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# Substances Acting on the Central Nervous System. II.* Derivatives of *N*-(α-bromoacyl)-2-phenylbutyramide**

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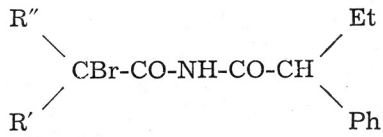
In connection with the investigation of substances acting on the central nervous system new *N*-substituted 2-phenylbutyramides (I—V) were synthesized. These amides were prepared by hydrolysis of the appropriate methyl *N*-substituted 2-phenyliminobutyrates (VI—IX).

In continuation of our studies in this series a number of the hitherto undescribed *N*-(α-bromoacyl)-2-phenyl butyramides (I—V) have been prepared for pharmacological evaluation as potential sedatives and soporifics. This type of compounds was described in the first publication[1] where it was pointed




I R′ = H, R″ = $CH_3$ III R′ = H, R″ = $CH(CH_3)_2$

II R′ and R″ = $CH_3$ IV R′ = H, R″ = $CH_2Br$

out that the majority of hypnotics and sedatives contain the -Ph-(Et)C-CO-NH- group. In the present paper we have combined this group with the R′-(R″)--CBr-CO- group which is characteristic for the well known sedatives and hypnotics, *e. g.*, 2-bromo-*N*,*N*-diethyl*iso*valerylamide[2], 2-bromo-2-ethyl-2-*iso*propylacetamide (Neodorm)[3], 2-bromo-2-ethylbutyramide (Neuronal)[4], 2-bromo-*iso*valeryl urea (Bromural)[5], 2-bromo-2-ethylbutyryl urea (Adalin)[6], and acetyl 2-bromo-ethylbutyryl urea (Abasin)[7].

A survey of the literature in this field reveals that similar attempts have been made to prepare biologically active compounds by the combination of two *active* groups within a single molecule. So Hill and Degnan[8] found that the extending of the -CO-NH- group from the acid amide to urea produces a favourable effect on the activity and the therapeutic index of the compounds of this class. Berger *et al.*[9] made a similar effort in the search for new sedatives by the combination of two *active* groups. They combined α-halogeno*iso*valeryl

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* Paper I, S. Kukolja and Lj. Polak, *Croat. Chem. Acta* **32** (1960) 23.

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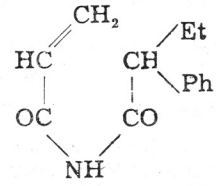
and urethane groups preparing in this manner the *N*-(α-halogeno*iso*valeryl) urethanes. A similar combination was described by Perelstein and Bürgi[10]. They found that certain aromatic acid amides containing the α-bromo*iso*valeryl group have hypnotic properties.

Besides α-bromo derivatives we have also synthesized *N*-acryloyl-2-phenylbutyramide (V). This compound is the structural analogue of 3-ethyl-3-phenyl--2,6-dioxo-piperidine (Doridene)[11] and therefore particularly of interest in the study of the correlation between of molecular shape and biological activity.



V

The *N*-(α-bromoacyl)-2-phenylbutyramides (I—IV) were prepared from methyl *N*-(α-bromoacyl)-2-phenylbutyrimidates (VI—IX) and these in turn from the methyl 2-phenylbutyrimidate and an appropriate α-bromoacyl halide by the procedure given in the first paper[1]. While hydrolysis of the most of methyl *N*-acyl-2-phenylbutyrimidates according to the standard method proceeds smoothly and in good yields, this is not the case with methyl *N*-(α-bromo--α-ethylbutyryl)-2-phenylbutyrimidate (X). Due to unexpected resistance to hydrolysis and susceptibility to side reaction we failed to obtain the expected *N*-(α-bromo-α-ethylbutyryl)-2-phenylbutyramide. By hydrolysis of methyl *N*-(*o*-chlorobenzoyl-2-phenylbutyrimidate (XI) according to the standard procedure *o*-chlorobenzamide, m. p. 141—142° was formed. This is obviously due to the electronegative effect of the chlorine atom in the ortho-position. The *N*-(α, β-dibromopropionyl)-2-phenylbutyramide (IV) was prepared by treating the *N*-acryloyl-2-phenylbutyramide (V) with pyridinium bromide perbromide.

The prepared *N*-substituted-2-phenylbutyramides are stable colourless compounds which can be crystallized from ethanol. The methyl *N*-(α-bromoacyl)-2-phenylbutyrimidates are colourless oils, fairly stable in closed flask at room temperature. They must be carefully protected from moisture throughout the course of the preparation and purification as they react with water to give corresponding amides and esters.

The results of the pharmacological studies will be published elsewhere.

## EXPERIMENTAL

All melting points are uncorrected.

*Methyl* N-(*α-bromopropionyl*)-*2-phenyliminobutyrate* (VI)

Prepared from 2-bromopropionyl chloride and methyl 2-phenyliminobutyrate as described in the general procedure given in the first paper[1]. Yield: 49%, b. p. 132—133° at 0.9 mm.

*Anal.* 15.03 mg. subst.: 29.69 mg. $CO_2$, 7.72 mg. $H_2O$
$C_{14}H_{18}BrNO_2$ (312.21) calc'd.: C 53.86; H 5.81%
found: C 53.90; H 5.74%

*Methyl* N-(*α-bromoisobutyryl*)-*2-phenyliminobutyrate* (VII)

Prepared from 2-bromo*iso*butyryl bromide[12] and methyl 2-phenyliminobutyrate. Yield: 57%, b. p. 125°/0.6 mm.

*Anal.* 11.29 mg. subst.: 22.75 mg. $CO_2$, 5.91 mg. $H_2O$
$C_{15}H_{20}BrNO_2$ (326.23) calc'd.: C 55.22; H 6.17%
found: C 54.99; H 5.85%

*Methyl* N-(*α-bromoisovaleryl*)-*2-phenyliminobutyrate* (VIII)

Prepared from 2-bromo*iso*valeryl chloride and methyl 2-phenyliminobutyrate. Yield: 43.5%, b. p. 149—150° at 1.5 mm.

*Anal.* 12.09 mg. subst.: 24.90 mg. $CO_2$, 6.64 mg. $H_2O$
$C_{16}H_{22}BrNO_2$ (340.26) calc'd.: C 56.48; H 6.51%
found: C 56.34; H 6.16%

*Methyl* N-*acryloyl*-*2-phenyliminobutyrate* (IX)

Prepared from acryloyl chloride[13] and methyl 2-phenyliminobutyrate. Yield: 47.5%, b. p. 126—128°/2.2 mm.

*Anal.* 10.70 mg. subst.: 28.40 mg. $CO_2$, 6.81 mg. $H_2O$
$C_{17}H_{14}NO_2$ (231.28) calc'd: C 72.70; H 7.41%
found: C 72.44; H 7.12%

*Methyl* N-(*α-bromo-α-ethylbutyryl*)-*2-phenyliminobutyrate* (X)

Obtained from 2-bromo-2-ethylbutyryl chloride[14] and methyl 2-phenyliminobutyrate. Yield: 53.5%, b. p. 147—149°/1 mm.

*Anal.* 13.46 mg. subst.: 28.27 mg. $CO_2$, 8.16 mg. $H_2O$
$C_{17}H_{24}BrNO_2$ (354.28) calc'd.: C 57.63; H 6.82%
found: C 57.32; H 6.78%

*Methyl* N-(*o-chlorobenzoyl*)-*2-phenyliminobutyrate* (XI)

Prepared from o-chlorbenzoyl chloride and methyl 2-phenyliminobutyrate. Yield: 71.3%, b. p. 178—185°/0.8 mm.

*Anal.* 13.20 mg. subst.: 33.81 mg. $CO_2$, 6.30 mg. $H_2O$
$C_{18}H_{18}ClNO_2$ (315.78) calc'd.: C 68.47; H 5.74%
found: C 68.66; H 5.34%

*N-(α-bromopropionyl)-2-phenylbutyramide* (I)

Prepared from o-chlorobenzoyl chloride and methyl 2-phenyliminobutyrate. in the general procedure given in the first paper[1]. Yield: 46%, colourless crystals from ethanol, m. p. 126—128°.

*Anal.* 10.91 mg. subst.: 20.80 mg. $CO_2$, 4.97 mg. $H_2O$
3.29 mg. subst.: 0.137 ml. $N_2$ (24°, 753 mm.)
$C_{13}H_{16}BrNO_2$ (298.18) calc'd.: C 52.37; H 5.41; N 4.59%
found: C 52.03; H 5.09; N 4.74%

N-(*α-bromopropionyl*)-*2-phenylbutyramide* (I)

Obtained as colourless crystals from methyl *N*-(α-bromo*iso*butyryl)-2-phenyliminobutyrate. Yield: 67%, m. p. 96—97° (from ethanol).

*Anal.* 11.48 mg. subst.: 22.75 mg. $CO_2$, 5.68 mg $H_2O$
3.72 mg. subst.: 0.156 ml. $N_2$ (24°, 756 mm.)
$C_{14}H_{18}BrNO_2$ (312.20) calc'd.: C 53.86; H 5.81; N 4.48%
found: C 54.08; H 5.53; N 4.79%

N-(α-*bromoisovaleryl*)-2-*phenylbutyramide* (III)

Prepared from methyl *N*-(α-bromoisovaleryl)-2-phenyliminobutyrate. Yield 45%, m. p. 106—109° (from ethanol).

*Anal.* 11.20 mg. subst.: 22.70 mg. $CO_2$, 5.90 mg. $H_2O$
$C_{15}H_{20}BrNO_2$ (326.23) calc'd.: C 55.22; H 6.18%
found: C 55.31; H 5.89%

N-*Acryloyl-2-phenylbutyramide* (V)

Obtained as colourless crystals from methyl *N*-acryloyl-2-phenyliminobutyrate. Yield: 38%, m. p. 107.5—108.5° (from *dil.* ethanol).

*Anal.* 11.00 mg. subst.: 28.82 mg. $CO_2$, 6.60 mg. $H_2O$
3.42 mg. subst.: 0.200 ml. $N_2$ (22°, 755 mm.)
$C_{13}H_{15}NO_2$ (217.26) calc'd.: C 71.86; H 6.96; N 6.45%
found: C 71.50; H 6.72; N 6.72%

N-(α, β-*dibromopropionyl*)-2-*phenylbutyramide* (IV)

To a solution of 1.1 g. of *N*-acryloyl-2-phenylbutyramide in 10 ml. of acetic acid 1.6 g. of pyridinium bromide perbromide[15] was added. The mixture was warmed on the steam bath during five minutes, cooled under the tap and then 1 ml. of water added. After keeping for two hours in a refrigerator the precipitated crystals were filtered off. The crude product (1.0 g., m. p. 112—114°) was recrystallized three times from ethanol and melted at 122—123°.

*Anal.* 13.06 mg. subst.: 19.75 mg. $CO_2$, 4.50 mg. $H_2O$
3.60 mg. subst.: 0.127 ml. $N_2$ (27°, 756 mm.)
$C_{13}H_{15}BrNO_2$ (377.09) calc'd: C 41.40; H 4.00; N 3.27%
found: C 41.27; H 3.85; N 3.99%

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## IZVOD

**Supstance koje djeluju na centralni nervni sistem. II. Derivati *N*-(α-bromacil)-2-fenilbutiramida**

*Lj. Polak i S. Kukolja*

U vezi sa istraživanjem spojeva koji djeluju na centralni nervni sistem pripravljeno je nekoliko do sada neopisanih *N*-supstituiranih 2-fenilbutiramida (I—V). Ovi amidi priređeni su hidrolizom odgovarajućih metil *N*-supstituiranih 2-fenilimino-butirata (VI—IX).


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