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AMINOACID DERIVATIVES WITH PSYCHOTOGENIC ACTIVITY

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ABSTRACT

As a part of an extensive programme concerned with the syntheses and investigation of a group of benzilyl-aminoacid and diphenylacetylaminoacid, piperidine esters possessing psychotogenic properties, attention has been directed towards the possible mechanism of action of some of the intermediates.
They were found to be potent anticholinergic agents through activating cholinesterase in brain tissues accompanied by increased norepinephrine and epinephrine levels leading to EEG desynchronization. They also exhibited metabolic and functional effects through their effect on blood glucose, tissue glycogen, blood and tissue pyruvic acid, lactic acid, ChE, AST and ALT.

INTRODUCTION

Compounds having amino-alcoholic as well as acetic acid moieties are known to possess a wide range of pharmacological activity (Biel *et. al.* 1955; Petyunin and khodyreva 1963). Later, derivatives of N-substituted-3-piperidinos were investigated and were found to be quite as active (Biel *et. al.*1952; Biel *et. al.*1955; Abood *et. al.* 1958; Biel 1961; Biel *et. al.* 1961; kadin and Cannon 1962). A large number of derivatives of N-diphenylacetyl piperidinols, has been prepared and was found to possess enhanced antispasmodic activity (Biel *et. al.* 1952). It is also known that benzilates as well as disubstituted glycolate esters of N-alkyl-piperidinols are powerful hallucinating agents in humans. A larger dose induced auditory hallucination and a complete loss of the environment (Biel 1961). On the other hand analogous compounds lacking the hydroxyl group as for example N-ethyl-3-piperidyl diphenylacetates are devoid of hallucinogenic properties ((Biel 1961).

Esters of benzilates and substituted hydroxy acetates were also found to be potent acetylcholine antagonists (Biel *et. al.* 1955) and possess potent psychotomimetic properties (Abood *et. al.*, 1958; Biel *et. al.* 1961; Kadin and Cannon 1962 and Biel *et. al.*, 1962).

On the other hand, a number of amino acids, such as methionine, glutamic acid, glutamine, serine, cysteine, arginene and threonine, were found to increase the rate of release of catecholamines (Nishikawa *et. al.*, 1982). It appears that the mechanism of action of the exogenous psychotropic drugs employed in the treatment of mental disorders involves mimicking, potentiating and/or inhibiting the action of the endogenous neurotransmitters, norepinephrine, seratonin or acetylcholine (Biel *et. al.* 1962).

This work aims at the synthesis of compounds with the general structure (I) combining the pharmacologically active piperidyl, amino acid and acetyl or benzilyl moieties. Preparation of these compounds led first to the formation of the intermediates (II) linking the acetyl and the amino acid moieties.

Preliminary biochemical investigation of some of the intermediate compounds (II a-i) are presented. Detailed discussion of the synthesis and pharmacological properties of the final compounds (I) will be the subject of a forthcoming publication.

EXPERIMENTAL

The following illustrates the general procedures:

a) 2,2-Diphenylacetyl-L-alanine.

L-Alanine (1.8g; 0.02m) was dissolved in a solution of 2.0g sodium hydroxide in 30 ml of water. The mixture was cooled in ice and 4.6g (0.02m) of diphenylacetyl chloride was added, portionwise, under vigorous stirring. Stirring was continued at room temperature for further 3 h., then extracted with ether. The alkaline solution was acidified to pH 3 with 10% HCl and the precipitated product was filtered off, washed with water and dried. Recrystallization from benzene-methanol gave 3.1g, (54%), m.p.128°.

b) N-Benzilyl-glycine

Was prepared in a similar manner, the mixture was heated at reflux for further two hours and was worked up. Recrystallization from benzene-methanol gave 4.4g; (62%) of N-benzilyl-glycine, m.p.190°.

c) Methylester of 2,2-Diphenylacetyl-L-Phenylalanine

To a mixture of 4.7g (0.022m) methylester hydrochloride of L-phenylalanine and 6.5g (0.06m) triethylamine in 40 ml of dry benzene, was added portionwise under

stirring, 4.6 g (0.02m) of diphenylacetyl chloride. The reaction mixture was then heated at reflux for 4 h. The benzene layer was successively washed with water, 10% HCl, 10% sodium bicarbonate, water, dried over anhydrous sodium sulphate and evaporated. Recrystallization of the residue from benzene-petroleum ether (b.r. 40-60°C) gave 5.7g (76%), m.p.116°.

d) Ethyl ester of 2,2-diphenylacetyl glycine.

Diphenylacetyl chloride (8.2g; 0.036m) was added in one portion to a mixture of glycine ethylester hydrochloride (5.0g; 0.036m), sodium bicarbonate (15.1g; 0.18m), ice (5g) and water (5ml). The reaction mixture was stirred vigorously for 2 h and filtered off. The precipitate was washed twice with cold water and recrystallized from benzene. The product was obtained in 70% yield, m.p. 124°.

e) Biochemical Analysis

A dose of 0.004 mg of each compound suspended in 0.2 ml saline was intraperitoneally tested in groups of ten rats. The results were statistically compared with corresponding values of control rats injected each with 0.2 ml saline. The methods of biochemical analysis applied were as follows:

1. Norepinephrine (NE) and epinephrine (E), (Euler, 1954).
2. Cholinesterase (ChE), (Biggs *et. al.*, 1958)
3. Aspartate aminotransferase (AST, GOT) and alanine aminotransferase (ALT, GPT) (Bergmeyer and Bert, 1974).
4. Lactic acid (LA) and pyruvic acid (PA), (Gloster and Harris, 1962).
5. Blood glucose (G), (Cooper and McDaniell, 1970).
6. Tissue glycogen (Gn), (Fong *et. al.*, 1953).
7. Mean blood pressure (M.B.P.), heart rate (H.R.) and the electrical activities of the parieto-occipital area of the brain (The alpha rhythm, EEG) were measured by the Washington 400 MD recording oscillograph.
8. Rate of normal and stimulated glycolysis in the *in-vitro* incubated sartorius muscle of the frog (R.G. in S.M.), (Smith and Abood, 1966).
9. Statistical analysis: Students test, (Bailey, 1959).

RESULTS AND DISCUSSION

Results are presented in tables (1) and (2) and the chemical formulae of the compounds are shown in Figure (1).

All the compounds retained their pharmacological activities. They increased the rate of release of norepinephrine (NE) and epinephrine (E), antagonizing acetylcholine and desynchronizing the EEG in rat brain. Compound IIg, not affecting norepinephrine and epinephrine, failed to desynchronize the EEG. The effect of compounds IIc and IIi on heart rate is not statistically significant, whereas compound IIg increased the mean blood pressure, compounds IIb and IIc did not show any statistically significant effect. The compounds caused variable changes in the blood and tissue glucose, glycogen, pyruvic acid, ChE, AST and ALT levels.

Table 1

Compounds	Procedure	Yield %	m.p.c.°	Molecular formula	Elemental Analysis %					
					Calculated			Found		
					C	H	N	C	H	N
IIa	a	66	154	$C_{16}H_{15}NO_3$	71.34	5.61	5.20	71.51	5.69	5.14
IIb	a	54	128	$C_{17}H_{17}NO_3$	72.05	6.05	4.94	72.17	6.13	4.87
IIc	a	83	195	$C_{23}H_{21}NO_3$	76.84	5.89	3.90	76.92	5.83	3.94
IId	d	70	123	$C_{18}H_{19}NO_3$	72.69	6.44	4.71	72.80	6.47	4.79
IIe	c	65	133	$C_{18}H_{19}NO_3$	72.70	6.44	4.71	72.82	6.47	4.51
IIf	c	76	117	$C_{24}H_{23}NO_3$	77.17	5.94	3.75	77.09	5.99	3.69
IIg	b	61	190	$C_{16}H_{15}NO_4$	67.36	5.3	4.91	67.51	5.39	4.84
IIh	b	60	145	$C_{17}H_{17}NO_4$	68.21	5.72	4.68	68.09	5.81	4.60
IIi	b	54	135	$C_{23}H_{21}NO_4$	73.58	5.64	3.73	73.62	5.70	3.81

Table 2

Biochemical Evaluation

	Brain							Liver					
Com-pound	NE	E	ChE	AST	ALT	LA	PA	ChE	AST	ALT	LA	PA	Gn
IIa	↑		↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
P<	0.01	N.S.	0.01	0.001	0.001	0.001	0.001	0.02	0.001	0.02	0.001	0.001	0.001
IIb	↑		↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
P<	0.001	N.S.	0.05	0.001	0.001	0.001	0.001	0.01	0.001	0.01	0.001	0.001	0.001
IIc	↑	↑	↑	↑	↑	↑	↑	↑	↓	↑	↑	↓	↑
P<	0.001	0.01	0.05	0.001	0.001	0.001	0.001	0.01	0.05	0.05	0.001	0.001	0.001
IId	↑		↑	↑	↑			↑	↓	↓	↑	↑	↓
P<	0.001	N.S.	0.01	0.001	0.001	N.S.	N.S.	0.01	0.001	0.01	0.001	0.001	0.001

Table 2 (Contd.)

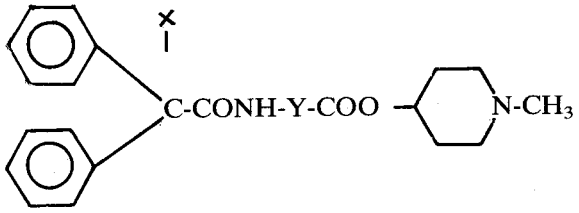
Brain								Liver					
Com-pound	NE	E	ChE	AST	ALT	LA	PA	ChE	AST	ALT	LA	PA	Gn
IIe	↑	↑	↑	↑	↑	↑	↑	↑	↑		↑		↓
P<	0.001	0.001	0.02	0.01	0.02	0.001	0.001	0.001	0.001	N.S.	0.001	N.S.	0.001
IIf	↑	↑		↑	↑	↑	↑	↑	↓		↑	↓	↓
P<	0.001	0.05	N.S.	0.001	0.001	0.001	0.001	0.001	0.05	N.S.	0.001	0.001	0.001
IIg			↑	↑	↑	↑		↑	↓		↑	↓	↓
P<	N.S.	N.S.	0.001	0.001	0.001	0.001	N.S.	0.001	0.001	N.S.	0.001	0.02	0.001
IIh	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓
P<	0.001	0.01	0.01	0.001	0.001	0.001	0.001	0.02	0.001	0.001	0.001	0.02	0.001
IIi	↑		↑	↑	↑	↑	↑	↑		↑	↑	↓	↑
P<	0.001	N.S.	0.01	0.001	0.001	0.001	0.001	0.01	N.S.	0.01	0.001	0.001	0.02

Muscle							Heart					
Compound	ChE	AST	ALT	LA	PA	Gn	ChE	AST	ALT	LA	PA	Gn
IIa	↑	↑	↑	↑		↑	↑		↑	↑		
P<	0.02	0.001	0.001	0.001	N.S.	0.001	0.001	N.S.	0.001	0.001	N.S.	N.S.
IIb		↑	↑	↑	↑		↑		↑	↑	↑	
P<	N.S.	0.001	0.001	0.001	0.001	N.S.	0.001	N.S.	0.001	0.001	0.001	N.S.
IIc	↑	↑		↑	↑	↑	↑	↓	↑	↑		↑
P<	0.05	0.001	N.S.	0.001	0.02	0.001	0.001	0.001	0.001	0.001	N.S.	0.001
IId	↑	↑	↑	↑	↓	↓	↑	↓	↑	↑	↑	↑
P<	0.05	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
IIe	↑	↑	↑	↑	↑	↓	↑	↓	↑	↑	↑	↑
P<	0.02	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
IIf		↑	↑	↑	↑	↑	↑	↓	↑	↑	↑	↑
P<	N.S.	0.001	0.001	0.001	0.001	0.02	0.001	0.001	0.001	0.001	0.01	0.001
IIg	↑	↑	↑	↑	↓	↓	↑	↓	↑	↑	↑	↑
P<	0.01	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
IIh		↑	↑	↑	↑	↑	↑	↓	↑	↑	↑	↑
P<	N.S.	0.001	0.001	0.001	0.01	0.001	0.001	0.05	0.001	0.001	0.001	0.001
IIi	↑	↑		↑	↑	↓	↑		↑	↑	↑	↑
P<	0.02	0.001	N.S.	0.001	0.001	0.01	0.001	N.S.	0.001	0.001	0.05	0.001

Table 2 (Contd.)

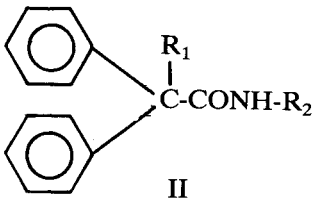
Compound	Blood or Serum						R.G. in S.M.			M.B.P.	H.R.	% of effect on EEG*
	ChE	AST	ALT	LA	PA	G	a	b	c			
IIa	↑	↑	↑	↑	↑	↓	↑	↑	↑	↓	↓	
P<	0.001	0.001	0.001	0.001	0.001	0.05	0.001	0.001	0.001	0.05	0.001	35
IIb	↑	↑	↑	↑	↑	↓	↓	↓	↓		↓	40
P<	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	N.S.	0.001	
IIc	↑	↑	↑	↑	↑	↓	↑	↑	↑			45
P<	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	N.S.	N.S.	
IId	↑	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓	15
P<	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.02	0.01	
IIe	↑	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓	75
P<	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	
IIf	↑	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓	80
P<	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	
IIg	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↓	
P<	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.02	
IIh	↑	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓	55
P<	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.01	0.001	
IIi	↑	↑	↑	↑	↑		↑	↑	↑	↓		75
P<	0.001	0.001	0.001	0.001	0.001	N.S.	0.001	0.001	0.001	0.01	N.S.	

a. Incubated in normal ringer solution (normal glycolysis)
b. Incubated in Ca-free (EDTA) (stimulated glycolysis)
c. Incubated in high K-ringer solution (stimulated glycolysis)
* EEG desynchronization
N.S. No significant change from control value
P< level of significance of difference from control value.
↑ Significant increase
↓ Significant decrease



I

X: H, OH
Y: CH_2, $CH(CH_3)$, $CH(CH_2Ph)$



II

R_1	R_2
a: H	glycine
b: H	L-alanine
C: H	L-β-phenylalanine
d: H	glycine ethylester
e: H	L-alanine methylester
f: H	L-phenylalanine methylester
g: OH	glycine
h: OH	L-alanine
i: OH	L-Phenylalanine

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تحضـــير مشتقات أحماض أمينيـــة ذات نشـــاط على الجهـــاز العصـــبي المركـــزي

حلمي إسماعيل هيبه - محمد عمر عبد الرحمن
سهير على النجدي و محمـــد منصـــور زهـره

يهدف البحث إلى تحضير مركبات تتكون من ثلاث وحدات بيولوجية مرتبطة عن طريق تفاعلات التكثيف والوحدات هي : حمض البنزيليك أو ثنائي فينيل الخليك مع حمض أميني مع بيبريدينول .

وهذا البحث يصف المركبات المتوسطة الناتجة من تفاعل وحدتي حمض البنزيليك أو ثنائي فينيل الخليك مع الأحماض الأمينية المختلفة .

وقد تم تحضير المركبات باتباع طرق التحضير التالية :

أ - تفاعل الحمض الأميني مع كلوريد حمض البنزيليك أو ثنائي فينيل الخليك في وجود ايدروكسيد الصوديوم .

ب - تفاعل هيدروكلوريد الاستر الميثيلي للحمض الأميني مع كلوريد حمض البنزيليك أو ثنائي فينيل الخليك في وجود بيكروبونات الصوديوم .

ج - تفاعل هيدروكلوريد الاستر الايثيلي للحمض الأميني مع كلوريد حمض البنزيليك أو ثنائي فينيل الخليك في وجود ثلاثي إيثيل الأمين .

ولقد أظهرت دراسة الفعالية البيولوجية للمركبات المحضرة على حيوانات التجارب أن لها تأثيراً واضحاً في زيادة نشاط إنزيم إستيريز الكولين وزيادة محتوى مادتي الايبينفـرين والفور ايبينفـرين في أنسجة المـخ مما أدى إلى تغيـر النشاط الكهربائي للمخ .

كما أظهرت المركبات فاعلية على بعض العمليات الحيوية في الجسم .