latter compounds may arise from steric limitations of the binding of these substituents to the calcium receptor site. The β-pyridyl compound also deviates markedly from this correlation. This compound is crystallographically unique in this series because the pyridyl nitrogen is involved in an intermolecular H bond with the N1 of the 1,4-dihydropyridine ring.

Though based on only six compounds, the correlation in Figure 11 is remarkable in two respects: (1) it provides definitive clues on how the potency of these compounds might be enhanced, and (2) it is the first time, to the authors' knowledge, that crystallographic data have been directly incorporated into a quantitative structure–activity relationship.

Supplementary Material Available: Fractional atomic coordinates (Table IV), intramolecular bond distances (in angstroms) (Table V), and intramolecular bond angles (in degrees) (Table VI) for structures I–VI (6 pages). Ordering information is given on any current masthead page.

# Preparation and Antiinflammatory Activity of 2- and 4-Pyridones

James Benjamin Pierce,* Zaven S. Ariyan,[†] and Gaye Stuart Ovenden

Research Laboratories, Uniroyal Ltd., Guelph, Ontario N1G 2Y8, Canada, and Chemical Division, Uniroyal Inc., Naugatuck, Connecticut 06770. Received March 6, 1981

Several N-alkyl- and N-arylacetoacetamides have been self-condensed to form pyridones. N-Alkylacetoacetamides give 2-pyridones, while N-arylacetoacetamides give 4-pyridones. In an attempt to develop nonacidic, nonsteroidal antiinflammatory agents, the pyridones were tested in a carrageenan-induced pedal edema assay in rats. While the 2-pyridones were not active, 9 of 17 4-pyridones tested were active, and one compound (**4g**) had antiinflammatory efficacy in a dose–response assay (ED_{50} values). Most compounds were considered nontoxic by determination of approximate LD_{50} values in mice by a standard multidimensional observational assay.

The continued interest in nonacidic, nonsteroidal, safe antiinflammatory agents is an ongoing search in most pharmaceutical laboratories. The separation of antiinflammatory activity from GI toxicity, however, has been a key factor in the search for safer compounds, since it is generally agreed that gastric irritation is associated in some way with the acidic nature of such drugs.[1,2] It is reported that pyridones and their hydrogenated products piperidones exhibit good antiinflammatory activity. For example, 3-phenyl-2(1H)-pyridone[3a] is said to have a high degree of antiinflammatory activity and, similarly, 1-cycloalkoxy-2(1H)-pyridones[3b,c] exhibit the same activities. The hydrogenated products, 2-piperidones, are said to be antiinflammatory, antipyretic, and analgesic compounds.[1c] In our continued effort to discover biologically active molecules, we found that the self-condensation of N-alkyl- and N-arylacetoacetamides yielded 2- and 4-pyridones, respectively. In view of the above reported pharmaceutical activity for similar compounds, the effect of the 2- and 4-pyridones on the antiinflammatory response was evaluated in the carrageenan-induced pedal edema assay in rats.

The 2- and 4-pyridones used in this study were prepared by the self-condensation of acetoacetamides. Self-condensations of acetoacetamides under both thermal and acid-catalyzed conditions has been the subject of a number of investigations. In 1960 a German patent by Ehm[4] described the self-condensation of a number of alkyl- and arylacetoacetamides to give 2-pyridones 1 (eq 1).


$$2RNHCCH_2CMe \longrightarrow \quad (1)$$

1
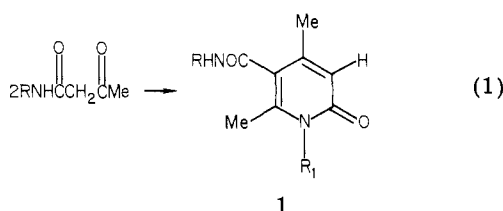
In 1966, Bukac and Sebenda[5] described a similar self-condensation for N-methyl- and N-ethylacetoacetamides. Subsequently, the isomeric structure 2 was proposed for

2   3

5   4
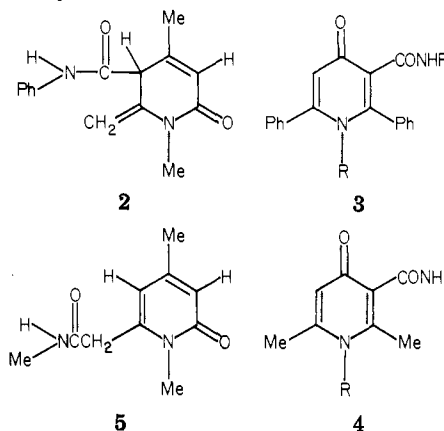
the compounds produced.[6] Zankowska-Jasinka et al.[7] have described the self-condensation of benzoylacetamides under acidic conditions to form 4-pyridones 3; in a related paper,[8] they described the succinic acid dichloride cata-

(1) E. Arrigoni-Martelli, "Inflammation and Antiinflammatories", Wiley, New York, 1977, p 208.

(2) K. D. Rainsford, K. Brane, and M. W. Whitehouse, "Aspirin and Related Drugs: Their Actions and Uses", Birkhauser, Verlag, Basel, Switzerland, 1977, p 67.

(3) (a) Merck and Co., Canadian Patents 865 755 (1971), 865 756 (1971), and 865 757 (1971); (b) Upjohn Co., U.S. Patent 3 213 100 (1965); (c) Merck and Co. Inc., U.S. Patents 3 754 088 (1973), 3 814 771 (1974), and 3 830 922 (1974).

(4) W. Ehm, German Patent 1 064 515 (1960).

(5) Z. Bukac and J. Sebenda, *Collect. Czech. Chem. Commun.*, 32, 3537 (1967).

(6) W. Ehm, *Liebigs Ann. Chem.*, 1642 (1977).

(7) W. Zankowska-Jasinska, Z. Kamela, and V. Zieba, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 23(11), 901 (1975).

(8) W. Zankowska-Jasinska and M. Reczynska-Dutka, *Zesz. Nauk. Uniw. Jagiellon., Pr. Chem.*, 21, 141 (1976).
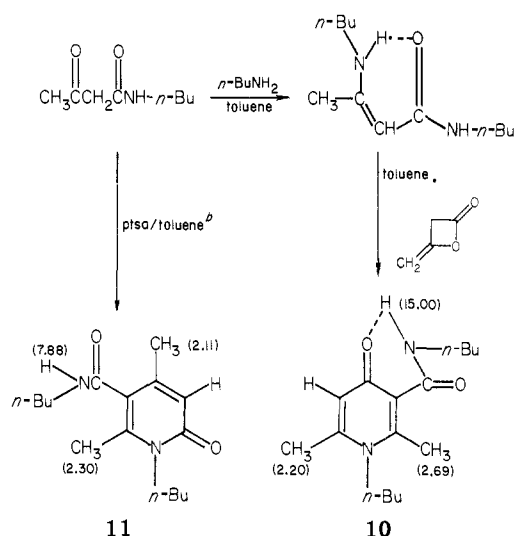
[†]Fairmount Chemical Co. Inc., Newark, NJ

Chart I[a]
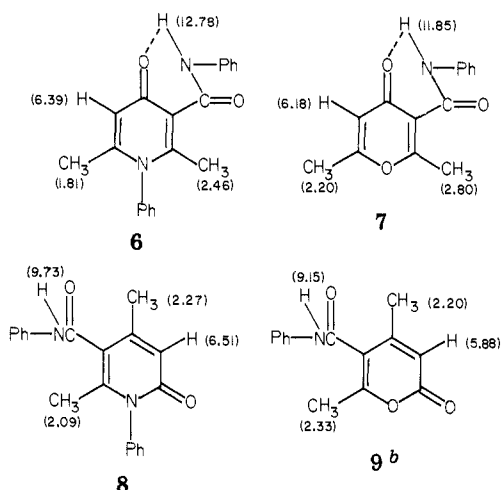
^{a} The values in parentheses are the proton chemical shifts (parts per million) for the indicated protons.
^{b} Reference 18.

Scheme I[a]

^{a} The values in parentheses are the proton chemical shifts (parts per million) for the indicated protons. ^{b} ptsa = p-toluenesulfonic acid.

lyzed self-condensation of both benzoyl and acetoacetamides to give both 4-pyridones (3 and 4) and 2-pyridones 1. Jayalakshmi et al.[9] have recently indicated that the self-condensation of N-methylacetoacetamide gives the compound 5 rather than 2 or 1 as claimed previously.

Synthetic Aspects. We have found that the self-condensation of N-arylacetoacetamides using p-tolunesulfonic acid in refluxing benzene or toluene with azeotropic removal of water gives the 4-pyridones 4, whereas N-alkyl- and N-cycloalkylacetoacetamides give mainly 2-pyridones of structure 1 and occasionally also those of structure 5. Structure 2 was also considered for these occasional products but was rejected on the basis of spectra and because attempted coversion to 1 by acid catalysis was unsuccessful.

The structures of the products were deduced mainly from a comparison of their NMR spectra with those of model pyranones. Chart I shows the structures of four related pyridones and pyranones and gives the chemical shifts for the pertinent protons. The methyl groups in both the 2-pyranone 9 and the 2-pyridone 8 have very similar shifts, and the N–H protons of the carboxanilide groups are in normal positions. However, in the 4-pyranone 7 and the 4-pyridone 6 the methyl on C_2 is in both cases at a very much different chemical shift than the methyl at C_6. This is a most notable difference between the 2- and 4-pyridones and, based on the very similar shifts noted for the known pyranones, allows a structure assignment. It is also noted that in both the 4-pyridones and the 4-pyranones the N–H of the carboxanilide group absorbs unusually far downfield (12.78 ppm) compared to what one would expect for a normal N–H of a carboxanilide group (8 to 10 ppm). This can be explained on the basis of the hydrogen bonding that can occur in the 4-keto structures 6 and 7. As expected, the N–H protons in the 2-keto structures 8 and 9 that cannot hydrogen bond absorb in the normal range. This hydrogen bonding also explains the very different chemical shifts of the C_2 vs. the C_6 methyls in the 4-keto compounds, since the C_2 methyl will be strongly influenced by the carbonyl of the hydrogen-bonded amide group in these compounds, whereas the C_6 methyl is in a more normal environment. These effects are not possible in the 2-keto

isomers, and hyrogens of both methyl groups have about the same chemical shift and appear at normal positions for such methyl groups.

As indicated above, the acid-catalyzed self-condensation of n-alkylacetoacetamides generally gives 2-pyridones. However, it has been found that the corresponding 4-pyridones are available by an adaptation of the method of Ziegler et al.[10] Thus, treatment of N-n-butylacetoacetamide with n-butylamine gave the corresponding enamine, which, when treated with diketene, gave the 4-pyridone 10. On the other hand, treatment of N-n-butylacetoacetamide with p-toluenesulfonic acid in toluene gave the 2-pyridone 11 (Scheme I). As shown in Scheme I, chemical shifts for the methyl and N–H protons were in agreement with the 4- and 2-pyridone structures, respectively.

Some chemical reactions of the pyridones were studied to provide additional compounds for testing. Both the 2- and 4-pyridones form hydrochloride salts that are only sparingly soluble in water. This often proves useful in isolating the 2- and 4-pyridones from their reaction mixtures. All the hydrochloride salts are, to some degree, unstable when heated above 100 °C, at which temperature they revert to the corresponding free base.

The 4-pyridones can be brominated with N-bromosuccinimide to form derivatives as shown in eq 2.

$$\text{Ar = Ph or } p\text{-ClPh} \tag{2}$$
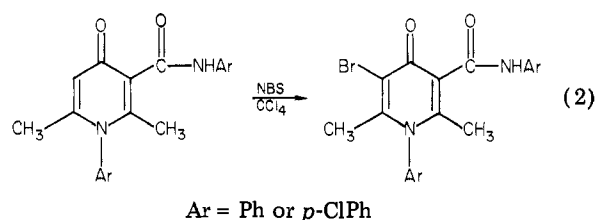
Typical preparations of the 2- and 4-pyridones 1 and 4 by the methods mentioned above are given under Experimental Section. Table I lists the compounds of type 1 and Table II those of type 4 that were prepared, along with elemental analysis, melting points, and yields for each compound.

(9)   R. Jayalakshmi, Parvathi Neelakatan, S. Nagalhuskan Rao, D. S. Iyengar, and U. T. Bhalerao, *Indian J. Chem.*, **18B**, 366 (1979).

(10)   E. Ziegler, M. Chiraza, and A. Ali, *Monatsh. Chem.*, **100**(1), 136 (1969).

Table I [a]

1a-k

no.	R	mp, °C	formula	anal.	yield, %
1a	Me	168.5–170	$C_{10}H_{14}N_2O_2$	C, H, N	67
1b	Ph·CH$_2$CH$_2$	99–102	$C_{22}H_{22}N_2O_2$	C, H, N	66.3
1c	*n*-hexyl	57–62	$C_{20}H_{34}N_2O_2$	C, H, N	63.8
1d	4-MeOPh-CH$_2$	150–154	$C_{24}H_{26}N_2O_4$	C, H, N	66.5
1e	cyclohexyl	234–236.5	$C_{20}H_{30}N_2O_2$	C, H, N	34.3
1f	cyclooctyl	176–179	$C_{24}H_{38}N_2O_2$	H, N; C [b]	31.9
1g	dodecyl	65–66	$C_{32}H_{58}N_2O_2$	C, H, N	78
1h	*n*-butyl	73.5–75.0	$C_{16}H_{26}N_2O_2$	C, H, N	69
1i	4-ClPh-CH$_2$	90–95	$C_{22}H_{20}Cl_2N_2O_2$	H, N; C [c]	21.7
1j	cyclopentyl	160.5–162	$C_{18}H_{26}N_2O_2$	C, H; N [d]	44
1k	Me(Et)-CHCH$_2$	109–110.5	$C_{18}H_{30}N_2O_2$	C, H, N	94

[a] The NMR and IR spectra of all compounds were in full accord with the proposed structures. [b] C: calcd, 74.57; found, 75.00. [c] C: Calcd, 63.04; found, 63.63. [d] N: calcd, 9.26; found, 8.54.

Table II [a]

4

no.	R	R′	R″	mp, °C	formula	anal.	yield, %
4b	2-MeOPh	Me	H	237–240	$C_{22}H_{22}N_2O_4$	C, H; N [b]	47
4d	2-MePh	Me	H	162–168	$C_{22}H_{22}N_2O_2$	C, H, N	40.5
4f	Ph	Me	H	200–205	$C_{20}H_{18}N_2O_2$	C, H, N	30
4n	Ph	Me	Br	207–210	$C_{20}H_{17}BrN_2O_2$	C, H, N	83
4h	4-ClPh	Me	H	262–268	$C_{20}H_{16}Cl_2N_2O_2$	C, H, N	44
4o	Ph	Ph	H	283–285	$C_{30}H_{22}N_2O_2$	C, H, N	9
4p	2,5-(MeO)$_2$Ph	Me	H	163–165	$C_{24}H_{26}N_2O_6$	C, H, N	43
4j	2,6-Me$_2$Ph	Me	H	156–157	$C_{24}H_{26}N_2O_2$	C, H, N	44
4m	2,4,6-Me$_3$Ph	Me	H	195–196.5	$C_{26}H_{30}N_2O_2$	C, H, N	39
	4-MeSPh	Me	H	224–226	$C_{22}H_{22}N_2O_2S_2$	C, H, N	48.5
	4-ClPh	Me	Br	292–293	$C_{20}H_{15}BrCl_2N_2O_2$	C, H, N	52
	2-MeO-5-ClPh	Me	H	214–216.5	$C_{22}H_{20}Cl_2N_2O_4$	C, H, N	64.8
	2,5-(MeO)$_2$-4-ClPh	Me	H	198.5–201	$C_{24}H_{24}Cl_2N_2O_6$	C, H; N [c]	39

[a] The NMR and IR spectra of all compounds were in full accord with the proposed structures. [b] N: calcd, 7.40; found, 6.67. [c] N: calcd, 5.52; found, 6.55.

Biological Results and Discussion

The effect of the 2- and 4-pyridones on the antiinflammatory response was evaluted at the primary level in the carrageenan-induced pedal edema assay[11] in rats. The compounds were studied for their effectiveness in preventing the edema caused by intraplanter injection of 0.5 mL of a sterile 0.1% solution of carrageenan. The compounds were administered orally and at a dose rate of 200 mg/kg 1 h prior to injection of the carrageenan into the left hind paw of the rats. At peak swelling time (3 h), the volume of edema was calculated by differential paw volume. Nonsteroidal antiinflammatory drugs, such as indomethacin, phenylbutazone, and aspirin, inhibit the formation of this edema.[12,13]

The test compound was administered at a rate of 200 mg/kg as the screening dose to detect antiinflammatory activity. If the compound was not active at this dose, it was not tested further. If is was active at this dose, subsequent lower doses were administered to determine an ED$_{50}$ value, which was calculated from a three-point dose–response curve based on the method of Swingard et al.[14] The criteria and the rationale for determining the ED$_{50}$ was defined as follows: Most compounds, including the positive standards, did not produce 100% inhibition of inflammation, even at maximally tolerated doses. Therefore, a 25% reduction in inflammation was considered a significant end point for antiinflammatory activity.

(11) C. A. Winter, E. A. Risley, and G. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(12) C. A. Winter, *Prog. Drug. Res.*, 10, 139 (1966).

(13) C. J. E. Niemegeers, F. J. Verbruggen, and P. A. J. Janssen, *J. Pharm. Pharmacol.*, 16, 810 (1964).
(14) E. A. Swingard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, 106, 319 (1962).

Table III. Pharmacology of 4-Pyridones and Their Hydrochloride Salts

no.	R	R'	R''	% reduction of Edema	ED_{50},[a] mg/kg	adrenal[b]	LD_{50},[c] mg/kg	salt or free base
4a	2-MeOPh	Me	H	26	28 (10.5-77.0)[f]	200	300	salt
4b	2-MeOPh	Me	H	6	d	d	562	free base
4c	2-MePh	Me	H	17	e	e	e	salt
4d	2-MePh	Me	H	49	80 (48.5-132)	84.8	562	free base
4e	Ph	Me	H	33	>200	d	562	salt
4f	Ph	Me	H	25	200	d	562	free base
4g	4-ClPh	Me	H	62	0.54 (0.36-0.81)	2.8	56	salt
4h	4-ClPh	Me	H	58	4.55 (2.65-7.83)	200	422	free base
4i	2,6-Me$_2$Ph	Me	H	31	e	e	e	salt
4j	2,6-Me$_2$Ph	Me	H	26	e	e	e	free base
4k	2-ClPh	Me	H	8	d	d	562	salt
4l	2-ClPh	Me	H	2	d	d	562	free base
4m	2,4,6-Me$_3$Ph	Me	H	53	e	e	e	salt
4n	Ph	Me	Br	23	d	d	562	free base
4o	Ph	Ph	H	0	d	d	562	free base
4p	2,5-(MeO)$_2$Ph	Me	H	0	d	d	562	free base
4q	2,3-Me$_2$Ph	Me	H	0	d	d	562	salt

[a] Dosage that reduced edema by at least 25% in 50% of the animals. [b] Determination the same as for the ED_{50} but using adrenalectomixed rats. [c] Determined by a standard multidimensional observational assay (ref 2). [d] Test not done because compound failed previous test. [e] Test not done. [f] Confidence limits.

The ED_{50} was thus defined as that dosage which reduced edema formation by 25% or more compared with the mean control response in 50% of the animals.

It was found that while the 2-pyridones showed little activity, several of the 4-pyridones or their HCl salts were active. The primary activity of the 4-pyridones is given in column 5 of Table III and those of the secondary carrageenan assays (ED_{50} values) are given in column 6.

Compounds that gave a satisfactory ED_{50} in the carrageenan assay were reevaluated in the adrenalectomized rat assay. The method was the same as that above except that the animals used were adrenalectomized several days prior to the assay. This test was carried out to see if the antiinflammatory activity of the test compound was indeed an observed activity of the compound or was caused by release of endogenous adrenocortical steroids. Results from this test are reported in column 7 of Table III.

From the above tests, the most active compounds were identified as 1,4-dihydro-2,6-dimethyl-N,1-bis(4-chlorophenyl)-4-oxo-3-pyridinecarboxamide (4h) and its hydrochloride salt (4g). The ED_{50} of 0.54 mg/kg (confidence limits 0.36-0.81) for compound 4g compared favorably with commercial products, such as indomethacin [ED_{50} = 1.6 mg/kg (1.1-4.9)], phenylbutazone [ED_{50} = 30 mg/kg (14-62)], and aspirin [ED_{50} = 224 mg/kg (102-490)]. However, as can be seen in Table III, there is a tenfold difference in ED_{50} and LD_{50} values between these two compounds in the normal animals but an almost 100-fold difference following adrenalectomy. One would therefore conclude that the observed antiinflammatory effect in the normal animal is probably due to the adrenal, i.e., release of endogenous adrenal cortical steroids.

We have also tested compound 4g in the developing and in the established arthritic state using the method of Newbold.[15] In this study on the developing disease, ad-

ministration of the test compound began on day 1, and on day 2 each animal was injected with 0.5 mL/kg of a 0.5% suspension of heat-killed mycobacterium tuberculosis into the plantar surface of the left paw. Foot volumes were measured by a water-displacement device on the day of administration of the mycobacterium and again on days 3, 10, and 17. The test compound was administered once daily. Compound 4g was tested at 2.5, 5, and 10 mg/kg, 5 mg/kg being more effective than 2.5 or 10 mg/kg. On day 10 of this assay, at 5 mg/kg there was a 23% inhibition in the primary lesion. This is about equivalent to what one would see with aspirin at 300 mg/kg.

For study in the established state of the disease, another group of rats was injected with the mycobacterium tuberculosis, and the foot volumes were measured; after 20 days, the foot volumes were again measured, and administration of the test compound was begun and continued for 11 days. Foot-volume measurements were repeated on day 27 and day 31. Compound 4g was almost inactive at 2.5 mg/kg, whereas at 5 mg/kg there was a significant reversal of the arthritic state. There was also a diminution in the numbers and extent of the secondary lesions in the animals. Thus, in this test 5 mg/kg would appear to be the lowest effective dose.

Experimental Section

The elemental analyses were performed by the Uniroyal Ltd. analytical group. The NMR spectra were measured on a Hitachi Perkin-Elmer R-20 spectrometer, and the IR spectra were taken on Perkin-Elmer Models 237B and 521 spectrophotometers. All spectra were in agreement with the proposed structures. Melting points are uncorrected. The following experiments were chosen to represent typical preparations of the 2- and 4-pyridones by the various procedures employed.

1,4-Dihydro-2,6-dimethyl-N,1-diphenyl-4-oxo-3-pyridinecarboxamide (4f). (A) By Self-condensation. A mixture consisting of 35.4 g (0.20 mol) of N-phenyl-3-oxobutanamide, 0.5 g of p-toluenesulfonic acid, and 200 mL of benzene was brought to reflux in a flask fitted with a Dean-Stark trap. After 24 h,

(15) B. B. Newbould, *Br. J. Pharmacol.*, 21, 127 (1963).

the mixture was cooled and washed twice with 50-mL portions of 10% aqueous NaOH to remove unreacted starting material. The benzene layer was separated and dried with anhydrous Na₂SO₄, and the benzene was then removed under reduced pressure to give a crystalline residue. This was recrystallized from 95% ethanol to give 9.5 g (30%) of the title compound, mp 200–205 °C.

(B) By Reaction of β-Anilinocrotonanilide with Diketene. To a mixture of 4 g (0.0159 mol) of β-anilinocrotonanilide in 100 mL of toluene was added dropwise 2.7 mL (0.0159 mol) of diketene (50% in acetone). The mixture was heated at reflux for 4 h and then cooled and treated with 10% HCl to precipitate the HCl salt of the desired 4-pyridone. This was filtered off and washed with acetone. It was then placed in a beaker and heated in a mixture of 50 mL of 10% aqueous NaOH and 50 mL of toluene until two clear phases were obtained. The phases were separated, and the toluene phase was cooled to precipitate the product, mp 205–207 °C. An infrared spectrum of this product was identical in every detail with the infrared spectrum of the product isolated above, i.e., that produced in A.

1,4-Dihydro-2,6-dimethyl-*N*,1-diphenyl-4-oxo-3-pyridinecarboxamide Hydrochloride (4e). A mixture consisting of 3.0 g (0.0094 mol) of 1,6-dihydro-2,6-dimethyl-*N*,1-diphenyl-4-oxo-3-pyridinecarboxamide in 50 mL of 5% aqueous hydrochloric acid was stirred in a small beaker. The solid gradually dissolved, and after 3 or 4 min the solution began to cloud and a precipitate formed. The mixture was warmed briefly on the steam bath to ensure complete reaction and then cooled and filtered. The precipitate was washed with acetone and air-dried. The yield of the title product was 3.2 g (96%), mp 260–265 °C. This hydrochloride was converted back to the free base by stirring with 10% sodium hydroxide.

***N*,1-Dibutyl-1,6-dihydro-2,4-dimethyl-6-oxo-3-pyridinecarboxamide (1h).** A mixture consisting of 34.0 g (0.216 mol) of *N*-butyl-3-oxobutanamide, 41.2 g (0.216 mol) of *p*-toluenesulfonic acid, and 400 mL of toluene was brought to reflux in a flask fitted with a Dean–Stark water trap. After 16 h, the reaction mixture was cooled. The toluene solution was washed with 250 mL of 10% NaOH and was then dried with anhydrous potassium carbonate. Addition of an equal volume to petroleum ether (bp 30–60 °C) and subsequent cooling led to the formation of crystals. The crystals were filtered to give 25.0 g of crude product. The product was recrystallized from toluene and petroleum ether (bp 30–60 °C) to give 20.9 g (69.4%) of the title compound, mp 73.5–75 °C.

***N*,1-Dibutyl-1,6-dihydro-2,4-dimethyl-6-oxo-3-pyridinecarboxamide Hydrochloride.** A solution of 5.0 g (0.018 mol) of *N*,1-dibutyl-1,6-dihydro-2,4-dimethyl-6-oxo-3-pyridinecarboxamide in 200 mL of toluene was treated with anhydrous HCl, which was bubbled in through a gas dispersion tube. A precipitate formed, and the treatment was continued until the formation of this product had ceased. The product was filtered and air-dried to give 5.3 g (94%) of the title compound, mp 145–151 °C. Anal. (C₁₆H₂₇ClN₂O₂) C, H, N.

1,4-Dihydro-2,6-dimethyl-*N*,1-di-*n*-butyl-4-oxo-3-pyridinecarboxamide (10). To a solution of 21.1 g (0.10 mol) of *N*-*n*-butyl-3-(*n*-butylamino)-2-butanamide (prepared from *N*-*n*-butyl-3-oxobutanamide and *n*-butylamine) in 200 mL of toluene was added 17 mL (0.10 mol) of diketene (50% in acetone). After complete addition, the reaction mixture was refluxed for 4 h and then allowed to cool. A solution of 100 mL of 10% aqueous HCl was then added, and the HCl salt of the above pyridone precipitated, mp 129–136 °C. This salt was filtered from the toluene–H₂O mixture and washed with toluene and then water. It was then mixed with a warm mixture of 50 mL of 10% NaOH and 150 mL of toluene. When everything was in solution the phases were separated, the toluene layer was dried with sodium sulfate, and the toluene was removed under reduced pressure to leave a yellow oil that did not crystallize. Infrared and NMR spectra of this oil were in full accord with the title structure (see Scheme I). Anal. Calcd for C₁₆H₂₆N₂O₂: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.60; H, 6.53; N, 10.63.

Self-condensation of *N*-Methylacetoacetamide (5 and 1a). A mixture consisting of 10 g (0.087 mol) of *N*-methylacetoacetamide, 0.25 g of *p*-toluenesulfonic acid, and 200 mL of toluene was brought to reflux in a flask fitted with a Dean–Stark water

trap. After 24 h the mixture was cooled and filtered to give 8.0 g of crude product. This product was recrystallized from isopropyl alcohol to give 2.3 g (14%) of 1,6-dihydro-6-oxo-*N*,1,4-trimethyl-2-pyridineacetamide (5), mp 183–185 °C (lit.⁹ mp 192 °C).

The 2-propanol and toluene filtrates were combined and the solvents were removed to leave a crystalline residue, which was taken up in cold 2-propanol; then the crystalline material was filtered off to give 3.1 g (18%) of 1,6-dihydro-1,4,6-trimethyl-6-oxo-*N*-phenyl-3-pyridinecarboxamide (1a): mp 168.5–170 °C after drying at 56 °C for 4 h; NMR (CDCl₃) δ 2.05 (s, 3 H, C₄ Me), 2.22 (s, 3 H, C₆ Me), 2.89 (d, *J* = 4.5 Hz, 3 H, NHMe), 3.29 (s, 3 H, NMe), 5.92 (s, 1 H), 7.95 (q, *J* = 4.5 Hz, 1 H, NHMe); IR (CHCl₃) ν_{max} 3450 (w), 3260 (m), 1650 (s), 1560 (s), 1530 (s), 1415 (m), 1375 (w), 1350 (m), 1315 (w), 1160 (w), 1140 (w), 1080 (w), 940 (w), 960 (m) cm⁻¹. Anal. (C₁₀H₁₄N₂O₂) C, H, N.

5-Bromo-1,4-dihydro-2,6-dimethyl-*N*,1-diphenyl-4-oxo-3-pyridinecarboxamide. A mixture consisting of 10.0 g (0.0316 mol) of 1,4-dihydro-2,6-dimethyl-*N*,1-diphenyl-4-oxo-3-pyridinecarboxamide (4f), 5.62 g (0.316 mol) of *N*-bromosuccinimide, a trace of benzoyl peroxide, and 150 mL of carbon tetrachloride was brought to reflux. After about 2 h the mixture had gelled so that stirring became difficult. The mixture was cooled and filtered. The precipitate was taken up in a hot 3:2 ethanol–water mixture, cooled to −20 °C, and then filtered to give 10.0 g (83%) of the title product, mp 200–205 °C. A small sample was recrystallized from 95% ethanol; mp 207–210 °C; NMR (CDCl₃) δ 2.18 (s, 3 H), 2.33 (s, 3 H), 6.80–7.85 (m, 10 H, aromatic), 11.99 (s, 1 H, NH); IR (CHCl₃) ν_{max} 1670 (s), 1595 (s), 1585 (s), 1530 (s), 1490 (s), 1445 (m), 1310 (m), 1270 (w), 1185 (w), 1080 (w), 1075 (w), 1005 (w), 995 (w), 700 (w), 675 (w).

1,4-Dihydro-2,6-dimethyl-*N*-phenyl-4-oxo-3-pyrancarboxamide (7). A mixture of 4.6 g (0.027 mol) of 1,4-dihydro-2,6-dimethyl-3-oxopyrancarboxylic acid¹⁶ and 7.18 g (0.027 mol) of triphenylphosphine in 50 mL of carbon tetrachloride was refluxed for 1 h to convert the acid to the acid chloride (method of Lee¹⁷). The solution was cooled and the precipitated triphenylphosphine oxide was filtered off. To the filtrate containing the acid chloride were added 2.55 g (0.027 mol) of aniline and 2.81 (0.027 mol) of triethylamine in 50 mL of carbon tetrachloride. The solution was heated to reflux for 2 h and then cooled and extracted with dilute hydrochloric acid. The organic phase was dried with Na₂SO₄, and then the solvent was removed under reduced pressure. The residue was crystallized from 95% ethanol to give 2.5 g of the title compound: mp 142–145 °C; NMR, see text; IR (CHCl₃) ν_{max} 1770, 1700, 1580, 1540, 1400, 1160, 860 cm⁻¹. Anal. (C₁₄H₁₃NO₃) C, H, N.

1,6-Dihydro-2,4-dimethyl-*N*,1-diphenyl-2-oxo-3-pyridinecarboxamide (8). The title compound can be prepared by the method of Zankowska-Jasinska et al.;⁷ however, we have prepared it in very low yield as a byproduct of the chlorination of *N*-phenyl-2-oxobutanamide with sulfuryl chloride. A mixture of 12 g (0.0678 mol) of *N*-phenyl-3-oxobutanamide in 40 mL of toluene was chlorinated by adding 9.15 g (0.0678 mol) of sulfuryl chloride dropwise but without stirring. The mixture was allowed to stand for 3 h and then was warmed to 60 °C under vacuum to remove SO₂ and HCl. The product is mainly a mixture of 2-chloro-*N*-phenyl-3-oxobutanamide 2,2-dichloro-*N*-phenyl-3-oxobutanamide, and starting material, which is mainly soluble in the toluene reaction solvent. However, some material remains insoluble in the toluene and is filtered off. This solid consists mainly of 2-chloro-*N*-phenyl-3-oxobutanamide and the desired title 3-pyridinecarboxamide. The latter was purified by mixing it with 20 mL of toluene and 10 mL of 10% aqueous HCl. The insoluble 3-pyridinecarboxamide hydrochloride salt was filtered off and air-dried, mp 222–230 °C. The free base was obtained by treatment with 10% aqueous NaOH: mp 250–253 °C; NMR, as in the text. IR (CHCl₃) ν_{max} 1660, 1600, 1545, 1500, 1445, 1325, 600 cm⁻¹. Anal. (C₂₀H₁₈N₂O₂) C, H, N.

Carrageenan-Induced Pedal Edema Assay.¹¹ Male Sprague–Dawley rats were used in the pedal edema assay. Five

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rats were used in each treatment group, the known standard group, and the vehicle control edema groups. All rats were fasted for 2 h prior to the test and water was available ad libitum. The tested compounds and standard were given orally and were dissolved or suspended in 0.25% methylcellulose. The edema control groups were administered the vehicle. One hour after administration of the test compounds, 0.05 cm³ of a 1% sterile carrageenan solution was injected into the left hindfoot pad of each rat. Three hours after injection, the paw volumes of the injected paws were measured using a modification of the apparatus described by Adamkiewicz et al.[19] In the primary assay the rate was at 200 mg/kg. ED_{50} values were obtained by using several rates to find the rate which reduced edema formation by at least 25% compared with the mean control in 50% of the rats.

Adjuvant-Induced Polyarthritis Assay.[15] Separate groups of 13 rats were used. For study in the developing arthritic state, compound **4g** was administered orally using methylcellulose as the vehicle beginning on day 1 and once daily thereafter. The dosages studied were 2.5, 5.0, and 10 mg/kg, respectively. On day 2 each animal was injected with 0.5 mL/kg of a 0.5% suspension of heat-killed mycobacterium tuberculosis into the plantar surface of the left paw. Foot volumes were measured on the day of administration of the mycobacterium and again on days 3, 10,

and 17. Body weights were recorded daily, and the animals were examined for the spread of the inflammation and the degree of secondary lesions.

For study of the established disease, another group of rats were injected with the mycobacterium and foot volumes were measured. After 20 days of foot volumes were again measured and administration of test compound was begun and continued for 11 days. Foot volume measurements were repeated on day 27 and day 31. The extent of the spread of the inflammation and the degree of lesions were recorded daily, as were the body weights. The effect of compound **4g** was measured by the percentage reduction in the paw volume as compared to the paw volume of the control groups.

LD_{50} Determinations. The LD_{50} values reported in Table III were determined by a standard multidimensional observational assay after the method of Litchfield and Wilcoxon.[20]

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α-Adrenergic Agents. 2. Synthesis and α₁-Agonist Activity of 2-Aminotetralins[1,2]

R. M. DeMarinis,* D. H. Shah, R. F. Hall, J. P. Hieble, and R. G. Pendleton

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. Received May 8, 1981

Substituted 2-aminotetralins are potent, selective, direct-acting agonists at postjunctional α₁ receptors. Within this series, substituent alterations on the ring, as well as on the nitrogen, change the potency of compounds by over three orders of magnitude (EC_{50} = 12 to >10 000 nM). It has been demonstrated experimentally that substitution at both the 5 and 8 positions of the aromatic ring produces optimum agonist potency. Removal of either substituent results in a loss of potency and efficacy relative to norepinephrine. Substitution at positions 6 and/or 7 is generally detrimental to activity. Methyl, ethyl, or dimethyl substitution on nitrogen is compatible with high agonist potency, while substitution with larger groups is not. The most potent agonist in this series is 5-(thiomethyl)-8-methoxy-2-aminotetralin, which has an EC_{50} of 12 nM.

In the last decade, a vast amount of research into the structure and function of the adrenergic nervous system has shown unequivocally that the classical α receptor can be subdivided into at least two distinct classes.[3-7] These can be pharmacologically differentiated by their ability to bind with differing affinities a series of agonists and antagonists, as well as by the physiological processes which they regulate. Since the pharmacological characteristics of the peripheral presynaptic receptor are different than those of the classical postsynaptic receptor,[3,7] agonists and

Scheme I
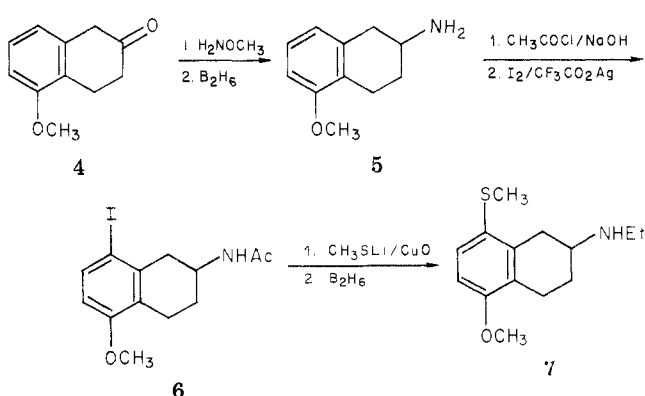
antagonists with different activities at both receptor subtypes can be found.[8]

In the peripheral vasculature, there are postjunctional receptors designed as α₁ which mediate vasoconstriction. There are also autoreceptors designated as α₂ which are

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