Synthesis and Anticonvulsant Activity of Some Substituted Lactams and Amides

Wayne J. Brouillette† and Gary L. Grunewald*,‡

Department of Chemistry, University of Alabama in Birmingham, Birmingham, Alabama 35294, and Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045. *Received June 6, 1983*

Thirteen derivatives of 3-phenyl-2-piperidinone were synthesized and evaluated for anticonvulsant activity. The most active compounds from this group included two simple lactams, 3-hydroxy-1-methyl-3-phenyl-2-piperidinone and 3-methoxy-3-phenyl-2-piperidinone, and two *N*-ethoxycarbonyl lactams, 1-(ethoxycarbonyl)-3-hydroxy-3-phenyl-2-piperidinone and 1-(ethoxycarbonyl)-3-methoxy-3-phenyl-2-piperidinone, whose anticonvulsant activity was comparable to or better than that for valproic acid. Four related acyclic amides were also prepared, but these were essentially inactive as anticonvulsants.

During the course of our synthetic studies on bicyclic imides,[1,2] several substituted lactams and amides were prepared as intermediates. These included compounds **1**, **4**, **11–15**, and **17** (See Table I). The structural similarity of lactam **4** to phenacemide (see Pharmacological Results and Discussion), as well as the reported[3] anticonvulsant activity of some simple amides, suggested that these compounds be tested as anticonvulsants. Indeed, **4** exhibited good protection in an assay using kindled rats,[4] and studies described here utilizing chemically or electrically induced convulsions confirmed the high activity of this new structural class of anticonvulsant. Furthermore, **4** showed minimal sedation. In an attempt to optimize this activity, we report here the synthesis and pharmacological evaluation of analogues of **4**.

Chemistry. Table I summarizes the structures that were evaluated in this study. We previously reported[1,2] the syntheses of compounds **1**, **4**, **11–15**, and **17**. The syntheses of the remaining compounds are described in Schemes I–III.

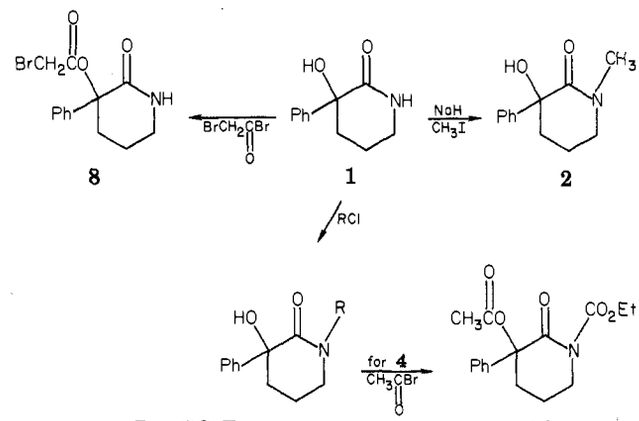
Scheme I depicts methods used for preparing *N*-acyl, *O*-acyl, and *N*-alkyl derivatives of hydroxy lactam **1**. The N-acylation procedure for preparing **6** and **7** was based upon that for the synthesis of **4**,[1] which involved heating the lactam in refluxing toluene with the appropriate chloroformate. No O-acylation was observed under these conditions, but selective O-acylation was obtained when **1** was treated under the same conditions with bromoacetyl bromide to yield **8**. Similarly, reaction of **4** with acetyl bromide provided acetate **10**. The reaction of **1** under basic conditions with methyl iodide gave a multicomponent mixture for which the major component was the *N*-methyl derivative **2**.

Scheme II gives the approach used to obtain *O*-alkyl analogues of **4**. Compound **22** was prepared from ethyl mandelate (**18**) as previously reported,[1] and hydrolysis of the tetrahydropyranyl ether in aqueous HCl afforded the hydroxy ester **23**. Treatment of **23** with NaH, followed by either methyl iodide or benzyl bromide, provided ethers **20** and **21**, respectively.

Methyl ether **20** was later prepared from ethyl mandelate (**18**) by an alternate method, also shown in Scheme II, which resulted in fewer steps and higher yield. In this method, **18** was directly converted to the methyl ether **19**, which underwent cyanoethylation to provide **20**.

Compound **20** was smoothly converted to methoxy lactam **3** via catalytic reduction of the nitrile (during which cyclization occurred), and **3** was treated with ethyl chloroformate as before to give product **5**. Reduction of the benzyl ether **21** under the same conditions similarly resulted in lactam formation, but simultaneous reduction of one of the benzyl aromatic rings occurred, providing the cyclohexylmethyl ether **24**; note that the more hindered 3-phenyl substituent remained unchanged. Compound **24**

Scheme I

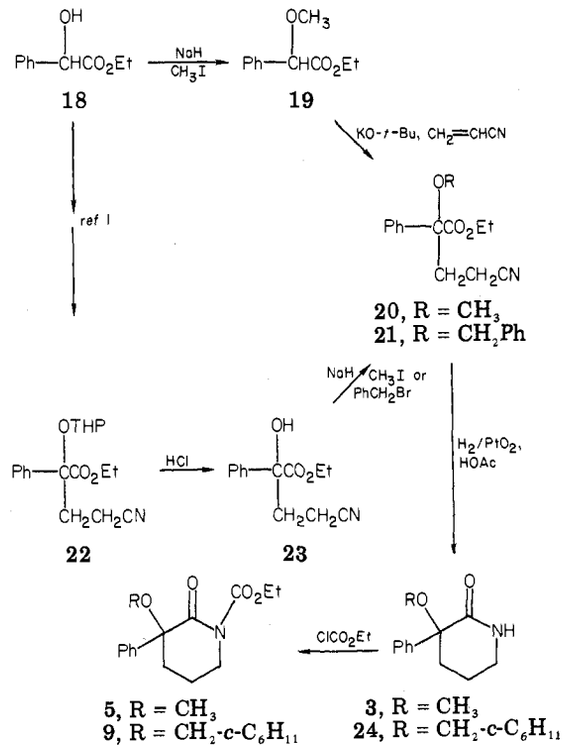


8 1 2

4, R = CO_2Et
6, R = $COCH_2Cl$
7, R = $CO_2CH(CH_3)CH_2CH_2CH_3$

10

Scheme II

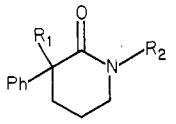


† University of Alabama in Birmingham.
‡ University of Kansas.

(1) Brouillette, W. J.; Smissman, E. E.; Grunewald, G. L. *J. Org. Chem.* **1979**, *44*, 839.
(2) Grunewald, G. L.; Brouillette, W. J. *J. Org. Chem.* **1978**, *43*, 1839.
(3) Vida, Julius A., Ed. *Med. Chem.* (*Academic*) **1977**, *15*, 1.

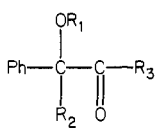
0022-2623/84/1827-0202$01.50/0

Table I. Substituted Lactams and Amides



1-13

compd	R_1	R_2	ref or scheme[a]
1	OH	H	1
2	OH	CH_3	I
3	OCH_3	H	II
4	OH	CO_2Et	2, I
5	OCH_3	CO_2Et	II
6	OH	$COCH_2Cl$	I
7	OH	$CO_2CH(CH_3)CH_2CH_2CH_3$	I
8	$OCOCH_2Br$	H	I
9	$OCH_2C_6H_{11}$	CO_2Et	II
10	$OCOCH_3$	CO_2Et	II
11	NH_2	CO_2Et	1
12	Cl	CO_2Et	1
13	H	CO_2Et	1

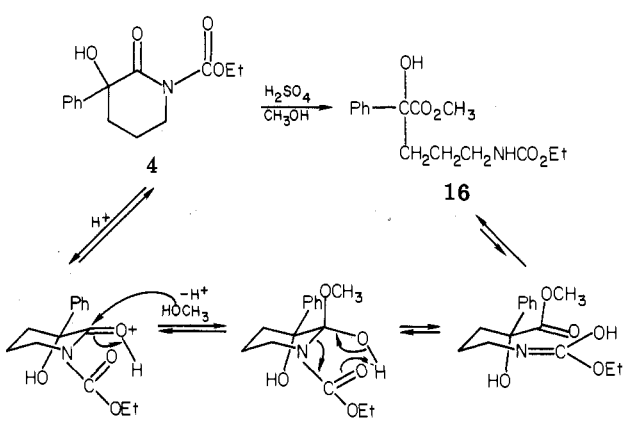


14-17

compd	R_1	R_2	R_3	ref or scheme[a]
14	H	Et	$NHCH_3$	1
15	CH_2Ph	Et	$NHCH_3$	1
16	H	$(CH_2)_3NHCO_2Et$	OCH_3	III
17	CH_2Ph	Et	$N(CH_3)CO_2Et$	1

[a] References and synthetic schemes are denoted by Arabic and Roman numerals, respectively.

Scheme III



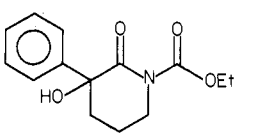
was then acylated with ethyl chloroformate as before to give **9**.

Scheme III illustrates a ring-opening reaction that was observed when **4** was treated with H_2SO_4 and CH_3OH to produce carbamate **16**. A possible mechanism is suggested.

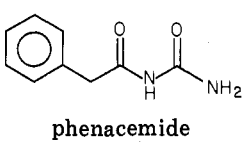
Pharmacological Results and Discussion

All compounds in Table I were evaluated as anticonvulsants in mice via the Anticonvulant Screening Project, which is conducted by the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke. The screening procedure has been described in detail by Krall et al.[5] Briefly, candidate compounds were initially subjected to a preliminary screen in a small number of mice (1-4) at dose levels of 30, 100, and 300 mg/kg. The smallest dose that produced activity was noted for separate tests involving subcutaneous Metrazol-induced convulsions (scMet), maximal electroshock-induced convulsions (MES), and a rotorod toxicity test. All tests were performed both at 30 min and 4 h following compound administration. Median effective (ED_{50}) and toxic (TD_{50}) doses were then determined in a secondary evaluation for those compounds that appeared most active in the preliminary screen. The results are given in Table II, along with the results of several known anticonvulsants as reference.

Among the compounds initially tested (**1**, **4**, **11-15**, and **17**), only carbamate **4** possessed significant anticonvulsant activity. As shown in Table II, compound **4** was found to be more potent and much less toxic than an acyclic amide such as benzochlorpropamide. Although not as potent as meprobamate (a carbamate) in the scMet test, compound **4** was approximately equipotent in the MES test and four times less toxic. As shown below **4** is structurally similar



4



phenacemide

to phenacemide, and the spectrum of activity is also similar. Note also that the overall activity for **4** is somewhat better than valproic acid, a widely used anticonvulsant.

Although **4** is structurally (and pharmacologically) similar to phenacemide, the effects of structural variations on activity appear to be different. In particular, replacement of the 3-hydroxyl group in **4** with H to provide **13** (a closer analogue of phenacemide than **4**) resulted in complete loss of activity. The importance of the hydroxyl group in **4** was further illustrated by the observation that the 3-amino analogue **11** and 3-chloro analogue **12** were significantly less potent as anticonvulsants.

Since free hydroxyl groups are good metabolic "handles" for drug conjugation and excretion, methyl ether **5** was prepared as a potential metabolically resistant analogue of **4**. However, while compound **5** was found to be as potent as **4** in the scMet test, it was less potent in the MES test. Acetate **10** (although formed from a tertiary alcohol and therefore possibly resistant to hydrolysis) was prepared as an analogue that might be transformed to **4** via ester hydrolysis in plasma, but **10** was essentially inactive as an anticonvulsant. Two analogues of **4** with presumably increased lipophilicity, **7** and **9**, also exhibited little or no anticonvulsant activity. Finally, the potential alkylating agent **6** was also found to be inactive.

While methylation did not increase the activity of **4**, both N-methylation and O-methylation of lactam **1** (inactive) resulted in greatly enhanced activity. The *O*-methyl ether **3** was the most potent of all compounds in the scMet test, the *N*-methyl derivative **2** was the most potent in the MES test, and both compounds exhibited good protective indices.

In summary, of the 17 compounds investigated for anticonvulsant activity in this study, two simple lactams (**2** and **3**) and two *N*-ethoxycarbonyl lactams (**4** and **5**) exhibited anticonvulsant activity that was comparable to or better than valproic acid and was more potent with less toxicity than a simple amide such as benzochlorpropamide.

(4) Albertson, T. E.; Peterson, S. L.; Stark, L. G. *Neuropharmacology* 1981, *20*, 597.

(5) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* 1978, *19*, 409-428.

Table II. Anticonvulsant Testing Results[a]

	preliminary screen			secondary evaluation		
	activity,[b] mg/kg			ED_{50},[c] mg/kg		TD_{50},[c] mg/kg
compd	scMet	MES	toxicity (rotorod)	scMet	MES	toxicity (rotorod)
1	>300 (0/1)[d]	>300 (0/1)	>300 (0/4)			
2	300 (4/4)	100 (1/1)	>300 (0/4)	128.24 [94.2-161.7][e]	84.40 [76.46-94.00]	350[f]
3	300 (4/4)	100 (1/1)	300 (4/4)	49.58 [32.9-73.0]	120.51 [97.4-144.6]	239.18 [211.0-272.5]
4	30 (1/1)	300 (1/1)	>300 (0/4)	123.51 [91.9-159.7]	131.71 [117.2-151.1]	451.18 [349.6-540.5]
5	300 (1/1)	300 (2/4)	>300 (0/4)	124.12 [96.0-155.5]	224.65 [195.9-260.0]	>300[g]
6	>300 (0/1)	>300 (0/1)	>300 (0/4)			
7	300 (1/4)	300 (1/1)	>300 (0/4)			
8	300 (3/4)	>300 (0/1)	>300 (0/4)			
9	>300 (0/1)	>300 (0/1)	>300 (0/4)			
10	>300 (0/1)	>300 (0/1)	>300 (0/4)			
11	300 (1/1)	300 (1/1)	100, 300 (1/4, 4/4)			
12	300 (1/1)	>300 (0/1)	>300 (0/4)			
13	>300 (0/1)	>300 (0/1)	>300 (0/4)			
14	>300 (0/1)	300 (1/1)	>300 (0/4)			
15	>300 (0/1)	>300 (0/1)	>300 (0/4)			
16	>300 (0/1)	>300 (0/1)	>300 (0/1)			
17	>300 (0/1)	>300 (0/1)	>300 (0/1)			
valproic acid[h]				149 [123-197]	272 [247-338]	426 [369-450]
phenacemide[h]				116 [70.8-150]	87.3 [73.9-99.5]	421 [337-549]
meprobamate[h]				31.5 [22.8-38.6]	120 [107-121]	125 [112-135]
benzchlorpropamide[h]				117 [127-225]	185 [158-380]	278 [245-6062]

[a] All compounds were administered intraperitoneally in 30% polyethylene glycol 400. [b] Determined 30 min after compound administration. All compounds were considerably less active (or inactive) at 4 h, and these data are therefore not included. [c] The molecular weights of 2-5 and the reference compounds are similar enough that results expressed in millimoles per kilogram would yield analogous trends. [d] Numbers in parentheses indicate number of animals protected or toxic over number tested. [e] Numbers in brackets are 95% confidence intervals. [f] Estimated graphically. [g] Value taken from preliminary screen. [h] Reference 5.

These results suggest that the above chemical classes may provide therapeutically useful anticonvulsant agents.

Experimental Section

Melting points were recorded on an Electrothermal or a Thomas-Hoover capillary metling point apparatus and are uncorrected. IR spectra were recorded on a Beckmann IR 33 or Acculab 6 spectrophotometer. ^1H NMR spectra were obtained with Varian Associates T60, EM360, or EM390 spectrometers with 1% Me_4Si as the internal standard. Electron-impact mass spectra were recorded on a Varian CH-5 spectrometer. R_f values were determined with Brinkmann precoated silica gel plates (silica gel 60 F-254, 5 × 10 cm, 0.25-mm layer). Elemental analyses, when indicated only by the symbol for the element tested, were within ±0.4% of the calculated values and were performed on a Hewlett-Packard 185B CHN Analyser at the University of Kansas or at Atlantic Microlab of Atlanta, GA.

3-Hydroxy-1-methyl-3-phenyl-2-piperidinone (2). To a solution of 2.5 g (0.013 mol) of hydroxy lactam 1[1] in 50 mL of benzene and 2.5 mL of Me_2SO (under Ar) was slowly added 0.67 g (0.38 g of NaH, 0.016 mol) of 57% NaH in mineral oil (previously washed with benzene). The mixture was stirred at 25 °C for 1 h, 1.9 g (0.013 mol) of methyl iodide was added, and stirring was continued overnight. The mixture was extracted with 3 × 20 mL of H_2O, followed by 20 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give a yellow oil. The oil was chromatographed on a 130-g silica gel column (5% EtOH/Et_2O). The fractions containing material with R_f 0.49 were combined and concentrated to provide 0.68 g (25%) of **2** as a white solid: mp 87.5–88.5 °C (Et_2O/hexane); NMR ($CDCl_3$) δ 7.3 (s, 5 H, aromatic), 4.0 (s, 1 H, OH), 3.4 (m, 2 H, CH_2N), 3.1 (s, 3 H, NCH_3), 2.5–1.5 (m, 4 H, $CH_2CH_2CH_2N$); IR (KBr) 1640 cm^{-1}. Anal. ($C_{12}H_{15}NO_2$) C, H, N.

3-Methoxy-3-phenyl-2-piperidinone (3). To a solution of 5.0 g (0.020 mol) of the nitrile **20** in 75 mL of glacial acetic acid was added 0.25 g of PtO_2. The mixture was hydrogenated on a Parr shaker at 47 psi for 7 h and filtered. The filtrate was adjusted to basic pH with 35% NaOH and extracted with 3 × 100 mL of $CHCl_3$, the extracts were dried ($MgSO_4$), and the solvent was removed under vacuum to provide 3.0 g (72%) of **3** as a white solid: mp 89.5–91 °C (Et_2O/hexane); NMR ($CDCl_3$) δ 7.3 (m, 6 H, aromatic and NH), 3.4 (m, 5 H, CH_2N and OCH_3), 2.5–1.5 (m, 4 H, $CH_2CH_2CH_2N$); IR (KBr) 1660 cm^{-1}. Anal. ($C_{12}H_{15}NO_2$) C, H, N.

1-(Ethoxycarbonyl)-3-methoxy-3-phenyl-2-piperidinone (5). A solution of 1.5 g (0.0073 mol) of methoxy lactam **3** and 1.9 g (0.018 mol) of ethyl chloroformate in 150 mL of toluene was heated at reflux for 7 h and concentrated in vacuo to yield 2.0 g (98%) of **5** as a clear oil. TLC (10% $Et_2O/CHCl_3$) showed only one spot, R_f 0.53: NMR ($CDCl_3$) δ 7.3 (s, 5 H, aromatic), 4.3 (q, 2 H, CH_2CH_3), 3.7 (m, 2 H, CH_2N), 3.3 (s, 3 H, OCH_3), 2.7–1.4 (m, 4 H, $CH_2CH_2CH_2N$), 1.4 (t, 3 H, CH_2CH_3); IR (liquid film) 1775, 1720 cm^{-1}; MS (70 eV), m/e 277 (M^+). Anal. ($C_{15}H_{19}NO_4$) C, H, N.

1-(Chloroacetyl)-3-hydroxy-3-phenyl-2-piperidinone (6). A solution of 3.0 g (0.016 mol) of lactam 1[1] and 1.9 g (0.017 mol) of chloroacetyl chloride in 300 mL of toluene was heated at reflux for 18 h and concentrated in vacuo, the residual oil was dissolved in 30 mL of Et_2O, and the solution was cooled for 12 h and filtered to yield 2.9 g (69%) of **6** as an amber solid. Recrystallization from $CHCl_3$/hexane yielded white needles: mp 106.5–108 °C; NMR ($CDCl_3$) δ 7.3 (s, 5 H, aromatic), 4.7 (s, 2 H, $COCH_2Cl$), 3.8 (m, 3 H, CH_2N and OH), 2.6–1.6 (m, 4 H, $CH_2CH_2CH_2N$); IR (KBr) 1710 (br) cm^{-1}. Anal. ($C_{13}H_{14}NO_3Cl$) C, H, N.

3-Hydroxy-1-[(2-pentyloxy)carbonyl]-3-phenyl-2-piperidinone (7). To a solution of 2.0 g (0.010 mol) of the hydroxy lactam 1[1] in 175 mL of toluene was added 4.6 g (0.030 mol) of (2-pentyloxy)carbonyl chloride.[6] The solution was heated at reflux

(6) Clinch, R. W.; Hudson, H. R. *J. Chem. Soc. B* 1971, 747.

for 24 h and concentrated in vacuo, the residue was dissolved in Et_2O, and the mixture was cooled to yield 0.93 g of starting material 1. The filtrate was concentrated, and the residue was again dissolved in Et_2O, cooled, and filtered to yield an additional 0.11 g of 1. Removal of the Et_2O yielded 1.5 g of yellow oil, which was placed on a 50-g silica gel column and eluted with 10% $CHCl_3/Et_2O$. The fractions containing material with R_f 0.40 were combined and concentrated to yield 1.1 g (72.5% based on unrecovered starting material) of **7** as a clear oil: NMR ($CDCl_3$) δ 7.4 (s, 5 H, aromatic), 5.0 [m, 1 H, $CO_2CH(CH_3)R$], 4.0 (br s, 1 H, OH), 3.7 (m, 2 H, CH_2N), 2.8–0.6 [m, 14 H, $CH_2CH_2CH_2N$ and $CO_2CH(CH_3)CH_2CH_2CH_3$]; IR (liquid film) 1775, 1720 cm^{-1}. Anal. ($C_{17}H_{23}NO_4$) C, H, N.

3-[(Bromoacetyl)oxy]-3-phenyl-2-piperidinone (8). A solution of 1.00 g (0.00525 mol) of lactam 1[1] and 1.13 g (0.00562 mol) of bromoacetyl bromide in 100 mL of benzene was heated at reflux for 4 h and concentrated in vacuo. The residual oil crystallized on standing. Recrystallization from $CHCl_3/Et_2O$ yielded 1.02 g (62.3%) of **8** as white needles: mp 188–189 °C; NMR ($CDCl_3$) δ 7.4 (m, 5 H, aromatic), 6.8 (br s, 1 H, NH), 4.0 (s, 2 H, $COCH_2Br$), 3.6–1.4 (m, 6 H, $CH_2CH_2CH_2N$); IR (KBr) 1740, 1690 cm^{-1}; MS (70 eV), *m/e* 313, 311 (M^+). Anal. ($C_{13}H_{14}NO_3Br$) C, H, N.

3-(Cyclohexylmethoxy)-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (9). A solution of 0.80 g (0.0028 mol) of the lactam **24** and 0.76 g (0.0070 mol) of ethyl chloroformate in 80 mL of toluene was heated at reflux for 12 h and concentrated to yield 1.0 g (100%) of **9** as a clear oil. TLC on silica gel (10% $Et_2O/CHCl_3$) showed only one spot, R_f 0.70: NMR ($CDCl_3$) δ 7.3 (s, 5 H, aromatic), 4.3 (q, 2 H, CH_2CH_3), 4.0–3.0 (m, 4 H, CH_2N and OCH_2R), 2.4–0.6 (m, 18 H, $CH_2CH_2CH_2N$ and cyclohexyl and CH_2CH_3); IR (liquid film) 1775, 1720 cm^{-1}. Anal. ($C_{21}H_{29}NO_4$) C, H, N.

3-(Acetyloxy)-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (10). A solution of 1.0 g (0.0038 mol) of lactam 4[2] and 0.48 g (0.0039 mol) of acetyl bromide in 100 mL of benzene was heated at reflux for 12 h and concentrated. The residual oil was crystallized from Et_2O/hexane to give 0.70 g (60%) of crude **10** as a pale yellow solid, which was recrystallized from Et_2O/hexane to give the analytical sample: mp 95.5–97 °C; NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 4.3 (q, 2 H, CH_2CH_3), 3.9 (m, 2 H, CH_2N), 3.2–1.6 (m, 7 H, $CH_2CH_2CH_2N$ and $COCH_3$), 1.3 (t, 3 H, CH_2CH_3); IR ($CHCl_3$) 1780, 1730 cm^{-1}; MS (70 eV), *m/e* 305 (M^+). Anal. ($C_{16}H_{19}NO_5$) C, H, N.

Methyl 5-[(Ethoxycarbonyl)amino]-2-hydroxy-2-phenylpentanoate (16). A solution of 0.5 g (0.002 mol) of lactam 4[2] and 2 mL of concentrated H_2SO_4 in 15 mL of anhydrous methanol was heated at reflux for 12 h and cooled, and concentrated aqueous ammonia was added until basic. The solution was filtered, the filtrate was diluted with an equal volume of water, and the aqueous mixture was extracted with 3 × 20 mL of Et_2O. The combined extracts were dried ($MgSO_4$), and the solvent was removed to yield 0.5 g of a pale yellow oil. This was crystallized from Et_2O/hexane to give 0.41 g (73%) of **16** as a white solid: mp 57–58.5 °C; NMR ($CDCl_3$) δ 7.7–7.1 (m, 5 H, aromatic), 4.8 (br s, 1 H, NH), 4.3–3.6 (m, 6 H, $CO_2CH_2CH_3$ and OH and CO_2CH_3), 3.1 (m, 2 H, CH_2NH), 2.4–1.0 (m, 7 H, $CH_2CH_2CH_2N$ and $CO_2CH_2CH_3$); IR (KBr) 1740, 1695 cm^{-1}; MS (70 eV), *m/e* 295 (M^+). Anal. ($C_{15}H_{21}NO_5$) C, H, N.

Ethyl 2-Methoxy-2-phenylacetate (19). To a solution of 10.0 g (0.0556 mol) of ethyl mandelate (**18**) in 150 mL of anhydrous DME was added 2.69 g (1.34 g of NaH, 0.0558 mol) of 50% NaH in mineral oil (previously washed with DME). To the yellow gelatinous mixture was added 7.92 g (0.0558 mol) of methyl iodide. This was stirred at room temperature for 2 h, reduced in volume on a rotary evaporator to 50 mL, and diluted with 150 mL of water, and the mixture was extracted with 3 × 75 mL of Et_2O. The combined extracts were dried ($MgSO_4$) and concentrated to yield 10.15 g (94.1%) of **19** as an orange oil. The oil was distilled to give 7.4 g of a clear oil: bp 139–141 °C (25 mm); NMR ($CDCl_3$) δ 7.6–7.3 (m, 5 H, aromatic), 4.8 (s, 1 H, PhC*H*), 4.3 (q, 2 H, CH_2CH_3), 3.5 (s, 3 H, OCH_3), 1.2 (t, 3 H, CH_2CH_3); IR (liquid film) 1745 cm^{-1}. Anal. ($C_{11}H_{14}O_3$) C, H, N.

Ethyl 4-Cyano-2-methoxy-2-phenylbutyrate (20). Procedure A. To a solution of 6.0 g (0.026 mol) of the hydroxy ester **23** in 60 mL of anhydrous DME was added 1.1 g (0.63 g NaH, 0.026 mol) of 57% NaH in mineral oil (previously washed with DME). The mixture was stirred at room temperature for 30 min, and 3.7 g (0.026 mol) of methyl iodide was added. This was heated at 40 °C for 30 min and at reflux for an additional 30 min. After stirring at room temperature for 4 h, the solution was concentrated under vacuum to half volume, diluted with 75 mL of water, and extracted with 3 × 50 mL of Et_2O. The extracts were dried ($MgSO_4$) and concentrated to provide 6.7 g of a gold oil. This was distilled to yield 5.2 g (82%) of **20** as a clear yellow oil, bp 110 °C (0.03 mm); NMR ($CDCl_3$) δ 7.3 (s, 5 H, aromatic), 4.2 (q, 2 H, CH_2CH_3), 3.3 (s, 3 H, OCH_3), 2.6 (m, 2 H, CH_2CH_2CN), 2.2 (m, 2 H, CH_2CH_2CN), 1.2 (t, 3 H, CH_2CH_3); IR (liquid film) 2250, 1730 cm^{-1}. Anal. ($C_{14}H_{17}NO_3$) C, H, N.

Procedure B. To a solution of 73.7 g (0.380 mol) of ester **19** in 400 mL of anhydrous DME was added, in portions, 4.8 g (2.4 g of NaH, 0.100 mol) of 50% NaH in mineral oil (previously washed with DME). A solution of 53.0 g (1.00 mol) of acrylonitrile in 50 mL of DME was added dropwise over 30 min, and the resulting mixture was stirred overnight at room temperature. To this were added (dropwise) 30 mL of EtOH, 150 mL of 10% HCl, and 150 mL of H_2O. The solution was extracted with 3 × 250 mL of Et_2O, the combined extracts were dried ($MgSO_4$), and the solvent was removed under vacuum to give a red oil. The oil was distilled to give 58.4 g (66.2%) of **20**, which was identical in every respect with the material produced by procedure A.

Ethyl 4-Cyano-2-(benzyloxy)-2-phenylbutyrate (21). To a solution of 5.0 g (0.021 mol) of hydroxy ester **23** in 75 mL of benzene and 2 mL of Me_2SO was added, in portions, 0.93 g (0.53 g of NaH, 0.022 mol) of 57% NaH in mineral oil. The mixture was heated at reflux for 30 min and cooled to room temperature, and 3.8 g (0.022 mol) of benzyl bromide was added. This was heated at reflux for 3 h, stirred overnight at room temperature, and extracted, respectively, with 75 mL of H_2O, 20 mL of 5% aqueous NH_3, and 50 mL of saturated aqueous NaCl. The organic layer was dried and concentrated under vacuum to yield 6.3 g of a yellow oil. The oil was chromatographed on a 150-g silica gel column (3-cm diameter) with $CHCl_3$ as eluent. The fractions containing material with R_f 0.34 were combined and concentrated to give 3.5 g (50%) of **21** as an oil. The analytical sample was obtained by chromatographing a portion of the oil on a preparative silica gel plate (20 × 20 × 0.2 cm, 10% $Et_2O/CHCl_3$), R_f 0.77: NMR ($CDCl_3$) δ 7.3 (m, 10 H, aromatic), 4.7–4.0 (m, 4 H, CH_2CH_3 and OCH_2Ph), 2.7 (m, 2 H, CH_2CN) 2.2 (m, 2 H, CH_2CN), 2.2 (m, 2 H, CH_2CH_2CN, 1.2 (t, 3 H, CH_2CH_3); IR (liquid film) 2250, 1735 cm^{-1}. Anal. ($C_{20}H_{21}NO_3$) C, H, N.

Ethyl 4-Cyano-2-hydroxy-2-phenylbutyrate (23). A solution of 15 g (0.047 mol) of the THP ether **22**[1] in 250 mL of absolute EtOH and 50 mL of 20% HCl was heated at reflux for 1 h and reduced under vacuum to half volume, 3 N NaOH was added until basic, and the resulting mixture was extracted with 3 × 100 mL of Et_2O. The combined extracts were dried ($MgSO_4$) and concentrated. The residual oil was dissolved in 20 mL of Et_2O and filtered through a bed of Celite, and the filtrate was again concentrated. Distillation of the residue afforded 5.8 g (53%) of **23** as a clear oil: bp 123 °C (0.018 mm); NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 4.2 (q, 2 H, CH_2CH_3), 3.9 (br s, 1 H, OH), 1.4 (m, 4 H, CH_2CH_2CN), 1.2 (t, 3 H, CH_2CH_3); IR (liquid film) 2250, 1730 cm^{-1}. Anal. ($C_{13}H_{15}NO_3$) C, H, N.

3-(Cyclohexylmethoxy)-3-phenyl-2-piperidinone (24). To a solution of 3.2 g (0.0099 mol) of nitrile **21** in 40 mL of glacial acetic acid was added 0.15 g of PtO_2. The mixture was hydrogenated on a Parr shaker at 47 psi for 11 h and filtered. The filtrate was diluted to 75 mL with water, adjusted to basic pH with 35% NaOH, and extracted with 3 × 65 mL of $CHCl_3$. The combined extracts were dried ($MgSO_4$) and concentrated to yield 2.8 g of an oil, for which the IR spectrum was consistent with a mixture of lactam and uncyclized amino ester. The oil was dissolved in 150 mL of toluene, heated at reflux for 3 h, and concentrated to afford an oil, which crystallized on standing. This was triturated with hexane and filtered to give 2.3 g (81%) of **24** as a white solid: mp 144–145 °C (Et_2O/hexane); NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromtic), 6.6 (br s, 1 H, NH), 3.3 (m, 4 H, OCH_2R and CH_2N), 2.5–0.5 (m, 15 H, $CH_2CH_2CH_2N$ and cyclohexyl); IR (KBr) 1680 cm^{-1}. Anal. ($C_{18}H_{25}NO_2$) C, H, N.

Acknowledgment. Support from the University of Alabama in Birmingham Graduate School (W.J.B.), NIH

Training Grant 1341 (W.J.B.), Research Grant NS 12429 (G.L.G.), and from the University of Kansas General Research Fund (G.L.G.) is gratefully acknowledged.

Registry No. 1, 65379-06-8; 2, 87532-76-1; 3, 87532-77-2; 4, 65379-07-9; 5, 87532-78-3; 6, 87532-79-4; 7, 87532-80-7; 8, 87532-81-8; 9, 87532-82-9; 10, 87532-83-0; 11, 68475-16-1; 12, 68475-11-6; 13, 68475-10-5; 14, 68475-17-2; 15, 68475-18-3; 16, 87532-84-1; 17, 68475-19-4; 18, 774-40-3; 19, 33224-90-7; 20, 87532-85-2; 21, 87532-86-3; 22, 65379-04-6; 23, 65379-03-5; 24, 87532-87-4; 2-pentyloxycarbonyl chloride, 20412-35-5; ethyl chloroformate, 541-41-3; chloroacetyl chloride, 79-04-9; bromoacetyl bromide, 598-21-0; acetyl bromide, 506-96-7; acrylonitrile, 107-13-1.

Synthesis of Imidazo[1,2-*a*]pyrazine Derivatives with Uterine-Relaxing, Antibronchospastic, and Cardiac-Stimulating Properties

Claire Sablayrolles,*[†] Gerard H. Cros,*[‡] Jean Claude Milhavet,[†] Eliane Recheng,[†] Jean-Pierre Chapat,[†] Maurice Boucard,[‡] Jean J. Serrano,[‡] and John H. McNeill*[§]

Laboratoire de Chimie Organique Pharmaceutique and Laboratoire de Pharmacodynamie, Faculte de Pharmacie, 34060 Montpellier-Cedex, France, and Division of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada, V6T 1W5. *Received July 29, 1982*

A series of imidazo[1,2-*a*]pyrazine derivatives was synthesized by condensation of α-halogenocarbonyl compounds and aminopyrazines. Various compounds resulted from competitive reactions or reagent isomerization and demonstrated in vitro uterine-relaxing and in vivo antibronchospastic activities. On isolated atria, 5-bromoimidazo[1,2-*a*]pyrazine showed positive chronotropic and inotropic properties; the latter was associated with an increase in the cyclic AMP tissue concentration. Potentiation of the isoproterenol positive inotropic effect of 5-bromoimidazo[1,2-*a*]pyrazine and the lack of blockade of the 5-bromoimidazo[1,2-*a*]pyrazine positive inotropic effect by propranolol suggested phosphodiesterase-inhibiting properties.

Several structural analogues of purines have been recently developed as potential chemotherapeutic and pharmacologically active agents.[1-3] Among the deazapurine homologues containing the pyrazine ring, only a few studies on the imidazo[1,2-*a*]pyrazine have been reported.[4-8] Recent work has shown that some compounds exhibit various pharmacological properties,[9,10] such as antiinflammatory[11,12] and β-blocking activities.[9]

The present work described the synthesis of a series of deazapurine derivatives, showing their uterine-relaxing and antibronchospastic properties and analyzing the cardiac properties and the mechanism of action of one compound of the series, the 5-bromoimidazo[1,2-*a*]pyrazine (**14**).

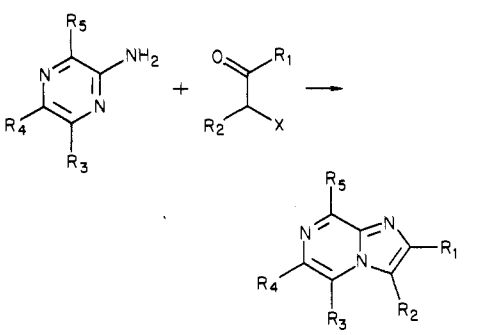
Chemistry. Condensation of α-halogenocarbonyl compounds with aminopyrazine led to some substituted imidazo[1,2-*a*]pyrazines, without the Dimroth-type rearrangement[5] (Scheme I).

In the case of ethyl 2-chloroacetoacetate condensation with aminopyrazine, three reactions occured competitively, giving simultaneously three different compounds: two imidazo[1,2-*a*]pyrazine derivatives **10** and **11** and one substituted 5*H*-pyrrolo[2,3-*b*]pyrazine, **12** (Scheme II). The ^{1}H NMR data of various final products are shown in Table I.

For most compounds (Scheme I) and both compounds **10** and **11**, the condensation resulted from a classic nucleophilic attack of the aminopyrazine endocyclic nitrogen on the 2-position of ethyl 2-chloroacetoacetate, followed by a cyclization between the primary amine function and one of the carbonyl groups (ketone or ester) of the lateral chain. For compound **11**, the chlorine atom in the 2-position can result from the rearrangement with dehydratation of an intermediate lactam–lactim hydrochloride.

Compound **12** resulted from a reaction mechanism similar to the former, in which the primary amine function of aminopyrazine was responsible for the initial nucleophilic attack. The further cyclization has been related to

Scheme I



1, $R_1 = R_2 = R_3 = R_4 = R_5 = H$; X = Cl
2, $R_1 = R_2 = R_3 = H$; $R_4 = R_5 = Br$; X = Cl
3, $R_1 = Me$; $R_2 = R_3 = R_4 = R_5 = H$; X = Cl
4, $R_1 = CH_2Cl$; $R_2 = R_3 = R_4 = R_5 = H$; X = Cl
5, $R_1 = CO_2Et$; $R_2 = R_3 = R_4 = R_5 = H$; X = Br
6, $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = CO_2Et$; X = Cl
7, $R_1 = CO_2Et$; $R_2 = R_3 = H$; $R_4 = R_5 = Br$; X = Br
8, $R_1 = CO_2Me$; $R_2 = R_3 = R_4 = R_5 = H$; X = Br
9, $R_1 = CH_2CO_2Et$; $R_2 = R_3 = H$; $R_4 = R_5 = Br$; X = Cl

[†] Faculte de Pharmacie, Laboratoire de Chimie Organique Pharmaceutique.
[‡] Faculte de Pharmacie, Laboratoire de Pharmacodynamie.
[§] University of British Columbia.

(1) Temple, D. L. Jr.; Yevich, J. P.; Catt, J. D.; Ovens, D.; Hanning, C.; Covington, R. R.; Seidehamel, R. J.; Dungan, K. W. *J. Med. Chem.* **1980**, *23*, 1188–48.
(2) Schneller, S. W.; Luo, J. K. *J. Org. Chem.* **1980**, *45*, 4045–48.
(3) Glennon, R. A.; Rogers, M. E.; Doyle Smith, J.; El-Said, M. K.; Egle, J. L. *J. Med. Chem.* **1981**, *24*, 658–61.
(4) Werbel, L. M.; Zamora, M. L.; *J. Heterocycl. Chem.* **1956**, *2*, 287–90.
(5) Guerret, P.; Jacquier, R.; Maury, G. *J. Heterocycl. Chem.* **1971**, *8*, 643–50.
(6) Arriau, J.; Chalvet, O.; Dargelos, A.; Maury, G. *J. Heterocycl. Chem.* **1974**, *11*, 1013–16.
(7) DePompei, M. F.; Paudler, W. W. *J. Heterocycl. Chem.* **1975**, *13*, 861–3.
(8) Bradac, J.; Furek, Z.; Janezic, D.; Molan, S.; Smerkolj, I.; Stanovnik, B.; Tisler, M.; Vercek, B. *J. Org. Chem.* **1977**, *42*, 4197–4201.

0022-2623/84/1827-0206$01.50/0