SYNTHESIS AND ANALGESIC POTENTIAL OF SOME SUBSTITUTED PYRROLIDINES

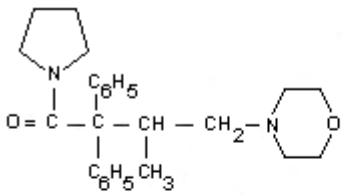
M.N. ABOUL-ENEIN
S.EL-DIFRAWY
N.A. ABDALLAH
N.M. KHALIFA
M.Y. EBEID
W. WERNER

SUMMARY: A series of 3-aroyloxy-1-methyl-5-phenyl pyrrolidines (5a-k) was prepared and screened for their analgesic potency as well as their local anaesthetic activity.

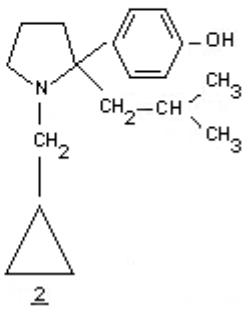
Key Words: Pyrrolidines, esters of 1-methyl-5-phenyl-3-pyrrolidinol analgesics, local anaesthetics.

INTRODUCTION

It has been reported that various substituted pyrrolidines display versatile pharmacological profiles, such as anticholinergics by Adamson *et al.* (1) and CNS stimulants by Seeger and Kottler (2), as antihistaminics by Weidmann *et al.* (3), Ondelli *et al.* (4), and atihypertensives by Rubin *et al.* (5). Also, among these profiles is the analgesic activity which has been disclosed by Keats *et al.* (6) in dextromoramide 1 and by Bowman *et al.* (7) in compound 2, which are more potent than morphine.



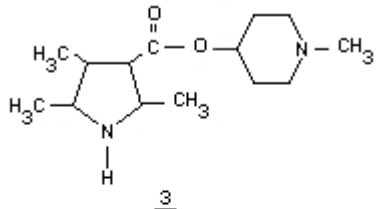
1



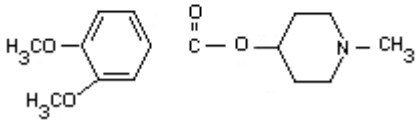
2

Laboratory of Pharmaceutical Science, National Research Centre, Dokki, Cairo, Egypt; Faculty of Pharmacy, Cairo University; Institut für Pharmazeutische Chemie der Westfalischen Wilhems Universitat of, Munster, West Germany.

On the other hand, Waters (8-10) reported that simple aromatic and heteroaromatic esters of non-quaternary carbon-4 piperirinols 3 and 4 exhibit potent antinociceptive potential comparable to that of morphine without featuring physical dependence liability.

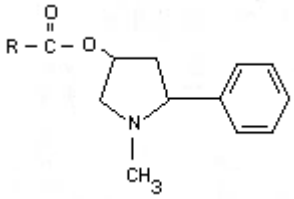


3



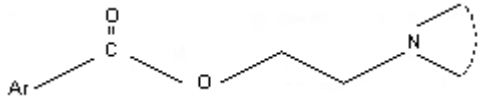
4

The present work describes the synthesis of some esters 5, of the novel 5-methyl-5-phenyl-3-pyrrolidinol 6, aiming to achieve compounds having antinociceptive properties.



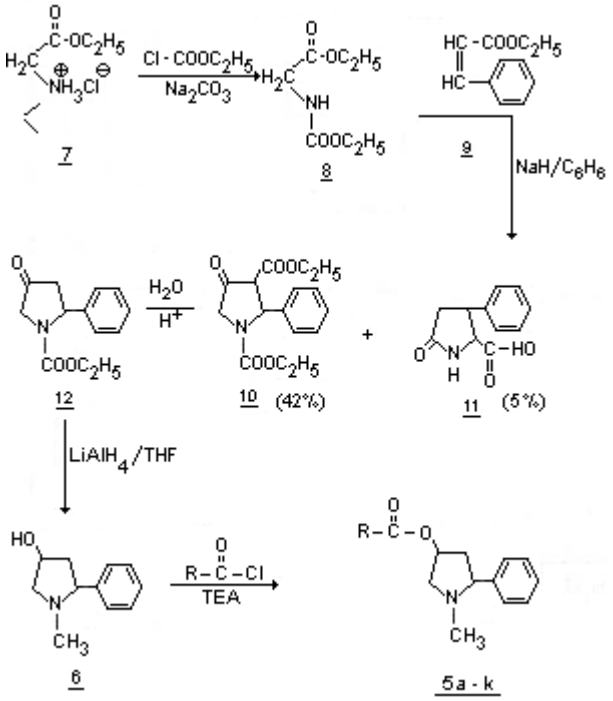
5

Moreover, the prepared compounds exhibit the structural features of the local anaesthetics basic esters having the general skeleton:



Therefore, the biological investigation is extended to involve the local anaesthetics activity.

The synthetic strategy of the target compounds is illustrated in scheme 1 (vide infra).



Scheme 1

MATERIALS AND METHODS

Melting points were determined on Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on Beckmann Infracord, model 4220. The microanalytical data were obtained from the National Research Centre, Dokki, Cairo. The analytical results deviated maximally ± 0.4% from the theoretical values for C, H and N. The ^{1}H-NMR ($CDCl_3$, TMS) were recorded on VARIAN (90 MHz ^{1}H). The mass spectrum was obtained on VARIAN CH-5 and CH-7 spectrometers. The mass spectrum was performed at the Institut für Pharmazeutische Chemie, Universitat Munster, FRG. Purification of the products were performed by using column chromatography using neutral aluminia activity I as an adsorbent and n-hexane / CH_2/Cl_2 (1:1) as the eluent. Compounds 7 and 8 were prepared as previously described by Marver, Brenner *et al.* and Mair *et al.* (11-13) respectively.

Diethyl 4-oxo-2-phenyl-1, 3-pyrrolidine dicarboxylate 10.

To a stirred suspension of 2.4 g (0.1 mol) of sodium hydride in 100 ml of dry benzene, 17.5 g (0.1 mol) of the diester 8 was added dropwisely. After the addition of one-quarter of 8, the mixture was gently heated, to initiate the reaction. The rest of the diester 8 was added at such a rate to maintain gentle reflux throughout the addition. The reaction mixture was stirred overnight at room temperature, then 17.6 g (0.1 mol) of ethyl cinnamate 9 was added dropwisely and stirred for additional 30 min. The reaction mixture was refluxed for 2 h, then treated with 2 ml of absolute ethanol and refluxed for further 18 h. After cooling, the whole was poured over 300 ml of ice-water. The benzene layer was separated, and washed with water (2X50 ml). The combined aqueous layers were shaken with ether (2x50 ml), then acidified to pH 3-4 with 10% H_2SO_4, extracted with ether (4x50 ml), dried ($MgSO_4$) and concentrated in vacuo where the cyclized product 10 (14-16) was crystallized from ether as white powder of 12.8 g (42%), mp 108-110°C.

IR (KBr, cm^{-1}): 3300 (OH), 1700, 1680 (C = O, esters) and 1640 (C= O of β-keto ester).

^{1}H-NMR ($CDCl_3$, TMS): δ(ppm)=0.9-1.36 (two t overlapping, 6H, two CH_3), 3.53-4.43 (broad m, 7H, two CH_2 and H in the 3-position), 5.53-5.71 (m, IH, H in the 2-position), 7.23 (s. 5H, aromatic protons).

The equeous acidic phase was concentrated to one-third of its volume, where the by product 3-phenyl-5-oxo-pyrrolidin-2-carboxylic acid 11 was precipitated as white crystals (5 %), mp 184-6°C.

IR(KBr, cm^{-1}): 3200-3220 (NH, OH), 1730 (C = O, carboxylic acid) and 1660 (C = O, amidic carbonyl group).

Ethyl 4-Oxo-2-phenyl-l-pyrrolidine carboxylate 12

A mixture of 30.5 g (0.1 mol of 10, 90 ml water and 0.9 ml concentrated hydrochloric acid, was refluxed under stirring for 15 h. The resulting reaction mixture was saturated with NaCl and extracted with CH_2Cl_2 (3x10 ml), dried ($MgSO_4$) and evaporated in vacuo to give 23.3 g (100 %) of 12 as reddish brown oil which was purified by column chromatography to give 22 g (95 %) of 12 as viscous oil (15).

IR (liquid film, cm^{-1}): 1770 (C = O, five membered ring ketone) and 1700 (C = O ester).

^{1}H-NMR ($CDCl_3$, TMS): δ(ppm)=1.16-1.3 (t, 3H-$NCOOCH_2CH_3$) 2.56-3.4 (broad m, 2H, CH_2 in the 3-position), 4.0-4.4 (broad m, 4H, CH_2 in the 5-position and -$NCOOCH_2CH_3$), 5.56-5.73 (m, 1H, CH in the 2-position), 7.36-7.56 (m, 5H, aromatic protons).

The semicarbazone of 12, mp 196-8°C (17).

1-Methyl-5-phenyl-3-pyrrolidinol 6

A solution of 23.3 g (0.1 mol) of 6 in 60 ml of dry THF was

added dropwise to a stirred cold suspension of 7.6 g (0.2 mol) of $LiAlH_4$ in 120 ml of dry THF. The mixture was refluxed for 24 h, then cooled and the complex formed was decomposed with a saturated solution of Na_2SO_4. After filtration, the solvent was evaporated in vacuo to give a viscous oil, which was acidified under cooling with 5N HCl and washed with ether (2x25 ml). The equeous acidic layer was basified under cooling with 10 % NaOH, extracted with CH_2Cl_2 (3x30 ml), dried ($MgSO_4$) and evaporated in vacuo to give 15 g (85%) of 6 as dark brown oil, which was purified by column chromatography to give 14.5 g (82 %) as golden viscous oil. Analy ($C_{11}H_{15}NO$).

	C	H	N
Calc.	74.54	8.52	7.90
Found	74.80	8.70	7.80

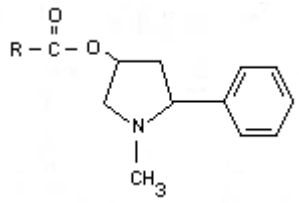
IR (liquid film, cm^{-1}): 3400 (OH, alcohol) and absence of carbonyl ester group.

^{1}H-NMR ($CDCl_3$, TMS) = δ(ppm) = 0.89-1.86 (broad m, 2H, CH_2 in the 4-position), 2.09 (s, 3H, CH_3 in the 1-position) 2.29-2.76 (m, 2H, CH_2 in the 2-position), 2.86-3.19 (M, 2H, CH and OH in the 3-position, OH exchangeable with D_2O), 4.13-4.33 (m, 1H, CH in the 5-position) 7.29 (s, 5H, aromatic protons).

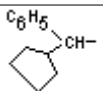
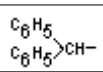
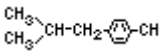
General procedure for the preparation of 3-aroyloxy-1-methyl-5-phenyl pyrrolidines (5a-k, c.f. Table 1).

To a solution of 1.77 g (0.01 mol) of 6 and 3g (0.03 mol) of triethylamine in 60 ml dry benzene, was added (0.015 mol) of the appropriate acide chloride. The mixture was refluxed and stirred overnight. The precipitated triethylamine hydrochloride was filtered off and washed with benzene (25 ml). The combined filterates

Table 1



5a-k

No. of Comp	R	mp, °C	Yield %	Formula (Mol. Wt)	Analysis %			
						C	H	N
5a	C_6H_5	73-5b	50	$C_{18}H_{19}NO_2$ (281.36)	Calc. Found	76.84 76.65	6.80 7.06	4.97 5.21
5b	4-Cl-C_6H_4	107-9b	40	$C_{18}H_{18}ClNO_2$ (315.78)	Calc. Found	68.46 67.85	5.74 5.97	4.43 4.13
5c	4-CH_3O-C_6H_4	106-8c	69	$C_{19}H_{21}NO_3HCl.1.3H_2O$ (371.26)	Calc. Found	61.46 61.52	6.67 6.44	3.77 3.83
5d	4-NO_2-C_6H_4	58-7b	76	$C_{18}H_{18}N_2O_4$ (326.35)	Calc. Found	66.24 66.10	5.56 5.23	8.58 8.12
5e	4-NH_2-C_6H_4	97-9b	91	$C_{18}H_{20}N_2O_2$ (296.36)	Calc. Found	72.94 73.19	6.80 6.87	9.45 9.27
5f	2,4-$(Cl)_2$-C_6H_3	58-60b	60	$C_{18}H_{17}Cl_2NO_2$ (350.24)	Calc. Found	61.72 61.70	4.89 4.20	3.99 3.93
5g	3,4,5-$(CH_3O)_3$-C_6H_2	127-9c	65	$C_{21}H_{25}NO_5.HCl.2H_2O$ (443.93)	Calc. Found	56.81 56.86	6.81 6.97	3.15 3.05
5h	C_6H_5-CH_2	95-7b	64	$C_{19}H_{21}NO_2$ (295.38)	Calc. Found	77.25 77.30	7.16 6.90	4.74 4.60
5i		Oild	68	$C_{24}H_{29}NO_2$ (363.49)	Calc. Found	79.30 79.60	8.04 7.80	3.85 3.80
5j		120-2b	70	$C_{25}H_{25}NO_2$ (371.47)	Calc. Found	80.83 80.60	6.78 7.05	3.77 4.01
5k		Oild	52	$C_{24}H_{31}NO_2$ (365.51)	Calc. Found	78.86 79.20	8.54 8.35	3.83 3.62

a) IR (KBr or liquid film, cm^{-1}) of 5a-k: 1730-1700 (C=0, ester)
b) Free base: which were crystallized from ether.
c) Hydrochloride: which were crystallized from 2-Propanol: ether.
d) Were separated as viscous oil and purified by column chromatography.

were evaporated in vacuo to give an oily product, which was treated with 5N HCl and the undissolved substance was extracted with ether (2 x 25 ml). The aqueous acidic layer was rendered alkaline with 10% NaOH extracted with CH_2Cl_2 (3 x 15 ml), dried ($MgSO_4$) and evaporated in vacuo (c.f. Table 1).

Compound 5e was obtained by catalytic hydrogenation of an ethanolic solution of 5d, using PtO_2 as catalyst.

5b: MS (m / z): 316 ($M^+C_{18}H_{18}NO_2$, 1%) base peak (M^+-157  100%). ^{1}H-NMR ($CDCl_3$, TMS): δ(ppm) of 5h:1.02-1.3 (m, 2H, CH_2 in the 4-position) 2.2 (s, 3H, CH_3-N), 2.47-2.8 (m, 2H, CH_2 in the 2-position), 3.0-3.43 (m, 1H, CH in the 3-position), 3.73 (s, 2H, CH_2-C_6H_5), 5.16-5.4 (m, 1H, CH in the 5-position), 7.4-7.56 (m, 10H, aromatic protons).

Pharmacology

Analgesic activity:

The test compounds 5a-k were evaluated for their analgesic activity using the hot-plate technique as described by Janssen *et al.* (18). Morphine HCl was used as reference. The dose producing analgesic activity in 50% of mice (ED_{50} and 95% confidence limits) was calculated by the graphical method of Litchfied and Wilcoxon (19).

Local anaesthetic activity:

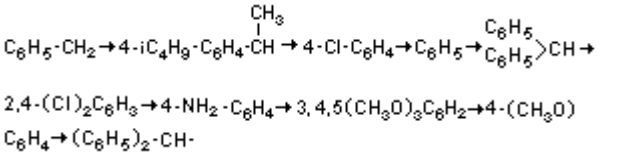
The procedure of Jones and Weaver (20) was adopted, using the cornea of the male albino mice and procaine hydrochloride as a reference six mice were used to locate each point on the dose response curve which was calculated by the method of Litchfield and Wilcoxon (19).

RESULTS AND DISCUSSION

Analgesic activity

Compounds 5a-k were evaluated for their analgesic activity (18) (Table 2). The most active compounds in this series are 5h and 5k. Both possess an analgesic effect about 6.4 % that of morphine hydrochloride.

With respect to the structure-activity relationship (SAR), the substitution in the aromatic moiety of 5 revealed the following potency order preference:



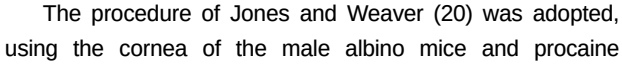
Local anaesthetic activity

Using albino mice for local anaesthetic evaluation (20) (Table 2) it was found that compounds 5c and 5g exhibited stronger local anaesthetic potency than the reference drug procaine hydrochloride. Compounds 5c and 5g possessed local anaesthetic potency 5.6 and 2.5 times that of the reference drug, respectively.

Table 2

Compound No.	Analgesic activity ED_{50}mg/kg (95% confidence limit)	Local anaesthetic activity ED_{50} mg/kg (95% confidence limit)
5a	48.8 (28.10-76.00)	58.4 (42.62-80.00)
5b	40.0 (28.70-55.60)	64.00 (52.89-77.44)
5c	63.6 (53.44-75.68)	7.6 (6.44-8.97)
5e	58.4 (48.26-70.66)	48.4 (28.30-82.76)
5f	57.2 (42.06-77.79)	53.6 (43.93-65.39)
5g	62.8 (50.24-79.00)	16.8 (8.40-34.40)
5h	34.5 (30.63-38.84)	-
5i	47.2 (32.55-68.44)	-
5j	64.4 (59.08-70.19)	-
5k	35.0 (22.70-54.00)	-
Reference drug	Morphine HCl	Procaine HCl
	2.23 (1.65-3.01)	42.5 (24.15-74.70)

With respect to the structure-activity relationship (SAR) the substitution in the aromatic moiety of 5 revealed the following potency order preference:



REFERENCES

1. Adamson BW, Barret PA, Wilkison S : Aminoalkyl tertiary carbinol and derived products Part IV. Spasmolytics, Phenyl-and Cyclohexylphenyl-carbinols. J Chem Soc, 52, 1951.

2. Seeger E, Kottler A : N-Substituted pyrrolidines and their salts and Quaternary ammonium compounds. Ger Pat 1, 093, 709, 1960; Chem Abstr: 55, 19950 (1961).

3. Weidmann H, Grauwiler J, Griffith R, Roemer D, M Taeschler, Zehnder Z : Pharmacology, Pharmacokinetics, and Toxicology of the new antihistamine HS 592 (Tavegil), Boll Chim Form, 106:107216, 1967.

4. Ondetti MA, Cushman DW : Compounds and method for alleviating angiotensin-related hypertension, US pat 4,053,651, 1977; Chem Abstr: 88, 136977 (1978).

5. Rubin B, Laffan RJ, Kotler GD, OKeefe HE, Demaio AD, Goldberg EM : SQ 14,25 (D-3-mercapto-2-methyl propanayl-L-proline), a novel orally active inhibitor of angiotensin I-converting enzyme, J Pharmacol Exp Therap, 204:271, 1978; Chem Abstr: 88, 136977 (1978).

6. Keats AS, Telford J, Kurosu Y : III Dextromoramide and a comparison of methods of estimating pain relief in man. J Pharmacol Exp Therap, 130:212, 1982.

7. Bawman RE, Collier HOJ, Hahersley PJ, Lockhart IM, Peters DJ, Schneider C, Webb NE, Wright M : Analgetics based on the pyroolidine Ring. J Med Chem, 16:1177, 1973.

8. Waters JA : Aromatic esters of nonquaternary carbon-4 piperidinols as analgesics. J Med Chem, 21:628, 1978.

9. Waters JA : Pyrrole esters of Tropanols and related structures as analgesics. J Med Chem, 20:1094, 1977.

10. Waters JA : Heterocyclic and piperonylic acid esters of 1-methyl-4-piperidinol as analgesics. J Med Chem, 20:1496, 1977.

11. Marvel CS : Glycine ethyl ester hydrochloride. Org Synth Coll 11: 310, 1943.

12. Brenner M, Huber W : Herstellung von ∝–Aminasäureestern durch Alkoholyse der Methylester. Helv Chim Acta, 36:1109, 1953.

13. Mair AC, Stevens MFG : Triazines and related products Part VII. Potential irreversible chymotrypsin inhibitors: 3-Alkyl-1,2,3-benzotriazin-4 (3H)-ones and o-Azidobenzamides. J Chem Soc, (C):2317, 1971.

14. Pachaly P : Die stereoselektive synthese von 2-cis-alkyl-2-trans-athoxycarbonyl-3-pyridyl-(3)-pyrrolidonen-5,Arch, Pharm 309:98, 1976.

15. Wu Y-H, Gould WA, Lobeck Jr WG, Roth HR, Feldkamp RF : Pyrrolidines VII. 3-hydroxyl-1-pyrrolidinecarboxylic acid esters. J Med Pharm Chem, 5: 752, 1962.

16. Wu Y-H, Lobeck Jr WG, Feldkamp RF : Pyrrolidines VII. 3-acyloxy-3-aryl-1-ethyl-and-1-methylpyrrolidines. J Med Pharm Chem, 5:762, 1962.

17. Kuhn R, Osswald G : Neue synthese von 3-pyrrolironen; darstellung von DL- γ-oxo- prolin, DL-allo-hydroxy-prolin und 4-Athoxy-pyrrol-carbonsaur-(2). Chem Ber, 89:1423, 1956.

18. Janssen PHJ, Jageneau AH, Van Proosdij-Hartzema EG, de Jongh DK : Pharmacology of a new potent analgesic. R 951 (3-(4-carbethoxy-4-phenyl piperidino) propiophenone hydrochloride. Acta physiol et pharmacol Nethrl, 7:373, 1958; Chem Abstr: 53, 3467 (1959).

19. Litchfield, JRJT, Wilcoxon F : A simplified method of evaluation dose-effect experiments. J Pharmacol Exp Therap, 96:99, 113, 1949.

20. Jones WR, Weaver LC : Ouantitative evaluation of surface anaesthetics in albino mice. J Pharm Sci, 52:500, 1963.

Correspondence:
M.N. Aboul-Enein
Lab. of Pharmaceutical Sciences
National Research Centre
Dokki, Cairo,
EGYPT.