sample of IVb. The reaction time was 4.5 hr, and a large amount of precipitate formed during the course of the refluxing, presumably the sodium salt of IVb. Also, IVc was hydrolyzed in 50% H_2SO_4 to IVb in 90% yield; identified with an authentic sample by mixture melting point and ir. The reaction mixture was refluxed 2 hr.

3-(2,5-Dioxo-4,4-diphenyl-1-imidazolidinyl)propanamide (Id).—A mixture of 8.6 g (26.5 mmoles) of Ib and 7.5 g (63 mmoles) of $SOCl_2$ was refluxed 30 min. The resulting viscous solution of the acid chloride of Ib was poured slowly, with rapid stirring, into 42.5 ml (62.5 mmoles) of concentrated NH_4OH, while maintaining the temperature below 5° with an ice bath. After standing for 30 min the solution was filtered to yield 8 g (94%) of amide Id; recrystallized from EtOH, yield 7 g (82%), mp 181–182°; λ_{max}^{MeOH} 264 mμ (ε 437), 257.5 mμ (ε 673); no change in MeOH–HCl or MeOH–KOH; nmr (CF_3CO_2H), δ 3.00 (t, 2, CH_2CO), 4.19 (t, 2, $CH_2N(CO)_2$), 7.42 (s, 10), 7.86 ppm (s, 1, $NHCO$). *Anal.* ($C_{18}H_{17}N_3O_3$) C, H, N.

3-(2,5-Dioxo-4,4-pentamethylene-1-imidazolidinyl)propanamide (IVd).—One gram (4.5 mmoles) of IVc was added to 20 ml of concentrated H_2SO_4. The reaction mixture was held at 45–50° for 20 min, then poured over iced H_2O, and the pH was adjusted to 11, yielding 0.4 g (40%) of IVd, which, after recrystallization from H_2O, melted at 236–237°. *Anal.* ($C_{11}H_{17}N_3O_3$) N.

3-(2,5-Dioxo-4,4-pentamethylene-1-imidazolidinyl)propionanilide (IVe).—A mixture of 2.4 g (0.01 mole) of IVb, 0.93 g (0.01 mole) of aniline, and 2 g (0.013 mole) of $POCl_3$ in 75 ml of dioxane was heated on a water bath for 30 min. The mixture was then neutralized with $NaHCO_3$, diluted with H_2O to 400 ml, then concentrated until crystallization occurred upon cooling. The crude product was washed with aqueous $NaHCO_3$; recrystallized from aqueous MeOH, yield 0.8 g (25%), mp 195.5–197°. Acidification of the $NaHCO_3$ solution produced 0.9 g of unreacted IVb; nmr (CF_3CO_2H), δ 1.80 (m, 10, $(CH_2)_5$), 3.05 (t, 2, CH_2CO), 4.15 (t, 2, $CH_2N(CO)_2$), 7.41 (s, 5), 7.72 (s, 1, alicyclic $NHCO$), 9.00 ppm (s, 1, acyclic $NHCO$); λ_{max}^{MeOH} 241 mμ (ε 5727); no change in MeOH–HCl or MeOH–KOH. *Anal.* ($C_{17}H_{21}N_3O_3$) N.

Acknowledgment.—The authors are indebted to the Public Health Service (Research Grant NB 05884-01) and the National Science Foundation (Undergraduate Research Participation Program) for support of this study.

Analgetics Based on the Azetidine Ring

D. C. BISHOP, J. F. CAVALLA, I. M. LOCKHART, M. WRIGHT,

Parke, Davis and Company, Hounslow, Middlesex, England

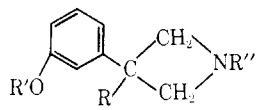
C. V. WINDER, A. WONG, AND M. STEPHENS

Parke, Davis and Company, Ann Arbor, Michigan

Received November 17, 1967

A series of azetidines of type I has been synthesized and examined for analgetic activity. The activity is comparable with that of pyrrolidines prepared previously. Relative activities within the azetidine series do not, however, closely parallel those of the corresponding pyrrolidines.

An earlier paper reported our discovery of a high level of analgesia in compounds based on the pyrrolidine ring[1] (*e.g.*, *m*-(1-methyl-3-propyl-3-pyrrolidinyl)phenol). We have now prepared several azetidines of type I.

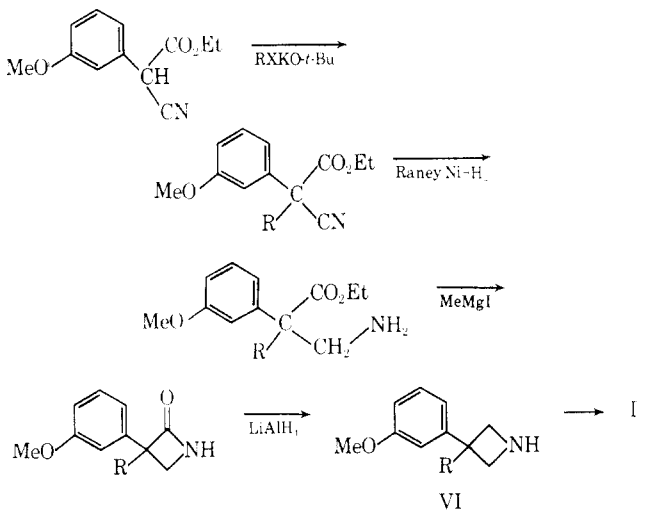


I

Even though lacking a two-carbon bridge between the basic center and the quaternary carbon atom, their relative activity as analgetics was developed to a level comparable with that of the earlier pyrrolidine compounds.

Chemistry.—Our synthetic route to key intermediates (Scheme I) closely follows that pioneered by Testa and his co-workers[2] with the exception of the method used to alkylate the aryl cyanoacetate II. It was found that using sodium ethoxide as the basic reagent[2] gave lower (~50%) yields of the C-alkylated ethyl α-(*m*-methoxyphenyl)cyanoacetate (III) than did sodium *t*-butoxide (~70%) or potassium *t*-butoxide (~90%). Ethyl α-alkyl-α-(*m*-methoxyphenyl)cyanoacetate (III) was catalytically reduced to the amine IV. An attempt

SCHEME I



VI

to prepare the azetidine by $LiAlH_4$ reduction of III and subsequent treatment of the amino alcohol with thionyl chloride and base, following our earlier method,[1] was not successful.

The catalytic reduction was markedly dependent upon the concentration of the reactants; for example, at a concentration of 5% w/v, the yield of IV (R = *n*-Pr) was 90%, at 40% w/v it was 50%. A smooth curve relating yield to concentration was obtained. These amino esters were readily cyclized to the azeti-

(1) J. F. Cavalla, D. C. Bishop, R. A. Selway, N. E. Webb, C. V. Winder, and M. Welford, *J. Med. Chem.*, **8**, 316 (1965).

(2) E. Testa, L. Fontanella, L. Mariani, and G. F. Cristiani, *Ann.*, **639**, 157 (1961); E. Testa, L. Fontanella, and G. F. Cristiani, *ibid.*, **626**, 114 (1959); E. Testa and L. Fontanella, *ibid.*, **625**, 95 (1959).

dinones V using a Grignard reagent[2] and reduced with $LiAlH_4$ to the azetidine VI. The inverse addition of the hydride to the azetidinone did not improve the yield, but purification of the product as its hydrochloride gave superior yields to those obtained by distillation.

Reductive methylation using formic acid and formaldehyde gave the N-methyl derivatives I (R'' = Me) which were converted to the phenols I (R' = H). Acetylation of the phenol was found to require milder conditions than those found satisfactory for the related pyrrolidines.[1] In certain cases, the benzyl group was used to protect the oxygen function while substitution was effected on the nitrogen atom. Notwithstanding the known stability[2] of some 3,3-disubstituted azetidine rings, we found that mild conditions were essential when acylating the nitrogen atom if untoward side effects were to be avoided.

Experimental Section[3]

The physical properties of the compounds prepared are collected in Tables I and II. The experimental details relate to those tables. The latter lists the substituted azetidines while the former gives details of the intermediates prepared.

Substituted Ethyl Cyanoacetates (III) (Table I).—Ethyl α-(*m*-methoxyphenyl)cyanoacetate[4] (II) (126 g) was slowly added to a cold solution of potassium *t*-butoxide [from potassium (22.5 g) and *t*-BuOH (500 ml)]. The resulting thick suspension was stirred during the immediate addition of an excess of the alkyl halide. The mixture, after 24 hr at 20°, was heated under reflux (1 hr), cooled, diluted with H_2O, and made just acid with dilute AcOH. The product was extracted into ether, dried ($MgSO_4$), and distilled.

Substituted Ethyl α-Aminomethylacetates (IV) (Table I).—The cyanoacetate (III) (0.1 mole) in EtOH (400 ml) was hydrogenated at 70° and 100 atm in the presence of Raney nickel (W 2, 10 g). The mildly exothermic reaction was complete in 1 hr. Filtration, concentration, and isolation with ether gave the primary amine as an oil.

Azetidinones (V) (Table I).—To a cold ethereal solution (150 ml) of MeMgI [from Mg (9.5 g) and MeI (27 ml)] was added the above amino ester (0.1 mole) in dry ether (50 ml); the mixture was left at room temperature for 3 days and hydrolyzed with NH_4Cl solution (20%, 50 ml) containing concentrated HCl (3 ml). Isolation of the neutral fraction gave the azetidinone (V).

Azetidines (VI) (Table II). Method A.—The azetidinone (0.1 mole) in dry THF (25 ml) was added dropwise to a vigorously stirred solution of $LiAlH_4$ (8 g) in dry ether (300 ml) at −20°. After addition, the mixture was stirred below 15° for 1 hr and refluxed for 3 hr, cooled to −5°, and treated with saturated NH_4Cl solution. The azetidine VI was isolated, with ether, as an oil, which was, in some cases, converted to the hydrochloride. Hydrochlorides were crystallized from *i*-PrOH–Et_2O.

N-Methylazetidines. Method B.—The above azetidine VI (0.03 mole) was treated with formaldehyde (40%, 7 ml) and formic acid (17.5 ml) following the method of Icke, *et al.*,[5] to give the N-methylazetidine as an oil.

N-Alkylazetidines. Method C.—The azetidine (VI) or 3-*m*-benzyloxyphenyl-3-propylazetidine (method H) (0.1 mole), the appropriate alkyl or phenalkyl bromide (0.1 mole), and K_2CO_3 (2 equiv) were stirred overnight in DMF (100 ml). The mixture was poured onto crushed ice and extracted with ether, and the products were distilled or recrystallized from a suitable solvent.

Azetidinylphenols. Method D.—The *m*-methoxyphenylazetidine (0.05 mole) in HBr (48%, 20 ml) was demethylated[1] to give the required azetidinylphenol, usually as a yellow powder.

Method E.—The *m*-methoxyphenylazetidine (0.02 mole) in CH_2Cl_2 (30 ml) was treated with BBr_3 (4 ml) in CH_2Cl_2 (10 ml) with stirring at −60° over a period of 15 min. The mixture was stirred at −60° for 1 hr and at room temperature for 0.5 hr. After cooling to −40°, MeOH (20 ml) was added and the solution was evaporated. The residual oil was dissolved in boiling 5 *N* NaOH. CO_2 was passed through the cooled solution and the gum which separated was extracted into ether; it normally crystallized as prisms on evaporation.

The method was slightly modified with an N-acetylazetidine. After addition of MeOH, the mixture was poured into $NaHCO_3$ solution. The phenol was isolated from the CH_2Cl_2 as a gum which was purified by distillation.

N-Acylazetidines. Method F.—The azetidine VI (0.15 mole) in redistilled triethylamine (120 ml) was treated with the appropriate acid chloride (0.15 mole) at 0° and stirred at 0° for 2 hr. The amide was isolated as an oil and purified by distillation.

1-Acetyl-3-*m*-benzyloxyphenyl-3-propylazetidine. Method G.—The N-acetylazetidinylphenol (I, R = *n*-Pr; R' = H; R'' = COMe) (0.013 mole) in DMF (10 ml) was added to a suspension of NaH [1 g, 50% suspension washed with petroleum ether (bp 40–60°)] in DMF (10 ml). The mixture was stirred for 15 min, benzyl chloride (0.014 mole) was added, and stirring was continued for 1.5 hr. The mixture was poured into H_2O, and the O-benzyl derivative was isolated from ether and recrystallized from EtOH.

Method H.—The above O-benzyl-N-acetylazetidine was hydrolyzed by refluxing with KOH in 66% aqueous EtOH at reflux for 21 hr. The azetidine was recrystallized from benzene–petroleum ether (bp 60–80°). The presumed 3-*m*-benzyloxyphenyl-3-propylazetidine (85%) had mp 130–132° but appeared to rapidly absorb CO_2. It did, however, yield satisfactory products on N-alkylation.

Method I.—The N-acetylazetidine (I, R = *n*-Pr; R' = CH_2-Ph; R'' = COMe) in ether was added to a suspension of $LiAlH_4$ (1.1 moles) in ether and refluxed for 8 hr. H_2O was added to the cooled mixture, which was filtered, and the product was isolated as an oil with EtOAc. The 3-*m*-benzyloxyphenyl-1-ethyl-3-propylazetidine was not purified but debenzylated directly (method J).

Method J.—Benzyloxyphenylazetidines were converted to the corresponding phenols by hydrogenation in EtOH in the presence of 10% Pd–C. In hydrogenating 3-(*m*-benzyloxyphenyl)-1-*p*-nitrophenethyl-3-propylazetidine, concentrated HCl (1–5% v/v) was added to the mixture; *m*-3-(1-*p*-aminophenethyl-3-propylazetidinyl)phenol hydrochloride was obtained.

***m*-3-(1-Methyl-3-propylazetidinyl)phenyl Acetate. Method K.**—*m*-3-(1-Methyl-3-propylazetidinyl)phenol (I, R = *n*-Pr; R' = H; R'' = Me) (5.9 g) and Ac_2O (6.1 ml) were boiled in ether (150 ml) for 2 hr. Freed from reagents, the product was distilled to give the acetate ester as a colorless oil.

1-Carbethoxy-3-*m*-methoxyphenyl-3-propylazetidine. Method L.—The azetidine VI (R = *n*-Pr) (3.7 g) in a 1:1 mixture of ether and Me_3N (30 ml) was treated dropwise below 10° with ethyl chloroformate (5 ml). The mixture was stirred at 20° (0.5 hr) and hydrolyzed on crushed ice and the 1-carbethoxy-3-*m*-methoxyphenyl-3-propylazetidine was isolated with ether.

3-(*m*-Methoxyphenyl)-3-propyl-1-azetidinecarboxamide. Method M.—The azetidine VI (R = *n*-Pr) as its hydrochloride (2.0 g) in H_2O (10 ml) was added to an aqueous solution (10 ml) of KCNO (0.67 g). The oil which separated solidified; the urea was recrystallized from aqueous EtOH.

Pharmacology

Acute lethal toxicities and antinociceptive (analgetic) activities were estimated in young male rats by the intraperitoneal route as described elsewhere[6] in some detail. The antinociceptive evaluation was based substantially on estimating doses causing equivalent elevations of the amount of mechanical pressure on the tail required to elicit squeaking.

(3) Melting points are corrected and were determined in a capillary tube; p*K* values were determined in 50% ethanol. Where analyses are indicated only by symbols of the elements or functions analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(4) D. K. Banerjee, J. Dutta, A. S. Rao, and E. J. Jacob, *Tetrahedron*, **8**, 163 (1960).

(5) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York N. Y., 1955, p 723.

(6) J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin, D. M. Temple, J. Wax, and C. V. Winder, *J. Med. Pharm. Chem.*, **4**, 1 (1961).

TABLE I

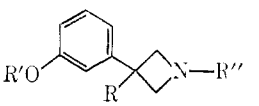
INTERMEDIATES

Compd	R	Bp, °C (mm)	pK	Yield, %	$n^{22}D$	Formula	Analyses
III	Me	112–114 (0.4)		95	1.5008	$C_{13}H_{15}NO_3$	C, H, N
III	Et	128–130 (1.0)		81	1.5040	$C_{14}H_{17}NO_3$	C, H, N
III	*n*-Pr	118–119 (0.3)		78	1.5032	$C_{15}H_{19}NO_3$	C, H, N
III	*n*-Bu	125–132 (0.5)		79	1.5043	$C_{16}H_{21}NO_3$	C, H, N
III	*n*-Am	139 (0.5)		88	1.4918	$C_{17}H_{23}NO_3$	C, H, N
IV	Me	130 (0.9)	7.56	71	1.5180	$C_{13}H_{19}NO_3$	C, H, N
IV	Et	146–150 (1.0)		43		$C_{14}H_{21}NO_3$	C, H, N
IV	*n*-Pr	143–145 (1.0)	7.77	90	1.5162	$C_{15}H_{23}NO_3$	C, H, N
IV	*n*-Bu	152–154 (1.2)		77		$C_{16}H_{25}NO_3$	C, N; H[c]
IV	*n*-Am	149 (0.7)	7.47	78	1.5065	$C_{17}H_{27}NO_3$	C, H, N
V	Me	81[a,b]		83		$C_{11}H_{13}NO_2$	C, H, N
V	Et	152–154 (0.6)		51		$C_{12}H_{15}NO_2$	C, H; N[d]
V	*n*-Pr	166 (0.6)		90	1.5360	$C_{13}H_{17}NO_2$	C, H, N
V	*n*-Bu	162 (0.5)		60		$C_{14}H_{19}NO_2$	C, H, N
V	*n*-Am	55–56[a,b]		80		$C_{15}H_{21}NO_2$	C, H, N

[a] Melting point. [b] From petroleum ether (bp 80–100°). [c] H: calcd, 9.0; found, 8.5. [d] N: calcd, 6.8; found, 6.3.

TABLE II

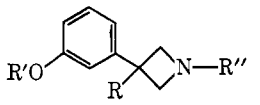
SUBSTITUTED AZETIDINES



R	R'	R''	Mp or bp, °C (mm)	pK	Method	Yield, %	$n^{22}D$	Formula	Analyses
Me	Me	H	152–153[a]	9.45	A	74		$C_{11}H_{16}ClNO$	C, H, N
Me	Me	Me	78–80 (0.2)	8.39	B	55	1.5230	$C_{12}H_{17}NO$	C, H, N
Me	H	Me	154–155	8.60	D	37		$C_{11}H_{15}NO$	C, H, N
Me	Me	$(CH_2)_2Ph$	140–142 (0.09)	8.34	C	50	1.5570	$C_{19}H_{23}NO$	C, H, N
Me	Me	$(CH_2)_2Ph$	149–150[a]		C	50		$C_{19}H_{24}ClNO$	C, H, N
Et	Me	H	114 (1.0)		A	84		$C_{12}H_{17}NO$	C, H, N
Et	Me	Me	88 (0.5)		B	74		$C_{13}H_{19}NO$	C, H, N
n-Pr	Me	H	115 (0.9)	9.44	A	60	1.5351	$C_{13}H_{19}NO$	C, H; N[g]
n-Pr	Me	H	184–185[a]	9.44	A	74		$C_{13}H_{20}ClNO$	C, H, N
n-Pr	Me	Me	117–118[a,b]	8.28	B	85		$C_{14}H_{22}ClNO$	H, N; C[h]
n-Pr	H	Me	147–149	8.53	D	85		$C_{13}H_{19}NO$	H, N; C[i]
n-Pr	COMe	Me	123–123 (0.8)	8.2	K	95	1.5074	$C_{15}H_{21}NO_2$	C, H, N
n-Pr	CH_2Ph	Me	52–53		B	53		$C_{20}H_{25}NO$	C, H, N
n-Pr	H	Et	121–123		IJ	72		$C_{14}H_{21}NO$	C, H, N
n-Pr	Me	$(CH_2)_2Ph$	174–178 (0.5)	7.6	C	50	1.5462	$C_{21}H_{27}NO$	H, N; C[j]
n-Pr	Me	$(CH_2)_2Ph$	140[a]					$C_{21}H_{28}ClNO$	C, N; H[k]
n-Pr	H	$(CH_2)_2Ph$	70–73[a,b]	11	D	50		$C_{20}H_{26}ClNO$	H, N; C[l]
n-Pr	CH_2Ph	$(CH_2)_2C_6H_4$-*p*-NO_2	114–115		C	91		$C_{27}H_{30}N_2O_3 \cdot 0.5H_2O$	C, H, N
n-Pr	Me	$(CH_2)_2C_6H_4$-*p*-NO_2	53–56	7.4	C	85		$C_{21}H_{26}N_2O_3$	C, H, N
n-Pr	Me	$(CH_2)_2C_6H_4$-*p*-NH_2	245–246[c]	3.5, 7.8	*d*	89		$C_{21}H_{30}Cl_2N_2O$	C, H, N
n-Pr	H	$(CH_2)_2C_6H_4$-*p*-NH_2	*e*		J	60		$C_{20}H_{28}Cl_2N_2O \cdot 2H_2O$	C, H, N
n-Pr	Me	COMe	162–163 (0.5)		F	65		$C_{15}H_{21}NO_2$	H, N; C[m]
n-Pr	H	COMe	98–100		E	96		$C_{14}H_{19}NO_2$	C, H, N
n-Pr	CH_2Ph	COMe	99–101		G	92		$C_{21}H_{25}NO_2 \cdot 0.25H_2O$	C, H, N
n-Pr	Me	COEt	160–163 (0.5)		F	42	1.5287	$C_{16}H_{23}NO_2$	H, N; C[n]
n-Pr	Me	CO_2Et	128–130 (0.1)		L	84		$C_{16}H_{23}NO_3$	C, H, N
n-Pr	Me	$CONH_2$	159–160		M	80		$C_{14}H_{20}N_2O_2$	C, H, N
n-Bu	Me	H	134 (1.5)		A	69		$C_{14}H_{21}NO$	C, H, N
n-Bu	Me	Me	113–114 (0.8)		B	82	1.5126	$C_{15}H_{23}NO$	C, H, N
n-Bu	H	Me	132–133		E	53		$C_{14}H_{21}NO$	C, H, N
n-Am	Me	H	104–105[a]	9.48	A	55		$C_{15}H_{24}ClNO$	C, H, N
n-Am	Me	Me	109–111 (0.45)	8.28	B	55	1.5110	$C_{16}H_{25}NO$	C, H, N
n-Am	H	Me	153–155	8.0	D	40		$C_{15}H_{23}NO$	C, H, N
n-Am	Me	$(CH_2)_2Ph$	75–82[f]		C	47		$C_{43}H_{51}NO_{10}$	C, H, N

[a] Hydrochloride. [b] Hygroscopic. [c] Dihydrochloride. [d] Prepared by catalytic hydrogenation of the corresponding nitro compound (5 g) in ethanol (60 ml) and concentrated HCl (2.8 ml) in the presence of 10% Pd–C (0.4 g). [e] Dihydrochloride dihydrate decomposing above 150°. [f] D-(−)-O,O'-ditoluyltartrate salt monohydrate, pK = 4.5 and 7.85 overlapping. [g] N: calcd, 6.8; found, 7.3. [h] C: calcd, 66.2; found, 65.7. [i] C: calcd, 76.05; found, 75.6. [j] C: calcd, 81.5; found, 81.0. [k] H: calcd, 8.9; found, 8.2. [l] C: calcd, 72.4; found, 72.9. [m] C: calcd, 72.8; found, 72.3. [n] C: calcd, 73.5; found, 72.9.

TABLE III
ACTIVITIES AND TOXICITIES



No.	R	R′	R″	Estd ip potency[a]	Estd av LD, mg of base/kg ip[b]	Pot. × LD[c] / 0.8 × 133
1	Me	H	Me	(0.3)[d,e]	141[d]	(0.4)[d,e]
2	Me	Me	H	(0.4)[e]	60	(0.2)[e]
3	Me	Me	Me	(0.3)[e]	81	(0.3)[e]
4	Me	Me	$(CH_2)_2Ph$	None[f]	63	...
5	Et	Me	Me	(1.0)[e]	35	(0.3)[e]
6	*n*-Pr	H	Me	2.4	173[g]	<3.9[g]
7	*n*-Pr	H	Et	(0.5)[e]	77	(0.4)[e]
8	*n*-Pr	H	$(CH_2)_2Ph$	1.0	...	...
				0.2[h]	244[h]	0.4[h]
9	*n*-Pr	H	$(CH_2)_2C_6H_4$-*p*-NH_2	1.6	85	1.3
10	*n*-Pr	Me	H	None[f]	65	...
11	*n*-Pr	Me	Me	1.7	63	1.0
12	*n*-Pr	Me	COEt	None[f,h]	346[h]	...
13	*n*-Pr	Me	$(CH_2)_2Ph$	0.6	109[g]	<0.6[g]
14	*n*-Pr	Me	$(CH_2)_2C_6H_4$-*p*-NH_2	(0.8)[e]	46	(0.3)[e]
15	*n*-Pr	Me	$(CH_2)_2C_6H_4$-*p*-NO_2	(0.1)[d,e]	291[d]	(<0.4)[d,e]
16	*n*-Pr	Me	$CONH_2$	(0.04)[d,e]	565[d]	(0.2)[d,e]
17	*n*-Pr	COMe	Me	2.1	122	2.4
18	*n*-Pr	CH_2Ph	Me	0.8	77[g]	<0.6[g]
19	*n*-Bu	H	Me	3.0	61	1.7
20	*n*-Bu	Me	Me	2.0	50	0.9
21	*n*-Am	H	Me	0.8	89	0.7
22	*n*-Am	Me	H	None[f]	77	...
23	*n*-Am	Me	Me	None[f,h]	71[h]	...
24	*n*-Am	Me	$(CH_2)_2Ph$	(0.1)[d,e]	210[d]	(0.3)[d,e]

[a] Relative to codeine (base/base), 30 min after treatment. [b] From small numbers of young, male, Sprague–Dawley rats of differing lots. [c] 1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidine[b] set equal to 1. [d] Suspended in saline–acacia. [e] Potency figure obtained by extrapolation. An effect equivalent to that of 11.3 mg of codeine base/kg was not actually obtained at one-fourth the estimated lethal dose. Such activity is of questionable quality.[6] [f] Inferior to 84 mg of aminopyrine/kg at one-fourth the lethal dose. [g] Incomplete solution, particularly at dose levels used for toxicity determinations. Hence, lethal dose and activity:toxicity ratio is biased upward. [h] Dissolved and/or suspended in vegetable oil.

Twenty-four of the 34 azetidines listed in Table II were studied as shown in Table III. Of the ten compounds not studied, three bases [I: R = R′ = Me, R″ = $(CH_2)_2Ph$; R = *n*-Pr, R′ = Me, R″ = H; and R = *n*-Pr, R′ = Me, R″ = $(CH_2)_2Ph$] had been substantially converted to respective hydrochlorides listed immediately following them in Table II. Two secondary amines (I: R = Et, R′ = Me, R″ = H; and R = *n*-Bu, R′ = Me, R″ = H) had been N-methylated, the tertiary amines presumably being more pertinent for study as analgetics (*cf.* pyrrolidines,[1] and azetidines **10** *vs.* **11** in Table III). Three ethers [I: R = *n*-Pr, R′ = CH_2Ph, R″ = $(CH_2)_2C_6H_4$-*p*-NO_2; R = *n*-Pr, R′ = Me, R″ = COMe; and R = *n*-Pr, R′ = CH_2Ph, R″ = COMe] had been used as intermediates for phenols [I: R = *n*-Pr, R′ = H, R″ = $(CH_2)_2C_6H_4$-*p*-NH_2; R = *n*-Pr, R′ = H, R″ = COMe; and R = *n*-Pr, R′ = H, R″ = Et] of greater potential interest (*cf.* pyrrolidines,[1] and azetidines **6** *vs.* **11** and **18**, **8** *vs.* **13**, and **9** *vs.* **14** in Table III). Of the second of these phenols, however, there was insufficient sample for evaluation. One compound (I, R = *n*-Pr; R′ = Me; R″ = CO_2Et) in which analgetic activity was not anticipated (*cf.* Table III, **12**) had been submitted for more general observation of effects on the central nervous system in mice without evidence of properties of interest (G. M. Chen and D. A. McCarthy, personal communication).

When possible, soluble hydrochloride salts, or bases with equivalent HCl, were dissolved in 1 ml of 0.9% w/v NaCl/100 g of rat. Exceptions forced by poor solubilities are noted in Table III.

Certain structure–activity relationships among these azetidines resemble those of the corresponding pyrrolidines.[1] Thus, substitution of an oxygen function in the *meta* position on the phenyl nucleus leads to antinociceptive activity though it has not been shown to be a requirement as was shown for the pyrrolidines. Among oxygen functions the phenol is again more active than the methyl ether (Table III, **6** *vs.* **11**, **8** *vs.* **13**, **9** *vs.* **14**, **19** *vs.* **20**, **21** *vs.* **23**) and less toxic (**9** *vs.* **14**, **19** *vs.* **20**, **21** *vs.* **23**). The activity of an ester was again intermediate (**6** > **17** > **11**) and, by analogy with the pyrrolidines, may be due to hydrolysis to the phenol. Limitations of substitution to positions 1 and 3 on the heterocyclic nucleus again allowed activity, though it was not shown to be superior to conditions of further alkyl substitution as in the pyrrolidines. Tertiary alkylation of the nitrogen was, apparently, again required for clear activity (**10** *vs.* **11**) and methylation was again, so far as studied, superior to higher unbranched alkylation (**6** *vs.* **7**).

However, on going from N-methylation to N-phenethylation, sharp divergence in structure–activity relationships occurs between the azetidines and the pyrrolidines. In the case of the azetidines, with or with-

out p-NO_2 or -NH_2 on phenethyl, clear activity is reduced by this substitution when the phenolic function is free (**8** and **9** *vs.* **6**) and in some cases lost when it is methylated (**14** and **15** *vs.* **11**). In the pyrrolidines, however, activity is reduced by N-phenethylation only in conjunction with O-methylation, remaining of clear quality; and when the phenolic function is left unmuzzled in otherwise optimal pyrrolidines, activity considerably increases on going from N-methyl to N-phenethyl (with or without p-NH_2) without proportionate increase in toxicity (ref 1 and unpublished work by the authors). Thus, a favorable interaction between the unmuzzled m-phenolic function and N-phenethylation allowed by the pyrrolidine nucleus is not present with the azetidine nucleus.

Furthermore, divergence between the azetidines and pyrrolidines occurs with respect to the optimal unbranched length of 3-alkylation. Whereas this was clearly propyl in the pyrrolidines as concerns both activity and activity : toxicity ratio,[1] it has shifted toward butyl in the azetidines, at least as concerns activity (**19** *vs.* **6** and **21**, **20** *vs.* **11** and **23**).

Substitution of a carbonyl function in place of methyl on the nitrogen led to inactivity or lack of clear activity (**12** and **16**).

In general, the levels of activity and activity : toxicity ratio achieved in the azetidines are surprisingly comparable with those achieved in the pyrrolidines.

Acknowledgments.—The authors are indebted to Dr. R. E. Bowman for advice and encouragement, to Mr. F. H. Oliver for microanalyses, to Miss E. M. Tanner for the physical chemistry measurements, and to Mr. J. D. Tomkinson for some technical assistance. M. Welford, L. Lembke, J. Wax, and R. Mills cooperated in the pharmacological work.

Analgetics Based on α-Phenyl-3-pyrrolidineacetic Acid

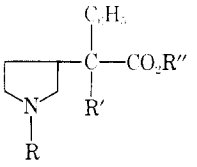
ALBERT D. CALE, JR., AND CARL D. LUNSFORD

Research Laboratories, A. H. Robins Company, Inc., Richmond, Virginia

Received December 5, 1967

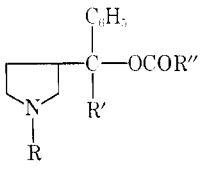
Several 1-alkyl-α-phenyl-3-pyrrolidineacetic acid esters were prepared and tested for their analgetic activity. The potencies of the compounds were similar to their reversed esters and were generally in the range of *d*-propoxyphene.

Continuing our investigation of drugs based on the pyrrolidine nucleus,[1] we have prepared a series of esters of substituted α-phenyl-3-pyrrolidineacetic acids (I) (Table I) for study as analgetics.



I

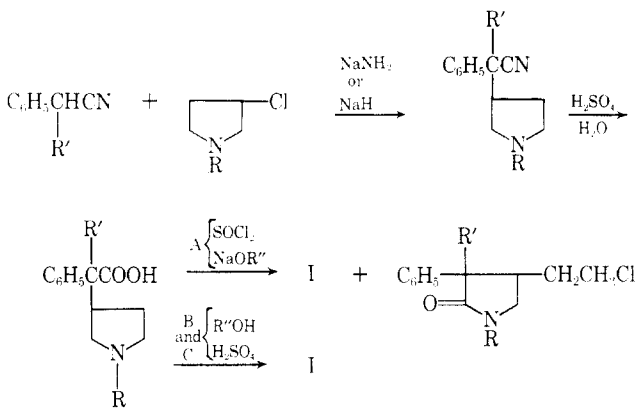
These compounds are structural analogs of meperidine and are the reversed esters of a series of analgetics (II) being reported simultaneously.[2] They were prepared by the alkylation of the appropriate phenylacetonitrile with a 1-substituted 3-chloropyrrolidine, hydrolysis of the product nitrile to the amino acid, and esterification as shown in Chart I.



II

An attempt to prepare the ethyl ester from 1-ethyl-α,α-diphenyl-3-pyrrolidineacetyl chloride hydrochloride by treating an ethanol solution with pyridine gave only rearrangement to 1-ethyl-4-(2-chloroethyl)-3,3-diphenyl-2-pyrrolidinone.[1] The acid chloride was successfully converted to its ethyl ester, however, by adding it to a solution of sodium ethoxide in ethanol.

CHART I



The analgetic activity of these compounds was determined by a modification of the Nilsen method[2,3] (electrical stimulation of a mouse tail) and is compared in the table with the activity of the corresponding reversed esters of structure type II.

When R′ ≠ C_6H_5, diastereoisomers exist for each structure. These were separated in two examples and the analgetic activity was determined for each of the racemates. No significant difference in analgetic potency was observed between the diastereoisomeric racemates in compounds of type I or II.

(1) (a) C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964); (b) A. D. Cale, Jr., H. Jenkins, B. V. Franko, J. W. Ward, and C. D. Lunsford, *ibid.*, **10**, 214 (1967).

(2) G. C. Helsley, J. A. Richman, C. D. Lunsford, H. Jenkins, R. P. Mays, W. H. Funderburk, and D. N. Johnson, *ibid.*, **11**, 472 (1968).

(3) P. Nilsen, *Acta Pharmacol. Toxicol.*, **18**, 10 (1961).