive. The straight-chain pentyl compound **18** and the cyclobutylmethyl compound **22** were inactive. Substitution of a methyl group on the nitrogen in **13** to give **23** lowered the potency while the same substitution in **14** to give **24** abolished activity. The conclusions reached from the above comparisons concerning the structural requirements for activity in the 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid series were that at position 6 of the pyridine ring there be attached a bulky group containing at least four carbon atoms or a bulky group containing at least three carbon atoms one methylene group from the ring. Also, extension of the chain attached to the branched carbon leads to diminished activity, and substitution on the nitrogen does not appear to be favorable. The only exception to these conclusions was the cyclobutylmethyl compound **22**.

The Table III data show that compounds **26**, **27**, **29**, and **30**, which may be converted to **14** in vivo, were active. The difference in potencies between **26** and **14** is mainly due to a lack of parallelism in the parallel line assay so that the statistician cannot assign an absolute value but must pick the best fit. Also, the absorption rates may be different. The carboxylic acid equivalent, the tetrazole **31**, was active. The decarboxylated compound **25**, the amide **28**, the acetic acid **38**, and compound **42**, which has the oxygen removed from position 2, were either inactive or had diminished activity.

Publications concerning more in-depth biological studies will be forthcoming from our colleagues.

Experimental Section

Chemistry. Infrared spectra (Perkin-Elmer Model 197 or 297), ^1H NMR spectra (Varian A-60A or EM-390), and low-resolution mass spectra (Varian Model MAT-CH5 or MAT-CH7A) were recorded for all new compounds. Combustion analyses for C, H, and N on all new compounds for which formulas are given were performed by the Upjohn Physical and Analytical Chemistry Laboratory or by the Spang Microanalytical Laboratory and were within ±0.4% of the theoretical values unless otherwise noted. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Column chromatography was conducted by gravity, utilizing silica gel 60 (E. Merck, 70–230 mesh) or acid-washed silica gel (Mallinckrodt, 200–325 mesh). The ketones used for the preparation of the nitriles either were purchases or can be found referenced in the literature except for 4,4-dimethyl-2-decanone, which was prepared by the general procedure of Siddall and Henrick[17] and was not fully characterized.

1,2-Dihydro-2-oxo-6-alkyl-3-pyridinecarbonitriles. Method A. The crude nitrile was prepared according to the procedure of Mariella.[2] The purification procedure used is described in method B.

Method B. A mixture of equimolar portions of the ketone and ethyl formate was added slowly to a stirred mixture of an equimolar portion of sodium hydride in toluene. If hydrogen evolution did not commence after 0.1 of the mixture had been added, the reaction mixture was heated slightly until the reaction commenced or a small amount of ethanol was added until the reaction commenced. The remainder of the ketone and ethyl formate was then added with caution. The mixture was allowed to stand overnight. If a solid formed, it was collected by filtration and dried. If no solid formed, the solvent was evaporated. A mixture of the sodium enolate and an equimolar portion of cyanoacetamide in pyridine was refluxed for 1–2 days. The mixture was diluted with H_2O, acidified with H_2SO_4, and extracted with CH_2Cl_2 or EtOAc. The extract was dried over $MgSO_4$ and filtered. The crude nitrile obtained by evaporating the solvent was purified by chromatography on SiO_2. The column was eluted with mixtures of EtOAc/CH_2Cl_2, acetone/CH_2Cl_2, or MeOH/CH_2Cl_2 as determined by TLC examination of the crude nitrile. Appropriate column fractions as determined by TLC were combined if pure or were crystallized.

1,2-Dihydro-2-oxo-4-(2,2-dimethylpropyl)-3-pyridinecarbonitrile (6). To a solution of 13.12 g (80 mmol) of sodium 3-oxo-5,5-dimethylhexanal[12] in 100 mL of concentrated NH_4OH was added 4.28 g (80 mmol) of NH_4Cl. The mixture was allowed to stand at ambient temperature with occasional shaking for 17 days and was then extracted with ether (2×). The combined extracts were washed with brine, dried over $MgSO_4$, and filtered. Evaporation of the solvent left an oil. A mixture of the oil, 9.4 g (80 mmol) of ethyl cyanoacetate, 20 mL of 25% $NaOCH_3$ in MeOH, and 60 mL of MeOH was refluxed for 19 h. After evaporation of the solvent the residue was mixed with H_2O and acidified with HOAc. The solid was collected by filtration, washed with H_2O, dried, and crystallized.

1-Methyl-1,2-dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarbonitrile (7). To a stirred solution of 35.1 g (0.99 mol) of 1,2-dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarbonitrile[2] and 80 g (2 mol) of NaOH in 1 L of H_2O was added 126 g (1 mol) of dimethyl sulfate dropwise during 15 min. The mixture was then heated on a steam bath for 5 min. The cooled mixture was extracted with EtOAc (3×). The combined extracts were washed with brine, dried over $MgSO_4$, and filtered. Evaporation of the solvent left an oil that was chromatographed on SiO_2 (1.2 kg, acetone/CH_2Cl_2, 5/95). Appropriate fractions as determined by TLC were combined and crystallized.

1-Methyl-1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile (8). A stirred mixture of 10.88 g (0.06 mol) of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile,[12] 20 g (0.09 mol) of Ag_2O, 114 g (0.8 mol) of CH_3I, and 150 mL of toluene was refluxed for 25 h. The cooled mixture was filtered. Evaporation of the solvent left an oil that was chromatographed on SiO_2 (600 g, acetone/CH_2Cl_2, 0/100, 2/98, and

(17) Siddall, J. B.; Henrick, C. A. U.S. Patent 3 728 396, 1973.

5/95). Appropriate fractions as determined by TLC were combined and crystallized.

1,2-Dihydro-2-oxo-6-(1,1-dimethylethyl)-3-pyridinecarboxylic Acid (12). A mixture of 14 g (79 mmol) of 1,2-dihydro-2-oxo-6-(1,1-dimethylethyl)-3-pyridinecarbonitrile,[18] 20 g (356 mmol) of KOH, and 250 mL of 80% EtOH was refluxed for 19 h. The solvent was evaporated. The residue was dissolved in H_2O, cooled in an ice bath, and acidified with concentrated HCl. The solid was collected by filtration, washed with H_2O, and dried. A mixture of the solid, 30 g of NaOH, and 120 mL of H_2O was refluxed for 16 h. The cooled mixture was diluted with H_2O, cooled in an ice bath, and acidified with concentrated HCl. The solid was collected by filtration, washed with H_2O, and dried. The solid was warmed in MeOH/EtOH/THF. The hot mixture was filtered to remove some insoluble material. Water was added to the warm filtrate. Cooling gave 12 g (78%) of **12**, mp 254–257 °C. Anal. ($C_{10}H_{13}NO_3$) C, H, N.

1,2-Dihydro-2-oxo-4-(2,2-dimethylpropyl)-3-pyridinecarboxylic Acid (15). A stirred mixture of 1.82 g (9.56 mmol) of **6** and 10 mL of concentrated H_2SO_4 was heated at 130 °C for 23 h. To the resulting solution cooled to room temperature was added dropwise during 6 min 0.2 of a solution of 1.32 g (19.12 mmol) of $NaNO_2$ in 5 mL of H_2O. Then, the mixture was cooled in an ice bath, and the remainder of the solution was added during 24 min. The ice bath was removed, and the mixture was stirred at ambient temperature for 4 h. The solution was then heated on a steam bath for 15 min and poured on ice. The solid was collected by filtration, washed with H_2O, dried, and crystallized from acetone/hexane to give 1.54 g (77%) of **15**, mp 236–239 °C dec. Anal. ($C_{11}H_{15}NO_3$) C, H, N.

1,2-Dihydro-2-oxo-6-(3-methylbutyl)-3-pyridinecarboxylic Acid (16). A mixture of 33 g of **1** and 300 mL of concentrated HCl was refluxed for 5 h. The mixture was poured into H_2O cooled in an ice bath. The solid was collected by filtration, washed with H_2O, dried, and crystallized twice from acetone/hexane to give 20.2 g (56%) of **16**, mp 198–201 °C. Anal. ($C_{11}H_{15}NO_3$) C, H, N.

1,2-Dihydro-2-oxo-6-(1,1-dimethylpropyl)-3-pyridinecarboxylic Acid (17). A mixture of 2.5 g of **2** and 25 mL of 90% (v/v) H_2SO_4 was heated at 120 °C for 21 h. The cooled mixture was poured into H_2O. The solid was collected by filtration. A solution of the solid in acetone was treated with activated carbon and filtered. The solid obtained after evaporation of the solvent was crystallized from CH_2Cl_2/hexane to give 1.2 g (48%) of **17**, mp 148–153 °C. Anal. ($C_{11}H_{15}NO_3$) C, H, N.

1,2-Dihydro-2-oxo-6-(1,1-dimethylheptyl)-3-pyridinecarboxylic Acid (20). A mixture of 1 g of **3** and 20 mL of phosphoric acid was heated at 120 °C for 48 h. The cooled solution was poured into H_2O. The solid was collected by filtration, dried, and crystallized from CH_2Cl_2/Skellysolve B to give 0.2 g (19%) of **20**, mp 120–122 °C. Anal. ($C_{15}H_{23}NO_3$) C, H, N.

1,2-Dihydro-2-oxo-6-(2,2-dimethyloctyl)-3-pyridinecarboxylic Acid (21). To a solution of 5.3 g (20 mmol) of **4** in 30 mL of MeOH was added a solution of 3.2 g (80 mmol) of NaOH in 15 mL of H_2O followed by 6.9 mL (67 mmol) of 30% H_2O_2. The resulting solution was stirred for 18 h. After an additional 1 mL (9.7 mmol) of 30% H_2O_2 was added, the mixture was heated at 50 °C for 1.5 h. The cooled mixture was acidified with HOAc. The solid was collected by filtration, dried, and crystallized from CH_2Cl_2/Skellysolve, giving 2.3 g of a mixture of amide and a small amount of **4**. To a solution of the 2.3 g (8.2 mmol) of amide in 10 mL of concentrated H_2SO_4 was added a solution of 2.26 g (33 mmol) of $NaNO_2$ in 2 mL of H_2O. Then, 1 g (15 mmol) of $NaNO_2$ was added followed by 10 mL of concentrated H_2SO_4. After the mixture had cooled to room temperature, H_2O was added. The solid was collected by filtration. A solution of the solid in CH_2Cl_2 was dried over $MgSO_4$ and filtered. Addition of ether to the filtrate gave 0.39 g (7%) of **21**, mp 143–147 °C. Anal. ($C_{16}H_{25}NO_3$) C, H, N: calcd, 5.01; found, 5.44.

1,2-Dihydro-2-oxo-6-(1-cyclobutylmethyl)-3-pyridinecarboxylic Acid (22). A solution of 2 g (11 mmol) of **5** in 12 mL of concentrated H_2SO_4 was heated at 120 °C for 1.5 h. After the solution had cooled to room temperature, three portions of 1.0 g (14 mmol) of $NaNO_2$ were added several minutes apart. After an additional 5 min the mixture was diluted with H_2O. The solid was collected by filtration and dried. The solid was chromatographed on acid-washed SiO_2 (125 g, HOAc/EtOAc, 1/99). Appropriate fractions as determined by TLC were combined to give 1.1 g (48%) of **22**, mp 173–175 °C. Anal. ($C_{11}H_{13}NO_3$) C, H, N.

1-Methyl-1,2-dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarboxylic Acid (23). A mixture of 17.55 g (92 mmol) of **7**, 20 g (356 mmol) of KOH, and 300 mL of 80% EtOH was refluxed for 20 h. The solvent was evaporated. The residue was mixed with H_2O and extracted with EtOAc (1×). The aqueous phase was cooled in an ice bath and acidified with concentrated HCl. The mixture was extracted with EtOAc (3×). The combined extracts were washed with H_2O and with brine, dried over $MgSO_4$, and filtered. Evaporation of the solvent left a solid that was crystallized twice from acetone/hexane to give 14.8 g (77%) of **23**, mp 118–119 °C. Anal. ($C_{11}H_{15}NO_3$) C, H, N.

1-Methyl-1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxylic Acid (24). A mixture of 3.67 g (18 mmol) of **8**, 8g (143 mmol) of KOH, and 100 mL of 80% EtOH was refluxed for 46 h. The solvent was evaporated. The residue was treated with H_2O and extracted with EtOAc (2×). A solid separated in the aqueous phase and was removed by filtration. The filtrate was acidified with HOAc. The solid was collected by filtration, washed with H_2O, dried, and crystallized from acetone/hexane to give 3.42 g (85%) of **24**, mp 150–152 °C. Anal. ($C_{12}H_{17}NO_3$) C, H, N.

6-(2,2-Dimethylpropyl)-2(1*H*)-pyridinone (25). A mixture of 2 g of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] and 24 mL of 50% (v/v) H_2SO_4 was refluxed for 7 h. The solution was siluted with 50 mL of H_2O and cooled at 15 °C overnight. The solid (**14**) was removed by filtration. The filtrate was mixed with 59 g of $NaOAc{\cdot}3H_2O$. The solid was collected by filtration and slurried with CH_2Cl_2. The mixture was dried over $MgSO_4$ and filtered. Addition of hexane to the filtrate gave 0.61 g (35%) of **25**, mp 147–149 °C. Anal. ($C_{10}H_{15}NO$) C, H, N.

Sodium Salt of 1,2-Dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxylic Acid Hydrate (4/1) (26). A mixture of 10 g (47.79 mmol) of **14**,[12] 1.82 g (45.5 mmol) of NaOH, and 150 mL of distilled H_2O was heated on a steam bath for 1.5 h. The majority of the solid dissolved. The mixture was allowed to stand at ambient temperature for 64 h. The mixture was filtered, and the filter cake was washed well with distilled H_2O. The combined filtrate and washing was lypholized to give 8.21 g (77%) of **26**, mp >300 °C. Anal. ($C_{11}H_{14}NaNO_3{\cdot}0.25H_2O$) C, H, Na; N: calcd, 5.94; found 5.48.

1,2-Dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarboxamide (28). A mixture of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] and 80 mL of concentrated H_2SO_4 was shaken until a solution was obtained. The solution was allowed to stand at ambient temperature for 24 h and was then poured on ice. The solid was collected by filtration and washed with H_2O. A solution of the solid in CH_2Cl_2 was washed with H_2O and with brine, dried over $MgSO_4$, and filtered. Addition of hexane gave 7.3 g (87%) of **28**, mp 240–241.5 °C. Anal. ($C_{11}H_{16}N_2O_2$) C: calcd. 63.55; found, 62.94; H, N.

1,2-Dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinemethanol (30). A mixture of 3 g (15.5 mmol) of **29**, 0.3 g of 10% Pd–C, and 150 mL of absolute EtOH was shaken for 4 h under an initial pressure of 3.2 kg/cm^2 of H_2. The mixture was filtered, and the solvent was evaporated. The solid obtained was chromatographed on SiO_2 (400 g, MeOH/CH_2Cl_2, 5/95). Appropriate fractions as determined by TLC were combined and crystallized from CH_2Cl_2/hexane, giving 2.2 g (73%) of **30**, mp 157–159 °C. Anal. ($C_{11}H_{17}NO_2$) C, H, N.

2-(Phenylmethoxy)-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile (32). A stirred mixture of 15 g (79 mmol) of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile,[12] 12.5 g (99 mmol) of benzyl chloride, 20 g (86 mmol) of Ag_2O, and 150 mL of toluene was refluxed for 23 h. The cooled mixture was filtered, and the filter cake was washed well with CH_2Cl_2. Evaporation of the solvent from the combined filtrate and washing left an oil. The oil was chromatographed on SiO_2 (750 g, CH_2Cl_2/Skellysolve B, 1/1). Appropriate fractions as determined by TLC were combined to give 16.67 g (75%) of **32** as a yellow

(18) Barbieri, W.; Bernardi, L. *Tetrahedron* **1965**, *21*, 2453.

oil. Anal. ($C_{18}H_{20}N_2O$) C, H, N.

2-(Phenylmethoxy)-6-(2,2-dimethylpropyl)-3-pyridinecarboxylic Acid (33). A mixture of 7.0 g (25 mmol) of **32**, 8 g (143 mmol) of KOH, and 100 mL of 80% EtOH was refluxed for 45 h. The solvent was evaporated. A solution of the residue in H_2O was acidified with HOAc and cooled in an ice bath. The solid was collected by filtration and washed with H_2O. A solution of the solid in CH_2Cl_2 was washed with brine, dried over $MgSO_4$, and filtered. Addition of hexane to the filtrate gave 5.8 g (78%) of **33**, mp 96–98 °C. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

2-(Phenylmethoxy)-6-(2,2-dimethylpropyl)-3-pyridinemethanol (34). To a stirred mixture of 10.8 g (285 mmol) of $LiAlH_4$ in 100 mL of dry THF was added a solution of 46.85 g (157 mmol) of **33** in 300 mL of dry THF during 50 min. The mixture was then stirred and refluxed for 3 h, cooled in an ice bath, and decomposed by the dropwise addition of 70 mL of EtOH followed by 70 mL of H_2O. The mixture was filtered. The filter cake was washed well with THF and then with CH_2Cl_2. Evaporation of the solvent from the combined filtrate and washing left an oil containing H_2O. Toluene was added and evaporated, leaving an oil. The oil was chromatographed on SiO_2 (1100 g, EtOAc/CH_2Cl_2, 1/9). Appropriate fractions as determined by TLC were combined to give 34.6 g (77%) of **34** as a yellow oil. Anal. ($C_{18}H_{23}NO_2$) C, H, N.

2-(Phenylmethoxy)-3-(chloromethyl)-6-(2,2-dimethylpropyl)pyridine (35). A stirred solution of 30.8 g (108 mmol) of **34** in 250 mL of CH_2Cl_2 was cooled in an ice/MeOH bath. Then, 12.04 g (119 mmol) of triethylamine was added followed by 13.63 g (119 mmol) of methanesulfonyl chloride. The mixture was stirred while being cooled for 15 min and then for 26 h at ambient temperature. The solution was washed with brine, dried over $MgSO_4$, and filtered. Evaporation of the solvent left an oil. The oil was chromatographed on SiO_2 (700 g, CH_2Cl_2/Skellysolve B, 1/4). Appropriate fractions as determined by TLC were combined to give 29.0 g (88%) of **35** as a pale yellow oil. Anal. ($C_{18}H_{22}ClNO$) C, H, Cl, N.

2-(Phenylmethoxy)-3-(cyanomethyl)-6-(2,2-dimethylpropyl)pyridine (36). A mixture of 26.23 g (86.3 mmol) of **35**, 8.46 g (173 mmol) of NaCN, 8.46 g (56 mmol) of NaI, and 400 mL of 90% EtOH was refluxed for 46.5 h. The solvent was evaporated. The residue was mixed with H_2O and extracted with EtOAc (3×). The combined extracts were washed with H_2O and with brine, dried over $MgSO_4$, and filtered. Evaporation of the solvent left an oil. The oil was chromatographed on SiO_2 (1100 g, EtOAc/Skellysolve B, 1/5). Appropriate fractions as determined by TLC were combined to give 18.14 g (70%) of **36** as a pale yellow oil. Anal. ($C_{19}H_{22}N_2O$) C, H, N.

2-(Phenylmethoxy)-6-(2,2-dimethylpropyl)-3-pyridineacetic Acid (37). A mixture of 15.77 g (54 mmol) of **36**, 16 g (400 mmol) of NaOH, and 200 mL of 50% EtOH was refluxed for 40 h. The solvent was evaporated. The residue was mixed with H_2O, acidified with HOAc, and extracted with EtOAc (3×). The combined extracts were washed with H_2O and with brine, dried over $MgSO_4$, and filtered. Evaporation of the solvent left an oil containing HOAc. Toluene was added and evaporated, leaving an oil. The oil was crystallized from acetone/hexane to give 14.82 g (88%) of **37**, mp 104–105 °C. Anal. ($C_{19}H_{23}NO_3$) C, H, N.

1,2-Dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridineacetic Acid (38). A mixture of 6.27 g (20 mmol) of **37**, 1 g of 10% Pd–C, and 150 mL of absolute EtOH was shaken for 21 h under an initial pressure of 3.9 kg/cm^2 of H_2. Some of the product precipitated during the hydrogenolysis. The mixture was filtered. The filter cake was washed with CH_2Cl_2. Evaporation of the solvent from the combined filtrate and washing left 0.66 g of solid. The filter cake was digested several times in boiling THF using a total of 2 L. The hot mixtures were filtered. Evaporation of the solvent from the combined filtrates left a solid that was combined with the 0.66 g of solid and crystallized from THF/hexane to give 3.3 g (74%) of **38**, mp 252–254 °C. Anal. ($C_{12}H_{17}NO_3$) C, H, N.

2-Chloro-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile (39). A mixture of 30 g (157 mmol) of 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile[12] and 61.22 g (314 mmol) of phenylphosphonic dichloride was heated at 180 °C for 4 h. The mixture was poured on ice. The mixture was brought to pH 10 by the addition of concentrated NH_4OH. The solid was collected by filtration and dried. The solid was chromatographed on SiO_2 (250 g, CH_2Cl_2/Skellysolve B, 1/1). Appropriate fractions as determined by TLC were combined to give 15 g (75%) of **39**. A 4-g portion was sublimed at 76–85 °C under vacuum to afford 3.4 g of **39**, mp 57–60 °C. Anal. ($C_{11}H_{13}ClN_2$) C, H, Cl, N.

2-Chloro-6-(2,2-dimethylpropyl)-3-pyridinecarboxamide (40). To a mixture of 20 g (96 mmol) of **39**, 4.9 g (123 mmol) of NaOH, 20 mL of H_2O, and 150 mL of MeOH was added 22 mL (247 mmol) of 30% H_2O_2. The resulting solution was stirred for 18 h at ambient temperature. The majority of the MeOH was evaporated. The residue was mixed with H_2O. The solid was collected by filtration and dried. The filtrate was extracted with EtOAc (3×). Evaporation of the solvent from the combined extracts left a solid that was dried. The two solids were combined and chromatographed on SiO_2 (1800 g, MeOH/CH_2Cl_2, 2/98). Appropriate fractions as determined by TLC were combined to give 2.6 g of pure **40** and 12.6 g of crude **40**. The 12.6 g was chromatographed on acid-washed SiO_2 (1 kg, EtOAc/hexane, 1/1). Appropriate fractions as determined by TLC were combined to give 2.8 g of pure **40** and 2.5 g of impure **40**. The 2.5 g was crystallized twice from ether/Skellysolve B, affording 1.3 g of pure **40**. The three portions totaled 6.7 g (28%) of **40**, mp 131–134 °C. Anal. ($C_{11}H_{15}ClN_2O$) C, H, Cl, N.

6-(2,2-Dimethylpropyl)-3-pyridinecarboxamide (41). A mixture of 6.4 g (28 mmol) of **40**, 2.85 g (28 mmol) of triethylamine, 1.39 g of 10% Pd–C, and 150 mL of absolute EtOH was shaken for 3.5 h under an initial pressure of 3.5 kg/cm^2 of H_2. The mixture was filtered. The solvent was evaporated. The solid obtained was slurried with H_2O and then collected by filtration. A solution of the solid in MeOH/CH_2Cl_2 (5/95) was dried over Na_2SO_4 and filtered. Evaporation of the solvent left a solid that was crystallized from MeOH/CH_2Cl_2/ether to give 2.45 g (45%) of **41**, mp 190–193 °C. Anal. ($C_{11}H_{16}N_2O$) C, H, N.

6-(2,2-Dimethylpropyl)-3-pyridinecarboxylic Acid (42). A mixture of 2.5 g of **41** and 25 mL of concentrated HCl was heated at 105 °C for 18 h. The solution was added to ice. Solid $NaHCO_3$ was added to the mixture to pH 8. The solution was extracted with EtOAc (3×). The combined extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvent left 2.4 g of crude **42**. The 2.4 g was sublimed at 130–170 °C under vacuum to give 1.97 g (78%) of **42**, mp 187–191 °C. Anal. ($C_{11}H_{15}NO_2$) C, H, N.

Hypoglycemic Assay. Upjohn colony rats of Sprague–Dawley ancestry weighing 120–130 g were fasted for 18 h prior to dosing. A 125-mg portion (100 mg/kg) of test compound in 5 mL or 62.5 mg (25 mg/kg) of tolbutamide in 10 mL of Upjohn sterile vehicle 100 (5 mg of carboxymethylcellulose, 4 mg of Polysorbate 80, 9 mg of sodium chloride, 9 mg of benzyl alcohol, and remainder H_2O in each milliliter) and glass beads were shaken overnight prior to administration. In groups of four, the rats were dosed by stomach tube with 0.5 mL of test compound in vehicle, 0.5 mL of tobutamide in vehicle, and 0.5 mL of vehicle. Then, immediately 1.0 mL of a 12.5% glucose solution in 0.9% saline was administered subcutaneously. After 110 min the rats were injected with 0.6 mL of aqueous 3% sodium 5-allyl-5-(2-cyclopenten-2-yl)barbiturate. After 9 min the abdominal cavity was opened, and 2 mL of blood was collected from the posterior vena cava. The method of blood glucose determination and criteria for compound activity are described in ref 1. After confirmation of the initial activity, the less active compounds were tested at half-dose intervals until an inactive dose was reached, while the more potent compounds were run at half-dose intervals along with the positive control and then the relative potency was determined statistically.

Acknowledgment. The biological data were provided by G. C. Gerritsen, M. C. Blanks, and E. V. Hubert. S. A. Nash provided some chemical support.

Registry No. **1**, 98482-94-1; **2**, 86776-95-6; **3**, 98482-95-2; **4**, 98482-96-3; **5**, 98482-97-4; **6**, 98482-98-5; **7**, 86777-00-6; **8**, 98482-99-6; **9**, 609-71-2; **10**, 38116-61-9; **11**, 98483-00-2; **12**, 86776-92-3; **13**, 5407-89-6; **14**, 75587-96-1; **15**, 98483-01-3; **16**, 98483-02-4; **17**, 86776-94-5; **18**, 98483-03-5; **19**, 75588-01-1; **20**, 98483-04-6; **21**, 98483-05-7; **22**, 98483-06-8; **23**, 86776-99-0; **24**, 98509-15-0; **25**, 98483-07-9; **26**, 98483-08-0; **27**, 75587-98-3; **28**, 98483-09-1; **29**, 80066-01-9; **30**, 86777-02-8; **31**, 80065-96-9; **32**, 98483-10-4; **33**, 98483-11-5; **34**, 98483-12-6; **35**, 98483-13-7; **36**, 98483-14-8; **37**, 98483-15-9; **38**, 98483-16-0; **39**, 98483-17-1; **40**,

98483-18-2; **41**, 98483-19-3; **42**, 98483-20-6; 3,3-dimethyl-2-pentanone, 20669-04-9; 3,3-dimethyl-2-nonanone, 62399-67-1; 4,4-dimethyl-2-decanone, 98483-21-7; 3-cyclobutyl-2-propanone, 13027-76-4; cyanoacetamide, 107-91-5; ethyl formate, 109-94-4; sodium 3-oxo-5,5-dimethylhexanal, 98483-22-8; ethyl cyanoacetate, 105-56-6; 1,2-dihydro-2-oxo-6-(2-methylpropyl)-3-pyridinecarbonitrile, 80065-99-2; 1,2-dihydro-2-oxo-6-(2,2-dimethylpropyl)-3-pyridinecarbonitrile, 75587-95-0; 1,2-dihydro-2-oxo-6-(1,1-dimethylethyl)-3-pyridinecarbonitrile, 4138-19-6.

Supplementary Material Available: The mass, infrared, and ^1H NMR spectral data of all new numbered compounds (4 pages). Ordering information is given on any current masthead page.

Antiandrogenic Activity of a Series of Des-A-Steroid Derivatives

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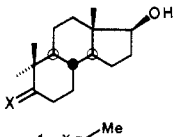
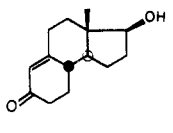
In the search for new antiandrogens, a number of des-A-steroids were prepared by condensation of Grignard reagents with lactone **3**. From the resulting key intermediates **5**, various structural modifications were performed such as the introduction of an additional unsaturation to afford dienones **8** and aromatic derivatives **10** or the introduction of an alkyl substituent mostly in position 10 (**11–13**) but also in some cases in position 16 (**22**). In addition, 13-ethyl analogues were also prepared from lactone **4**. The relative binding affinities (RBAs) for the androgen receptor of these compounds were determined under various conditions. Some compounds exhibit a capacity to interact with the receptor comparable to that of testosterone. One of the most potent compounds is 17β-hydroxy-des-A-androsta-9,11-dien-5-one (**8b**), RBA value 73% of that of testosterone. More interestingly, several compounds were found to have an antiandrogenic profile in vitro and in vivo. One of the most effective compounds is 10-ethyl-17β-hydroxy-des-A-estra-9-en-5-one (**5c**), which exhibits a strong local antiandrogenic activity in hamsters, without any significant systemic antiandrogenic effects. The corresponding 17β-acetyl derivative (RU 38882) has been selected for extended pharmacological studies.

Although some nonsteroidal compounds are known to interact with the androgen receptor and to have antiandrogenic activities,[1-3] most of the known androgens and/or antiandrogens of therapeutic interest belong to the steroid series.

However, it was reported a few years ago that several derivatives not having the usual tetracyclic system of the steroids such as 16,17-secosteroids or compounds lacking either the D or the A ring of the steroid nucleus[5-7] exhibited some weak androgenic and/or antiandrogenic activity in animals. Of particular interest is the result of Wolff and Zanati, which showed weak androgenic activity for the tricyclic derivative **1** while no hormonal activity was found for the closely related compounds **2**[7] and **5a** (racemate).[8]



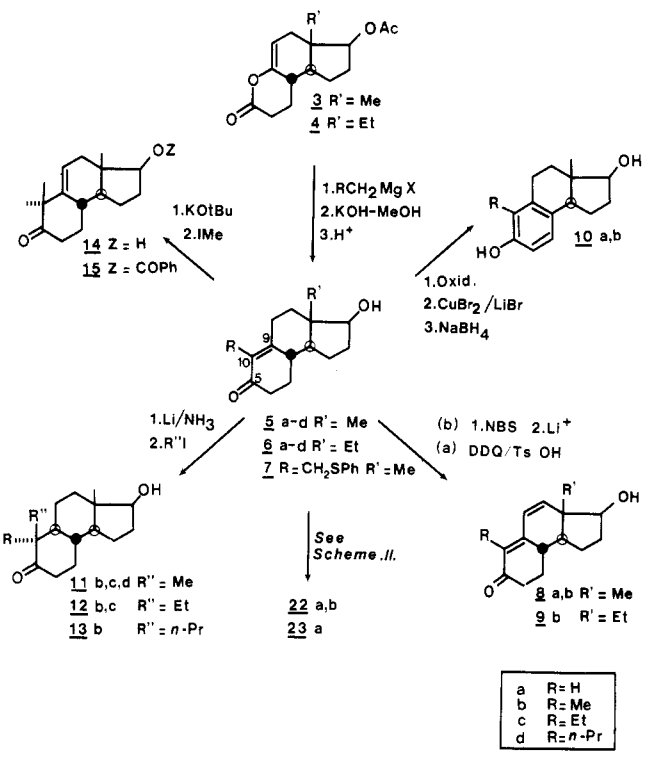
1 X = Me, H
2 X = CH_2
11b X = O



5a

As part of our steroid antihormone program, compounds **1** and **2** were prepared again and were found to be practically devoid of hormonal activities as measured by their ability to interact with the hormonal receptors. But interestingly, some intermediates of their synthesis such as the closely related ketone **11b** exhibited a relatively good affinity for the androgen receptor. This unexpected result led us to prepare a certain number of des-A-steroids starting from enones of general formulas **5** and **6**. The synthetic modifications were principally concentrated on obtaining derivatives mono- or dialkylated in position 10 with various degrees of unsaturation in the steroid nucleus

Scheme I



(Scheme I). In addition, some substrates were further alkylated in position 16 (Scheme II) since in steroid series

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(3) Raynaud, J. P.; Bonne C.; Bouton, M. M. *J. Steroid Biochem.* **1979**, *11*, 93.

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