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Substances Acting on the Central Nervous System. IV.* Derivatives of 2-Ethyl-2-phenylbutyramide**

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A number of *N*- and *p*-substituted 2-ethyl-2-phenylbutyramides have been synthesized for pharmacological evaluation as potential substances acting on the central nervous system (CNS).

The report of Chapman *et al.*[1] in which it was shown that certain substituted acetamides are powerful narcotic and hypnotic agents stimulated us to investigate further this interesting group of compounds. The most active compound seems to be 2-ethyl-2-phenylbutyramide (26), which was found to be twice as active as methylpentynol, but also more toxic.

In our study of the relationship between structure and CNS activity attempts have been made by varying the structural details of 2-ethyl-2-phenylbutyramides to obtain compounds with equal or greater activity and with lower toxicity .With this purpose we have synthesized a number of *N*- and *p*-substituted derivatives of 26.

The *N*-substituted amides listed in Table I were prepared by the reaction of equivalent amounts of acid chloride and amines in the presence of sodium carbonate, usually in a solvent such as benzene or dimethylformamide. The *N*-acyl amides listed in Table II were obtained by treatment of 2-ethyl-2-phenylbutyramide with sodium amide and subsequent refluxing with the appropriate acid chloride in dry benzene.

In addition to amides substituted on the amide nitrogen atom we have also synthesized *p*-substituted derivatievs of 26 outlined in Chart A and described synthesized *p*-substituted derivatives of 26 outlined in Chart A and described details of their preparations are given in the Experimental Section. Chapman *et al.*[1], prepared the key intermediates, 2-ethyl-2-phenylbutyric acid (25) and 2-ethyl-2-phenylbutyramide (26), by hydrolysis with potassium hydroxide in amyl alcohol. In our hands hydrolysis of 2-ethyl-2-phenylbutyronitrile to the corresponding amide with sulphuric acid and subsequent treatment of the intermediate amide with butyl nitrite in acetic acid according to the procedure of Sperber, Papa and Schwenk[2] proved to be more successful. We failed to prepare the amide 21 and 23 by teatment of the corresponding esters 18 and 19 with ammonia under pressure.

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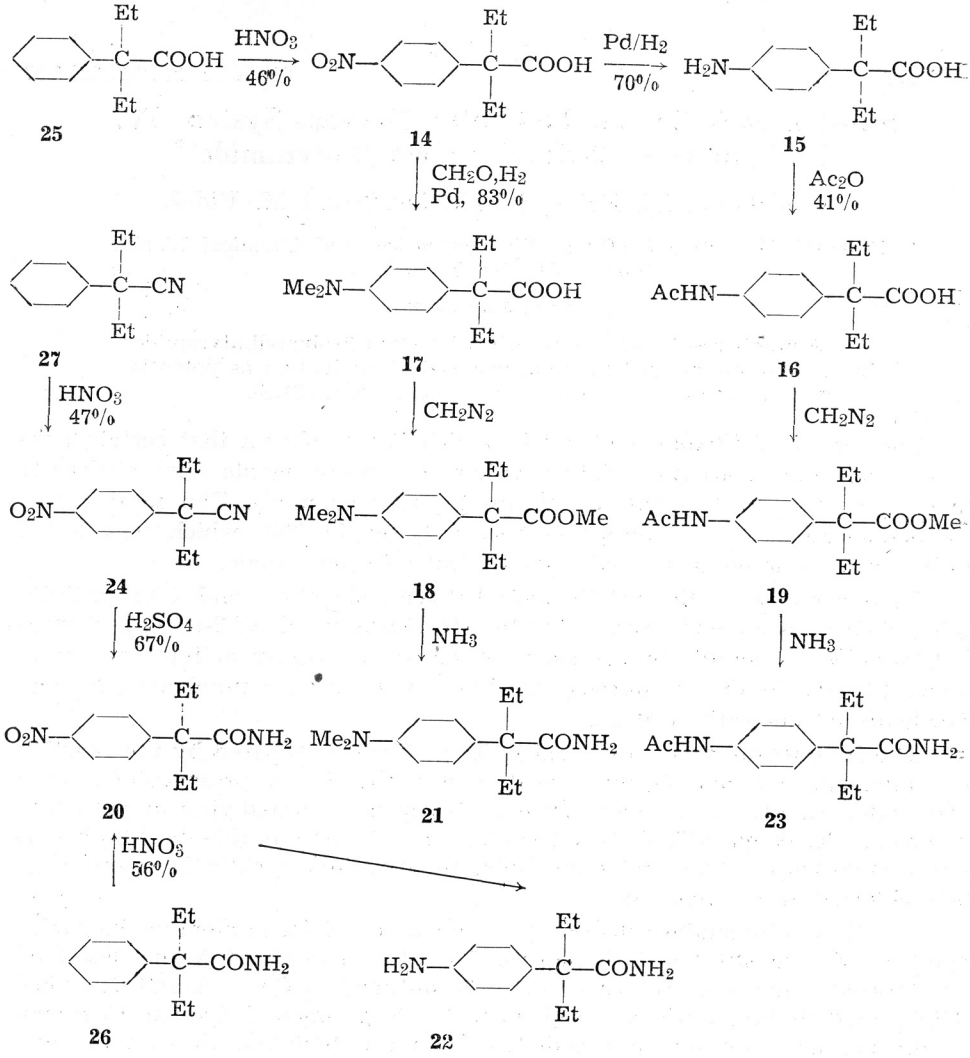
* Paper III, S. Kukolja, D. Grgurić, and L. Lopina, *Croat. Chem. Acta* 33 (1961) 25.

** S. Kukolja, Lj. Polak, H. Krnjević, and M. Videk, *Yugoslav. Patent Application P* 23401, June 22, 1961.

CHART A



Preliminary pharmacological screening tests have revealed that some derivatives described in this paper possess sedative and hypnotic activity. The results of the pharmacological investigation will be published elsewhere.

EXPERIMENTAL

N-*Substituted 2-ethyl-2-phenylbutyramides*

Compounds 1—9 of Table I were obtained using 2-ethyl-2-phenylbutyryl cloride and the appropriate amine by the procedure described below.

To a solution of 0.1 mole of 2-ethyl-2-phenylbutyric acid in 200 ml. of dry benzene 40 ml. of thionyl chloride was added. The solution was refluxed for 2 hours, and the solvent and excess thionyl chloride were removed by distillation. Without further purification the crude acid chloride was dissolved in 50 ml. of dry benzene

(or dimethylformamide) and 0.05 mole of anhydrous sodium carbonate and 0.1 mole of the appropriate amine were added. The mixture was heated on the water-bath for 2 hours and allowed to stand at room temperature overnight. Sodium chloride was filtered off and washed with 10 ml. of dry benzene. After removing the solvent the residue which solidified on cooling was recrystallized. The solvents, melting points, yields and analyses are recorded in Table I.

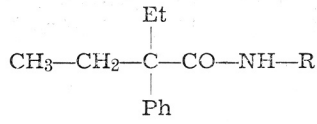
N-Acyl-2-ethyl-2-phenylbutyramides

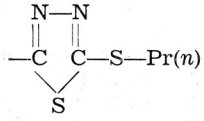
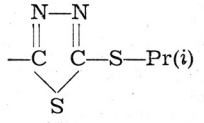
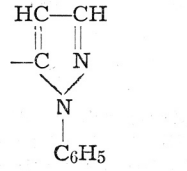
Compounds 10—13 of Table II were prepared using 2-ethyl-2-phenylbutyramide and the corresponding acid chlorides by the procedure described below.

A suspension of 0.02 mole of 2-ethyl-2-phenylbutyramide and 0.022 mole of sodium amide in 15 ml. of dry benzene was refluxed for 2 hours. After cooling, a solution of 0.025 mole acid chloride was added, the mixture refluxed for further 2 hours, and allowed to stand at room temperature overnight. Next morning 10 ml. of water was added, the benzene solution separated and dried over anhydrous sodium sulphate. After the solvent was removed, a semi-crystalline mass remained,

TABLE I

N-Substituted 2-ethyl-2-phenylbutyramides



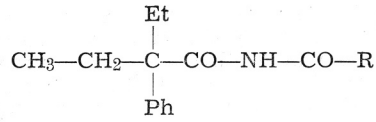
No.	R	M. P.[a,b] deg. C	Yield[c]	Formula	Calc'd. C	Calc'd. H	Found C	Found H
1	$-CH_2CH_3$	103—104	90	$C_{14}H_{21}NO$	76.66	9.65	76.86	9.93
2	$-CH_2CH_2NEt_2$[d]	164—165[ba]	60	$C_{18}H_{31}ClN_2O$	66.13	9.56	65.83	9.28
3	$-CH_2CH_2OH$	66—67.5[bc]	81	$C_{14}H_{21}NO_2$	71.45	9.00	71.34	8.73
4	$-CH_2CH_2-$	107—109[bc]	80	$C_{26}H_{36}N_2O_2$	76.43	8.88	76.21	8.73
5	$-C_6H_5$	85—86.5	89	$C_{18}H_{21}NO$[e]	80.86	7.92	80.94	7.87
6	$-CH_2C_6H_5$	120—122	85	$C_{19}H_{25}NO$	81.10	8.24	80.98	8.29
7		89—91	78[f]	$C_{17}H_{25}N_3OS_2$	58.43	6.63	58.28	6.33
8		91—93	61[g]	$C_{17}H_{23}N_3OS_2$	58.43	6.63	58.30	6.34
9		126—128	70	$C_{21}H_{23}N_3O$	75.64	6.95	75.90	6.66

[a] Melting points are not corrected. [b] Recrystallization solvent is ethanol unless otherwise specified. [ba] ethanol: ether, [bc] benzene: petrol ether. [c] Yields based on recrystallized product. [d] Hydrochloride. [e] Anal. Calc'd.: N 5.24%. Found; N 5.23%. [f] Anal. Calc'd.: N 6.00. Found: N 6.30. [g] Anal. Calc'd.: N 4.85. Found: N 5.03%.

which was filtered off. The crystals were recrystallized from ethanol. The oily filtrates were discarded. The melting points, yields and analyses are recorded in Table II.

TABLE II

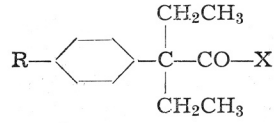
N-Acyl-2-ethyl-2-phenylbutyramides



No.	R	M. P.[a,b] deg. C.	Yield[c] %	Formula	Calc'd. C	Calc'd. H	Found C	Found H
10	$-CH_3$	89—92	18	$C_{14}H_{19}NO_2$[f]	72.07	8.21	71.85	7.89
11	$-CH_2CH_3$	100—102	15	$C_{15}H_{21}NO_2$	72.84	8.56	72.76	8.34
12	$-C_6H_5$	123—125	12	$C_{19}H_{21}NO_2$[g]	77.25	7.77	77.58	7.67
13	$-CHCH(CH_3)_2$ | Br	114—116	10	$C_{17}H_{24}BrNO_2$	57.63	6.83	58.08	6.69

TABLE III

p-Substituted Derivatives of 2-Ethyl-2-phenylbutyric acid



No.	R	X	M. P. deg. C	Yield %	Formula	Calc'd. C	Calc'd. H	Calc'd. N	Found C	Found H	Found N
14	NO_2	OH	144—146	46	$C_{12}H_{15}NO_4$	60.75	6.37	5.90	60.49	6.67	6.17
15	NH_2	OH	166—167	70	$C_{12}H_{17}NO_2$	69.54	8.27	6.76	69.40	8.16	7.03
16	NHAc	OH	197—198	41	$C_{14}H_{19}NO_3$	67.44	7.68	5.62	67.24	7.46	5.94
17	NMe_2	OH	145—146	83	$C_{14}H_{21}NO_2$	71.45	9.00	5.95	71.38	8.78	6.19
18	NHAc	OMe	143—144	90	$C_{15}H_{21}NO_3$	68.41	8.04	5.32	68.34	7.73	5.77
19	NMe_2	OMe	79—80	90	$C_{15}H_{23}NO_2$	72.25	9.30	5.62	72.54	9.01	6.03
20	NO_2	NH_2	127—128	54	$C_{12}H_{16}N_2O_3$	61.00	6.83	11.86	60.65	6.69	11.80
21	NMe_2	NH_2	119—120	79	$C_{14}H_{22}N_2O$	71.75	9.46	11.96	71.59	9.17	12.22
22	NH_2	NH_2	142—143	53	$C_{12}H_{18}N_2O$	69.87	8.80	13.58	70.17	8.55	

2-Ethyl-2-(p-nitrophenyl)-butyric acid (14)

A stirred and cooled solution of 10 g. of 2-ethyl-2-phenylbutyric acid in 40 ml. of concentrated sulphuric acid was treated during 20 minutes with 4 ml. of fuming nitric acid. The temperature of the solution was maintained at 0—10° for further 30 minutes. The mixture was poured onto ice and the crude solid filtered off, washed and dried; yield 12 g. (97%). This mixture of isomers was recrystallized twice from benzene to give a total of 5.7 g. (46%) of the *para* isomer, m.p. 142—144°. Further recrystallization from benzene gave the pure acid as pale yellow prisms, m.p. 144—146°.

2-Ethyl-2-(p-aminophenyl)-butyric acid (15)

A solution of 2.4 g. of the nitro-compound and 0.5 g. of anhyd. sodium carbonate in 15 ml. of water containing 0.05 g. of 5% palladium on charcoal was hydrogenated at room temperature and normal pressure. After removing the catalyst the filtrate was neutralized with hydrochloric acid; 1.4 g. (70%) of crude acid (m.p. 156—158°) was obtained by filtration. Recrystallization from methanol gave the pure acid melting at 166—167°.

2-Ethyl-2-(p-acetylaminophenyl)-butyric acid (16)

A solution of 1 g. of the amino-compound in 10 ml. of acetic anhydride was refluxed for 2 hours. After evaporating excess anhydride the semi-crystalline mass was dissolved in a 10% solution of sodium carbonate. The sodium carbonate solution was separated and acidified with hydrochloric acid; 0.5 g. (41.5%) of crude acid, m.p. 190—192°, was obtained by filtration. Recrystallization from 50% ethanol gave the pure acid melting at 197—198°.

2-Ethyl-2-(p-dimethylaminophenyl)-butyric acid (17)

Following the procedure of Bowman and Stroud[3] the mixture of 2.3 g. of 2-ethyl-2-(*p*-nitrophenyl)-butyric acid, 1 g. of sodium acetate, 1 g. of charcoal, 20 ml. of ethanol, 25 ml. of water, and 0.2 g. of palladium chloride (dissolved in 1 ml. of 2 *N*-hydrochloric acid) was hydrogenated with stirring at room temperature. After filtration and extraction of the catalyst with ethanol, the combined solutions were concentrated by evaporation until crystallization commenced. The crude-dimethylaminoacid (2.3 g. (93%), m. p. 140—145°) was recrystallized from 54% ethanol.

Methyl 2-ethyl-2-(p-dimethylaminophenyl)-butyrate (18)

To a solution of 0.5 g. of 2-ethyl-2-(*p*-dimethylaminophenyl)-butyric acid in 10 ml. of ether 10 ml. of an ethereal solution of diazomethane[4] (obtained from 1 g. nitrosomethyl-urea) was gradually added while cooling and stirring. After standing for one hour the solvent and excess diazomethane were evaporated under reduced pressure giving colourless crystals, which after recrystallization from methanol melted at 79—80°.

Methyl 2-ethyl-2-(p-acetaminophenyl) butyrate (19)

Prepared from 0.6 g. of the pure acid with diazomethane as described for compound 18.

2-Ethyl-2-(p-nitrophenyl)-butyramide (20)

A. From 2-ethyl-2-phenylbutyramide. — Fifty milliliters of concentrated sulphuric acid were placed in a 100 ml. round bottomed flask equipped with a mechanical stirrer and a thermometer. The flask was immersed in an ice bath and with stirring, 10 g. of the finely powdered amide 26 added. To this solution 4 ml. of fuming nitric acid was added dropwise during 20 minutes. The temperature of the mixture was maintained at 0—10°. After keeping in an ice bath for 30 minutes the mixture was poured onto ice and the crude product filtered off, washed and dried. Three recrystallizations from ethanol gave 7 g. (56%) of the nitro-amide as colourless prisms which melted at 127—128°.

B. From 2-ethyl-2-(*p*-nitrophenyl)-butyric acid. — To a solution of 1 g. of 2-ethyl-2-(*p*-nitrophenyl)-butyric acid (14) in 10 ml. of dry benzene 2 ml. of thionyl chloride were added. The solution was refluxed for 2 hours, and then the solvent and excess thionyl chloride were removed by distillation. Without further purification the crude acid chloride was dissolved in 10 ml. of dry benzene and the solution saturated with dry ammonia. The solvent was evaporated, and the crude product after recrystallization from ethanol gave 0.4 g. (40%) of crystals with the m.p. 127—128°, which showed no depression when mixed with the above compound.

C. From 2-ethyl-2-(*p*-nitrophenyl) butyronitrile. — The mixture of 3 g. of 2-ethyl-2-(*p*-nitrophenyl)-butyronitrile and 10 ml. of 96% sulphuric acid was heated on the water-bath at 70° for 8 hours. The dark brown reaction product was poured on ice and the viscous oil extracted with benzene. The benzene layer was washed

with 10% sodium carbonate solution, and then with water. The solvent was distilled; the viscous residue solidified upon standing; yield 2.3 g. (67%), m.p. 118—122°. Recrystallization gave the pure amide melting at 127—128° which showed no depression in m.p. when mixed with authentic specimens.

2-Ethyl-2-(p-dimethylaminophenyl)-butyramide (21)

The pure dimethylamino amide was prepared from the corresponding nitro-amide by simultaneous reduction and methylation, using a procedure similar to that given above for compound 18.

2-Ethyl-2-(p-aminophenyl)-butyramide (22)

Prepared from the corresponding nitro-amide by reduction, using a procedure similar to that given above for compound 15.

2-Ethyl-2-(p-nitrophenyl)-butyronitrile (24)

The title compound was prepared by nitrating 2-ethyl-2-phenylbutyronitrile[1] using a procedure similar to that given above for compound 14. From 10 g. of nitrile, 6 g. (47.5%) m. p. 76—80°, were obtained. Further recrystallization from benzene gave crystals with m.p. 81—83°.

Anal. $C_{12}H_{14}N_2O_2$ (218.24) calc'd.: C 66.03; H 6.47; N 12.84%
found : C 66.35; H 6.63; N 13.05%

2-Ethyl-2-phenylbutyric acid (25)

A mixture of 85 g. of 2-ethyl-2-phenyl-butronitrile, 250 ml. of concentrated sulphuric acid and 25 ml. of water was heated with stiring on a steam-bath for four hours. The mixture was cooled, poured onto ice and extracted with benzene. The benzene solution was washed with water and the solvent distiled; the viscous residue solidified upon standing; yield 77 g. (81%), m. p. 49—51°. (Chapman *et al.*,[1] reported the m.p. 51—52°; yield 70%).

Treatment of the crude amide (77 g., m. p. 49—51°) with butyl nitrite in acetic acid in the same way as described by Sperber *at al.*,[2] gave 70 g. (90%) 2-ethyl-2-phenyl-butyric acid, m.p. 90—91° (73% over-all yield from the nitrile).

The microanalyses were carried out in our microanalytical laboratory by Mrs. Škoda, D. Boršić, and by Mrs. A. Častek from the Institute of Organic Chemistry, Faculty of Pharmacy, Zagreb.

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3. R. E. Bowman and H. H. Stroud, *J. Chem. Soc.* **1950**, 1342.
4. F. F. Arndt, *Org. Synth., Coll. Vol.* **3** (1955) 165.
5. K. Dostal and D. Kolbach, *Acta Pharm. Jug.* **11** (1961) 15.

IZVOD

Supstance, koje djeluju na centralni nervni sistem. IV. Derivati 2-etil-2-fenilbutiramida

S. Kukolja, Lj. Polak, H. Krnjević i M. Videk

U svrhu ispitivanja odnosa između strukture i djelovanja na centralni nervni sistem priređeni su dosad neopisani *N*- i *p*- supstituirani derivati 2-etil-2-fenilbutiramida.

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH
I KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 24. srpnja 1961.

ERRATUM:

Beginning with line 27, the first two sentences read:

In addition to amides substituted on the amide nitrogen atom we have also synthesized *p*-substituted derivatives of 26 outlined in Chart A and described in Table III. These compounds were prepared by conventional syntheses and details of their preparations are given in the Experimental Section.