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Original Scientific Paper

Substances Acting on the Central Nervous System. V.* Derivatives of *N*-Substituted-2(1-cyclohexenyl)butyramide**

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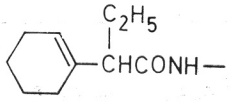
In a study od the relationship between structure and central nervous system activity a number of *N*-acyl-2(1-cyclohexenyl)butyramides (IX—XV), 2-ethyl-2(1-cyclohexenyl)butyramide, 2-phenyl-2(1-cyclohexenyl)butyronitrile and a series of *N*-alkyl-2(1-cyclohexenyl)butyramides (XVI—XXVII) have been synthesized.

In earlier papers of this series[1–3] we described *N*-substituted 2-phenyl- and 2-ethyl-2-phenylbutyramides. Comparing change in physiological properties provoked by substituting the phenyl group by cyclohexenyl group in barbituric acid derivatives[4] (Phenobarbital-Cyclobarbital) we considered it of interest to prepare partially hydrogenated 2-phenyl butyramides and to compare the properties of this two classes of compounds and their activity on the central nervous system (CNS). With this purpose we have synthesized a series of *N*-acyl-2(1-cyclohexenyl)butyramides containing the 2(1-cyclohexenyl)butyramide group:



The *N*-acyl-2(1-cyclohexenyl)butyramides have been prepared from 2(1-cyclohexenyl)butyronitrile by application of the McElvain-Stevens modification[5] of Pinner's synthesis.[6].

Methyl *N*-acyl-2(1-cyclohexenyl)butyroimidates have been prepared by reacting the so obtained methyl 2(1-cyclohexenyl)butyroimidates with various acid chlorides (Table I). The resulting acylated imido esters have been converted to *N*-acyl-2(1-cyclohexenyl)butyramides by treatment with concentrated HCl (Table II).

Methyl *N*-acyl-2(1-cyclohexenyl)butyroimidates are colourless oils unstable at room temperature. *N*-Acyl-2(1-cyclohexenyl)butyramides are well cristallizable colourless substances, soluble in ethanol, insoluble in water.

The *N*-alkyl-2(1-cyclohexenyl)butyramides listed in Table III were prepared by the reaction of equivalent amounts of the respective acid chlorides with various amines in the presence of sodium carbonate.

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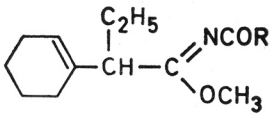
* Part. IV.: S. Kukolja, Lj. Polak, H. Krnjević, and M. Videk, *Croat. Chem. Acta* **33** (1961) 121.

** Taken from the thesis submitted by Lj. Polak, in partial fulfilment of the requirements for degree of Doctor of Chemistry at University of Zagreb.

TABLE I

Methyl N-acyl-2(1-cyclohexenyl)butyroimidates



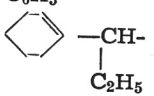
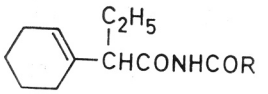
Compound	R	Yield %	B. p. °C/mm	Formula	Calc'd. (%)			Found (%)		
					C	H	N	C	H	N
II	CH_3-	49.3	114—117/0.08	$C_{13}H_{21}NO_2$	69.92	9.48	6.27	69.66	9.25	6.38
III	CH_3CH_2-	49.5	108—110/1.2	$C_{14}H_{23}NO_2$	70.85	9.77	5.90	70.92	9.61	5.66
IV	$CH_3CH_2CH_2$-	39.8	124—125/1.8	$C_{15}H_{25}NO_2$	71.67	10.03	5.57	71.41	9.75	5.93
V	$CH_3CH_2CH(C_6H_5)$-	61.2	170—172/1	$C_{21}H_{29}NO_2$	77.02	8.93	4.28	76.58	8.73	4.70
VI	$C_6H_5CH_2$-	80.6	170—172/1	$C_{19}H_{25}NO_2$	76.22	8.42	4.68	76.38	8.35	4.90
VII	C_6H_5-	59.6	187—190/1	$C_{18}H_{23}NO_2$	75.75	8.12	4.91	75.50	7.91	5.12
VIII		69.4	190—192/1	$C_{21}H_{33}NO_2$	76.09	10.03	4.23	76.24	10.04	4.53

TABLE II

N-Acyl-2(1-cyclohexenyl)butyramides



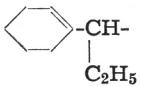
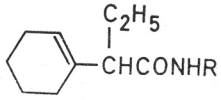
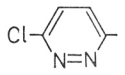
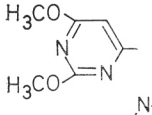
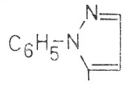
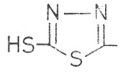
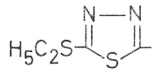
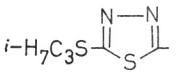
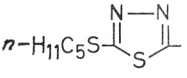
Compound	R	Yield %	M. p. °C	Formula	Calc'd. (%)			Found (%)		
					C	H	N	C	H	N
IX	CH_3-	57.4	82—84	$C_{12}H_{19}NO_2$	68.86	9.15	6.69	68.62	9.30	6.95
X	CH_3CH_2-	35.8	54—56	$C_{13}H_{21}NO_2$	69.92	9.48	6.27	69.81	9.39	6.57
XI	$CH_3CH_2CH_2$-	62.4	43—45	$C_{14}H_{23}NO_2$	70.85	9.77	5.90	71.12	9.75	6.09
XII	$CH_3CH_2CH(C_6H_5)$-	42.5	86—88	$C_{20}H_{27}NO_2$	76.64	8.68	4.47	76.41	8.57	4.34
XIII	$C_6H_5CH_2$-	58.7	85—86	$C_{18}H_{23}NO_2$	75.75	8.12	6.91	75.60	8.37	6.91
XIV	C_6H_5-	49.3	117—118	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.06	7.97	5.17
XV		55.5	89—90	$C_{20}H_{31}NO_2$	75.91	9.84	4.41	75.91	9.60	4.71

TABLE III

N-Alkyl-2(1-cyclohexenyl)butyramides



Compound	R	Yield %	M. p. °C	Formula	Calc'd. Found (%) C	H	N
XVI	$C_6H_5-CH_2-$	41.7	72—73	$C_{17}H_{23}NO$	79.33 79.25	9.01 8.71	5.44 5.56
XVII	C_6H_5-	82.3	73—75	$C_{16}H_{21}NO$	78.97 78.85	8.70 8.49	5.76 6.03
XVIII	$C_6H_5-CH(CH_3)-$	42	113—114	$C_{18}H_{25}NO$	79.68 79.49	9.29 9.07	5.16 5.13
XIX		61.47	133—134	$C_{15}H_{20}N_2O$	73.73 73.54	8.25 8.17	11.47 11.73
XX		30.6	105—106	$C_{14}H_{19}N_3O$	68.54 68.28	7.81 7.65	17.13 17.03
XXI		71.6	94—95	$C_{14}H_{18}N_3OCl$	60.12 59.88	6.49 6.44	15.02 15.23
XXII		63	90—93	$C_{16}H_{23}N_3O_3$	62.93 62.79	7.59 7.79	13.76 14.05
XXIII		74.2	94—96	$C_{19}H_{23}N_3O$	73.75 73.77	7.49 7.68	13.58 13.32
XXIV		88.3	168	$C_{12}H_{17}N_3OS_2$	50.88 51.09	6.05 5.89	14.83 14.60
XXV		44.7	110—111	$C_{14}H_{21}N_3OS_2$	54.01 54.03	6.80 6.54	13.50 13.73
XXVI		86.1	114—115	$C_{15}H_{23}N_3OS_2$	55.37 55.60	7.13 7.39	12.92 12.68
XXVII		90	80—82	$C_{17}H_{27}N_3OS_2$	57.77 57.50	7.70 7.95	11.89 12.07

In order to prepare 2-ethyl-2(1-cyclohexenyl)butyramide, we tried to hydrolyse 2-ethyl-2(1-cyclohexenyl)butyronitrile[7]. However, conventional procedures

using sulphuric acid[8], a mixture of acetic and sulphuric acid[9], phosphoric acid[8] or potassium hydroxide in ethylene glycole solution[10] were unsuccessful and only the starting material could be isolated. The hydrolysis was eventually achieved by heating at 100° with 80% H_2SO_4.

Our attempts to hydrolyse 2-ethyl-2(1-cyclohexenyl)butyramide to the corresponding acid or to prepare its *N*-acyl derivatives, have so far been unsuccessful, illustrating the unusual stability of the 2-ethyl-2(1-cyclohexenyl) butyramide.

2-Phenyl-2(1-cyclohexenyl) butyronitrile was prepared from cyclohexylidenephenyl-acetonitrile[11] by alkylation with ethyl iodide according to a general procedure previously applied for the alkylation of malonic ester derivatives[12].

Preliminary pharmacological screening tests have shown that some of the derivatives possess sedative and hypnotic activity. The results of the pharmacological investigation will be published elswhere.

EXPERIMENTAL*

Methyl 2(1-cyclohexenyl)butyroimidate (I)

Dry hydrogen chloride was bubbled through an ice-cold mixture of 25 ml. (0.6 mole), of absolute methyl alcohol and 74.5 g. (0.5 mole) of 2(1-cyclohexenyl)butyronitrile until 19 g. (0.59 mole) was absorbed. The crystallisation set in after keeping the resulting reaction mixture for 4 days in an ice-box. An equal volume of dry ether was then added and the precipitate was filtered off. The yield of I HCl was 65.2—70 g. (60—64%), m. p. 100—105° C.

70 g. (0.308 mole) of I HCl was neutralised with a solution of 69 g. (0.5 mole) of potassium carbonate in 100 ml. of water and immediately taken up in 200 ml. of ether. The layers were separated and the aqueous layer was extracted with one 50 ml. portion of ether. The combined ether extracts were dried over magnesium sulphate and distilled. The yield of methyl 2(1-cyclohexenyl)butyroimidate, b. p. 109—110° C/14 mm, was 54.36 g. (60%).

Anal. $C_{11}H_{19}NO$ (181.27) Calc'd.: C 72.88; H 10.57; N 7.73%
Found: C 72.72; H 10.44; N 7.63%

Methyl N-acyl-2(1-cyclohexenyl)butyroimidates

Compounds II—VIII of Table I were obtained by the following general procedure:

To a solution of 0.1 mole of methyl 2(1-cyclohexenyl)butyroimidate in 25 ml. of ether 0.05 mole of the appropriate acid chloride in 20 ml. ether was gradually added and the mixture stirred and cooled in an ice-bath. After standing for 10 hr. at room temperature the precipitated imido ester hydrochloride was filtered off and washed with ether. The solvent was evaporated and the oily residue distilled *in vacuo* giving methyl *N*-acyl-2(1-cyclohexenyl)butyroimidates.

N-Acyl-2(1-cyclohexenyl)butyramides

Compounds IX—XV of Table II were obtained by the following general procedure:

To an ice-cold solution of 0.02 mole of methyl *N*-acyl-2(cyclohexenyl)butyroimidate in 20 ml. of ether a few drops of concentrated hydrochloric acid were added. The mixture was kept three hours at room temperature and after evaporation *in vacuo* N-acyl-2(1-cyclohexenyl)butyramides precipitated and were recrystallised from dilute ethanol.

N-Substituted-2(1-cyclohexenyl)butyramides

Compounds XVI—XXVII in Table III were prepared from 2(1-cyclohexenyl) butyryl chloride and an appropriate amine by the following general procedure:

* All melting points are uncorrected.

To a solution of 0.02 mole of 2(1-cyclohexenyl)butyryl chloride in 20 ml. of dry benzene (or dimethylformamide) and 0.01 mole of anhydrous sodium carbonate were added 0.1 mole of the appropriate amine. The mixture was heated on the wather-bath for 2 hr. and allowed to stand at room temperature overnight. After removing the solvent, the residue, which solidified on cooling, was recrystallised. Melting points, yields and analyses are recorded in Table III.

2-Ethyl-2(1-cyclohexenyl)butyramide (XXVIII)

In a two-liter, three necked flask equipped with a stirrer and a reflux condenser were added 93 ml. of 80% sulphuric acid and 17.7 g. (0.1 mole) 2-ethyl-2(1-cyclohexenyl) butyronitrile. The reaction mixture was heated and stirred vigorously for 12 hr. on a steam-bath. The dark brown reaction product was poured on ice and the viscous oil extracted with chloroform. The chloroform layer was washed with a 10% aqueous sodium carbonate solution and then with water. The solvent was removed *in vacuo* and the viscous residue distilled. Yield 12.1 g. (61.9%), b. p. $140^0/10^{-3}$ mm.

Anal. $C_{12}H_{21}NO$ (195.3) Calc'd.: C 73.79; H 10.84; N 7.17%
Found: C 73.79; H 10.60; N 7.44%

2-Phenyl-2(1-cyclohexenyl)butyronitrile (XXIX)

To freshly prepared sodium amide [from 1.2 g. of sodium in liquid ammonia (30 ml.)] 9.85 g. (0.05 mole) of 2-phenyl-cyclohexylidene acetonitrile dissolved in 50 ml. dry benzene was added. Stirring was continued at room temperature for 1 hr. and for another 2 hr. under reflux, while the reaction mixture was freed from ammonia. The reaction mixture was then cooled and 9.35 g (0.06 mole) ethyl iodide was added dropwise with gentle cooling. After heating and refluxing on the water bath for 10 hr., 100 ml. of water were added. The mixture was neutralized with hydrochloric acid to pH 7 and extracted three times with 100 ml. of benzene. The benzene extracts were washed until neutral with water and dried over anhydrous sodium sulphate. Benzene was removed by distillation and the residual oil distilled at 125^0 C/0.5 mm to yield 6.12 g. (50%) of 2-phenyl-2(1-cyclohexenyl)butyronitrile.

Anal. $C_{16}H_{19}N$ (225.32) Calc'd.: C 85.28; H 8.50; N 6.22%
Found: C 85.50; H 8.63; N 6.17%

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IZVOD

Supstancije koje djeluju na centralni nervni sistem. V. Derivati 2(1-cikloheksenil)butiramida

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Djelovanjem kiselinskih klorida na metil 2(1-cikloheksenil)butiroimidat u eteru priređeni su pripadni metil *N*-acil-2(1-cikloheksenil)butiroimidati (II—VIII). Pripravljeni imidobutirati prevedeni su djelovanjem koncentrirane solne kiseline u eteru u *N*-acil-2(1-cikloheksenil)butiramide (IX—XV).

Ovi amidi izolirani su u obliku stabilnih kristaliziranih spojeva. Djelovanjem amina na 2(1-cikloheksenil)butiroil klorid u prisutnosti natrijeva karbonata priređeni su *N*-alkil-2(1-cikloheksenil) butiramidi (XVI—XXVII). Hidrolizom 2-etil-2(1-cikloheksenil)butironitrila sa 80%-tnom sumpornom kiselinom pripravljen je 2-etil-2(cikloheksenil)butiramid, a iz cikloheksiliden fenil acetonitrila reakcijom sa ekvivalentnom količinom natrium amida u tekućem amonijaku, a zatim alkiliranjem sa etil jodidom pripravljen je 2-fenil-2(1-cikloheksenil)butironitril.

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ZAGREB

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