Notes

Synthesis and Biological Activity of a Series of 1-Aryl-3-pyrazolidinones

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The synthesis and biological evaluation of a series of 1-aryl-3-pyrazolidinones for antiinflammatory, antifertility, and, in one case, prostaglandin-like activity are presented. No significant levels of activity were observed.

The research effort involving the prostaglandins has been as ubiquitous geographically as the natural products are anatomically. Initially identified through their vasodepressor action and effect on smooth muscle, they are endogenous to most tissues and exhibit a variety of pharmacological actions when administered to animals.[1]

Due to their likely implications in cell biology, pathology, and therapeutics, as well as the synthetic challenge of their stereochemistry, an overwhelming chemical research effort has resulted, including a flood of elegant total syntheses.[2]

The attention of several laboratories has now been directed toward the synthesis of heteroprostaglandins. The synthesis of 7-thia,[3] 9-thia,[4] 11-thia,[5] 7-oxa,[6] 9-oxa,[7] 11-oxa,[8] 8-aza,[9] 9,11-dioxa,[10] and 8,12-diaza[11] prostanoids has been reported.

With the declared intention of preparing a protaglandin analogue as devoid of stereochemical features as possible, a synthetic program having as its goal the synthesis of 1-(*m*-alkoxyphenyl)pyrazolidin-3-on-2-ylalkanoic acid derivatives (1) was established. Such an approach, while reducing one's chances of finding a desirable level of activity, significantly simplifies and shortens the experimental process.

It was anticipated that pyrazolidin-3-one 1 might possess some of the structurally important features of the natural product, cf. PGE (A), namely, the five-membered ring with two polar, hetero units, the fatty acid side chain, and the hydrocarbon side chain containing an unsaturated oxygen moiety. The structural similarities of 1 and the antiinflammatory drug, phenylbutazone (B), especially in light of the remarkable correlation between potency of prostaglandin synthetase inhibitors and their antiinflammatory activity[12] should also be noted.

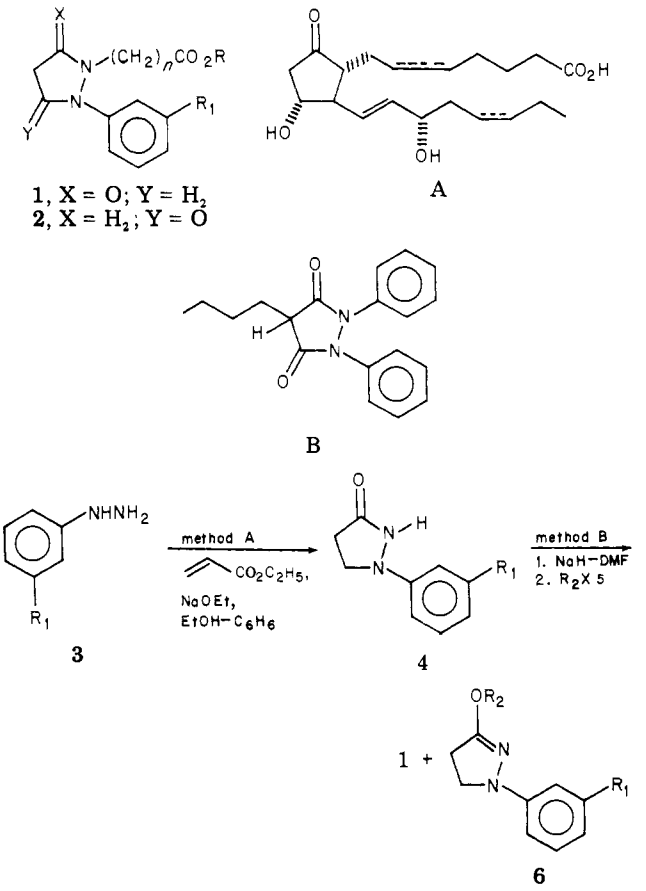
The *O*-alkyl substituent R_1 was limited to methyl and *n*-butyl. Similarly, the isomeric 3-pyrazolidinones 2[13] will not be considered.

N-Alkylation of 1-aryl-3-pyrazolidinone 4 under the appropriate conditions should, it was argued, provide the desired pyrazolidinones 1. Of the several literature procedures for pyrazolidinone ring formation,[14-16] Kendall's[14] method of heating the known hydrazine 3[17,18] and ethyl acrylate in a 50% ethanol–benzene solution containing 1.3 equiv of sodium ethoxide proved the most reliable.

Alkylation of the anion from pyrazolidinone 4 and sodium hydride in DMF with the appropriate alkyl halide 5 afforded the desired diazaprostaglandins 1 (Table I). In several cases, the O-alkylation product 6 could also be isolated. Amino acids 1m and 1n were prepared by hydrolysis of the corresponding amino esters 1d and 1c in 50% aqueous trifluoroacetic acid.

Pharmacology. As indicated in Table I, none of the pyrazolidinones 1 tested displayed more than a marginal level of antiinflammatory activity in the rat carrageenan-induced edema test.[19] All 19 compounds included in Table I were similarly devoid of antifertility activity in female rats and CNS activity in gross behavioral studies.

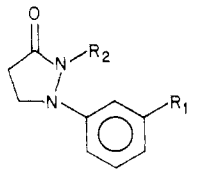
The effects of a representative amino acid, 1n, on (1) PG synthetase inhibition,[20] (2) gastric secretion,[21] (3) the rat uterus in vitro,[22] (4) the rat uterus in situ,[7] (5) the rat stomach strip,[23] and (6) the rat colon[24] were measured. Only in the rat uterus in situ was any desirable biological activity noted ($0.004 \times PGF_{2\alpha}$). On the basis of the results obtained with 1n, no further compounds were submitted for PG screening.



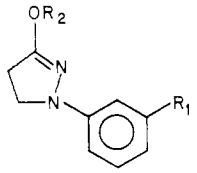
Conclusions

The structural similarities between the 1-(*m*-alkoxyphenyl)pyrazolidin-3-on-2-ylalkanoic acid derivatives

Table I. 3-Pyrazolidinones 1 and 4 and Pyrazolines 6



1 and 4



6

Compd	Mp or bp (mm), °C	Yield (%),[a] method	R_1	R_2	Emp formula	Analyses[b]	Carrageenan foot edema, % inibn[c]
1a	160-163 (0.1)	56, B	CH_3O	$CH_2CO_2C_2H_5$	$C_{14}H_{18}N_2O_4$	C, H, N	15
1b	175-185 (0.15)	69, B	n-C_4H_9O	$CH_2CO_2C_2H_5$	$C_{17}H_{24}N_2O_4$	C, H, N	12
1c	195-197 (0.5)	43, B	CH_3O	$(CH_2)_5CO_2C_2H_5$	$C_{18}H_{26}N_2O_4$	C, H, N	0
1d	270-275 (0.5)	54, B	n-C_4H_9O	$(CH_2)_5CO_2C_2H_5$	$C_{21}H_{32}N_2O_4$	C, H, N	15
1e	201-205 (0.1)	26, B	CH_3O	p-$FC_6H_4CO(CH_2)_3$	$C_{20}H_{21}N_2O_3F$	C, H, N	
1f	233-237 (0.15)	18, B	n-C_4H_9O	p-$FC_6H_4CO(CH_2)_3$	$C_{23}H_{27}N_2O_3F$	C, H, N	18
1g	97.5-98.5[d]	56, B	CH_3O	$(CH_2)_3N(CH_3)_2$	$C_{19}H_{27}N_3O$	C, H, N	21
1h	205-207 (0.1)	68, D	CH_3O	p-$FC_6H_4CHOH(CH_2)_3$	$C_{20}H_{23}N_2O_3F$	C, H, N	
1i	170-180 (0.1)	59, B	Cl	$CH_2CO_2C_2H_5$	$C_{13}H_{15}N_2O_3Cl$	C, H, N, Cl	6
1j	71-72	63, B	CF_3	$CH_2CO_2C_2H_5$	$C_{14}H_{15}N_2O_3F_3$	C, H, N	12
1k	154-164 (0.1)	50, B	CH_3O	$CH_2CH{=}CHCO_2CH_3$	$C_{15}H_{18}N_2O_4$	C, H, N	0
1l	147-151 (0.1)	51, B	n-C_4H_9O	$CH_2CH{=}CHCO_2CH_3$	$C_{18}H_{24}N_2O_4$	C, H, N	17
1m	205-210 (0.1)	85, C	n-C_4H_9O	$(CH_2)_5COOH$	$C_{19}H_{28}N_2O_4$	C, H, N	12
1n	195-205 (0.1)	81, C	CH_3O	$(CH_2)_5COOH$	$C_{16}H_{22}N_2O_4$	C, H, N	17
4a	127-128	79, A	CH_3O	H	$C_{10}H_{12}N_2O_2$	C, H, N	
4b		54, A	n-C_4H_9O	H	$C_{13}H_{16}N_2O_4$	C, H, N	
4c	125-127[e]	28, A	Cl	H	$C_9H_9N_2OCl$	C, H, N, Cl	
4d	102-103[f]	50, A	CF_3	H	$C_{10}H_9N_2OF_3$	C, H, N	
6a	54-55	37, B	CH_3O	$(CH_2)_5CO_2C_2H_5$	$C_{18}H_{26}N_2O_4$	C, H, N	
6b	205-212 (0.1)	32, B	Cl	$CH_2CO_2C_2H_5$	$C_{13}H_{15}N_2O_3Cl$	C, H, N, Cl	
6c	59.5-61.5	14, B	CF_3	$CH_2CO_2C_2H_5$	$C_{14}H_{15}N_2O_3F_3$	C, H, N	

[a] Isolated yield, not optimized. [b] Unless otherwise stated, analyses are within ±0.4% of the theoretical value. [c] A dose of 100 mg/kg po. [d] Maleate salt. [e] See ref 15. [f] Supplied by Dr. M. Eberle, Sandoz, Hanover.

described in this publication and PGE were not sufficient enough to have provided them with prostaglandin-like activity. From these data, one might postulate the requirement of both the allylic and ring hydroxyl moieties for biological activity. The pyrazolidinones also lacked the antiinflammatory activity of the structurally related phenylbutazones.

Experimental Section

General Comments. Pharmacology. The carrageenan-induced edema test[19] in rats at a dose of 100 mg/kg per os was used as the indicator of antiinflammatory activity. Fertility control testing consisted of the rat antifertility[25] test, in which a dose of 5 mg/rat/day was administered for 7 days to two female rats.

Prostaglandin-like activity was measured in the (1) PG synthetase inhibition,[20] (2) gastric secretion,[21] (3) rat uterus in vitro,[22] (4) rat uterus in situ,[7] (5) rat stomach strip,[23] and (6) rat colon[24] tests.

Chemistry. The ir spectra were recorded on a Perkin-Elmer 257 or 457 spectrometer and ^1H NMR spectra were recorded using either a Varian T-60 or A-60A spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Silica gel (0.063–0.2 mm) was used in preparing column chromatograms and analytical thin-layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of silica gel G with fluorescent indicator. In all workup procedures, the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation.

Method A.[14] Preparation of 1-Aryl-3-pyrazolidinones 4. m-Methoxyphenylhydrazine[17] (52.0 g, 0.38 mol) and ethyl acrylate (250 ml) were added to a solution prepared by dissolving Na (12.4 g, 0.54 mol) in a mixture of EtOH (225 ml) and C_6H_6 (225 ml). The resulting mixture was heated at reflux under N_2 and shielded from light for 18 h. After evaporation under reduced pressure, the residue was dissolved in H_2O and saturated with CO_2 at 0°. The resulting solid was collected by filtration and triturated with refluxing Et_2O to give 57.5 g (79%) of 1-(m-methoxyphenyl)-3-pyrazolidinone (**4a**) as a white solid, mp 127–129°.

In a similar manner, 1-(m-butoxyphenyl)hydrazine[18] gave 1-(m-butoxyphenyl)-3-pyrazolidinone (**4b**, 54%) as a white solid, which was unstable in air but could be stored under N_2 at 0° in an amber container. The m-trifluoromethyl- (**4d**) and m-chloro- (**4c**) pyrazolidinones[15] were prepared in a similar manner.

Method B. Preparation of 1-Aryl-2-alkyl-3-pyrazolidinones 1. To a suspension of NaH (2.5 g of 57% mineral oil dispersion, 60 mmol) in anhydrous DMF (200 ml) under an atmosphere of N_2 was added dropwise a solution of 1-(methoxyphenyl)-3-pyrazolidinone (**4a**, 11.5 g, 60 mmol). The mixture was stirred an additional 1 h at room temperature and then added dropwise to a refluxing solution of ethyl 6-bromohexanoate (13.8 g, 62 mmol) in anhydrous THF (100 ml). After refluxing for an additional 8 h, the mixture was cooled and filtered and the filtrate evaporated to dryness. Chromatography of the residue over silica gel (30:1) with $CHCl_3$ (500 ml) as elutent gave 7.30 g (37%) of ethyl 1-[3-(methoxyphenyl)-2-pyrazolin-3-yloxy]hexanoate (**6a**) as an oil which crystallized on standing. Recrystallization from EtOH at 0° gave **6a** as a light brown solid, mp 54–55°. Further elution with $CHCl_3$ (2 × 500 ml) provided ethyl 5-oxo-2-(m-methoxyphenyl)-1-pyrazolidinehexanoate as an oil. Distillation gave 8.60 g (43%) of **1c**, bp 195–197° (0.5 mm), as a yellow oil.

The N-alkylation products **1d–g,k,l** (Table I) were prepared in a similar manner. In the case of pyrazolidinone **1a,b,i,j** and O-alkylation products **6b,c** (Table I) the reaction was performed at room temperature.

Method C. Hydrolysis of Amino Esters 1. A solution of amino ester **1c** (0.751 g, 2.35 mmol) in 50% aqueous trifluoracetic acid (15 ml) was stirred at room temperature for 2 days. The solution was evaporated to dryness and the residue distilled affording 5.86 g (81%) of 5-oxo-2-(m-methoxyphenyl)-1-pyrazolidinehexanoic acid (**1n**) as a yellow oil: bp 195–205° (0.1 mm); homogeneous by TLC.

Amino acid **1m** was prepared in a similar manner in 85% yield.

Method D. Reduction of 3-Pyrazolidinone Ketone (1e). Sodium borohydride (0.760 g, 20 mmol) was added portionwise to a solution of ketopyrazolidinone **1e** (4.2 g, 11.8 mmol) in EtOH (50 ml) at 0°. After an additional 0.5 h at 0°, the mixture was added to H_2O (100 ml) and extracted thoroughly with Et_2O. The combined Et_2O extracts were dried and evaporated to give an oil that contained two components, as determined by TLC. Chromatography over silica gel (30:1) with $CHCl_3$–MeOH (98:2) gave 2.87 g (68%) of 2-[4-(*p*-fluorophenyl)-4-hydroxybutyl]-1-(*m*-methoxyphenyl)-3-pyrazolidinone (**1h**) as a yellow oil pure by TLC. Distillation [205–207° (0.1 mm)] provided an analytical sample.

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Diester Derivatives as Apomorphine Prodrugs

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A series of diesters of apomorphine was synthesized to serve as prodrugs. They were converted in vivo to free apomorphine, which could be detected in the brain. Stereotyped gnawing behavior and unilateral rotation similar to that produced by apomorphine were induced by all of the diesters but the time course of action of the latter was prolonged. The duration of action generally increased with the size of the ester substituent and appeared to correlate inversely with the rate of hydrolysis of the esters by liver extracts. It is concluded that the diesters serve as prodrugs of apomorphine and their prolonged duration is partly explained by a decreasing rate of hydrolysis attributable to increased steric hindrance at the acyl carbon atoms.

Literature reports have suggested the potential utility of apomorphine (1), a putative agonist of dopamine receptors, as an effective agent in the treatment of Parkinson's disease[1-7] and as an antagonist of prolactin release.[8] However, the inherent disadvantages of its short-lived neuropharmacologic effects and poor oral bioavailability have severely limited its therapeutic usefulness.

In previous communications from these laboratories[9,10] we have described the novel preparation of *O,O'*-diacetylapomorphine (2) and compared its behavioral effects to apomorphine in the rat. These drugs produced identical stereotyped gnawing behavior and provoked turning toward the contralateral side in rats previously lesioned electrothermally in the left nigrostriatal tract.[10] The dose–response relationship and time course of these effects were similar for the two drugs at the lower dose levels but the diester had a somewhat longer lasting effect at higher doses. Apomorphine, but not its diester, stimulated the

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