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## Substances Acting on the Central Nervous System. I. Derivatives of *N*-Acyl-2-phenylbutyramide

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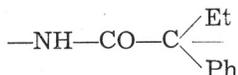
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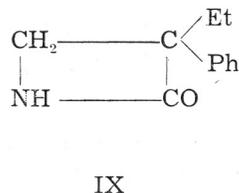
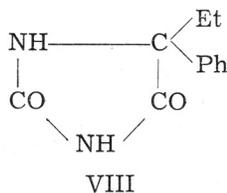
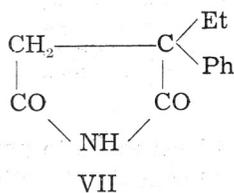
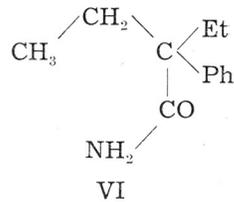
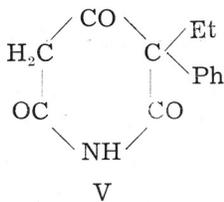
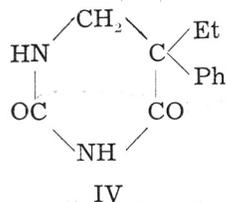
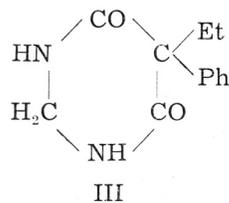
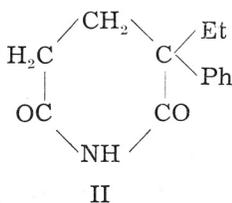
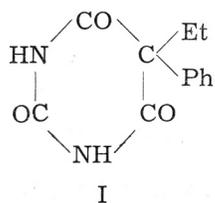
In search of compounds which may have hypnotic and sedative as well as anticonvulsant activities, the *N*-acyl-2-phenylbutyramides (X—XIVb) have been prepared. These substances have been synthesized by treating the alkyl *N*-acyl iminoesters with hydrochloric acid and the latter (X—XVa) by condensation of the iminoesters with appropriate acyl chlorides.

During the last few years numerous attempts have been made to prepare compounds with hypnotic and sedative as well as anticonvulsant activities without disadvantages of the barbiturates. With this purpose some work towards synthesis of the substituted succinimides, oxazinediones, partially or completely hydrogenated pyridines and pyrimidines has been done. Among these may be cited 3-ethyl-3-phenyl-2,6-dioxo-piperidine<sup>1,2</sup>, 5-ethyl-5-phenyl-4,6-dioxo-hexahydropyrimidine<sup>3</sup>, *N*-methyl-3-ethyl-3-phenyl-2,5-dioxo-pyrrolidine<sup>4</sup>, 5-ethyl-5-phenyl-2,4-dioxo-oxazine-(1,3), 3-ethyl-3-phenyl-2-oxo-azetidione, 5-ethyl-5-phenyl-2,4-dioxo-hexahydropyrimidine<sup>5</sup>, 3,3-diethyl-2,4-dioxo-tetrahydropyridine<sup>6</sup>, 3,3-diethyl-2,4-dioxo-piperidine<sup>7</sup>, 3-phthalimido-2,6-dioxo-piperidine<sup>8</sup> and 3-ethyl-3-phenyl-2,4,6-trioxo-piperidine<sup>9</sup>. Moreover a series of acyclic hypnotics has been synthesized and examined for narcotic activity<sup>10,11</sup>.

From the structural formulas of the phenobarbital (I), 3-ethyl-3-phenyl-2,6-dioxo-piperidine (II), 5-ethyl-5-phenyl-4,6-dioxo-hexahydropyrimidine (III), 5-ethyl-5-phenyl-2,4-dioxo-hexahydropyrimidine (IV), 3-ethyl-3-phenyl-2,4,6-trioxo-piperidine (V), phenyldiethylacetamide (VI), 3-ethyl-3-phenyl-2,5-dioxo-pyrrolidine (VII), 5-ethyl-5-phenyl hydantoine (VIII), and 3-ethyl-3-phenyl-2-oxo-azetidione (IX) it can be seen that they all contain the following group.\*

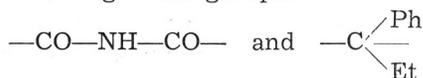


\* Note added in Proof. — A synthesis of 3-ethyl-3-phenyl-2,6-dioxo-piperazine has been recently reported by P. T. Izzo and S. S. Safir (*J. Am. Chem. Soc.*; **81** (1959) 4668; see ref. 4.), while E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani published a paper (*Helv. Chim. Acta* **42** (1959) 2370.) dealing with the preparation of 3-ethyl-3-phenyl-2,4-dioxo-azetidione. These hypnotics and sedatives contain also the -Ph(Et)-C-CO-NH-CO- group.

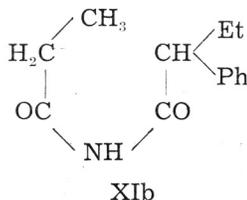
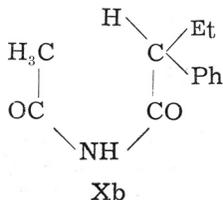


It seemed to us that it would be of certain interest to elucidate (i) which group in these compounds is responsible for the activity on the central nervous system, (ii) which effect will have the extension of characteristic group  $\text{-NH-CO-C(Et)Ph-}$  with  $\text{RCO-}$  or/and  $\text{RCH}_2\text{-}$  radical on the one or another side and (iii) relationship between cyclic and acyclic compounds of this type and its activity.

It has been known for a long time that certain acid amides exhibit strong hypnotic and sedative effect. In order to study the correlation between structure and activity on the central nervous system and to answer some of the above mentioned questions, we prepared some derivatives of the *N*-acyl-2-phenylbutyramide containing these groups:

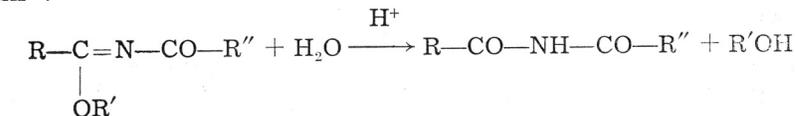


We consider that *N*-acetyl-2-phenylbutyramide (Xb) and *N*-propionyl-2-phenylbutyramide (XIb) are particularly interesting because they are acyclic



analogs of the 3-ethyl-3-phenyl-2,5-dioxo-pyrrolidine and 3-ethyl-3-phenyl-2,6-dioxo-piperidine respectively.

The *N*-acyl-2-phenylbutyramides described in this paper were prepared by treating the alkyl *N*-acyl iminoesters with concentrated hydrochloric acid according to the procedure reported by Wheeler *et al.*<sup>12</sup> and McElvain and Stevens<sup>13</sup>.



	(a)		(b)
X	R = Ph(Et)CH	R' = Me	R'' = Me
XI	R = Ph(Et)CH	R' = Me	R'' = Et
XII	R = Ph(Et)CH	R' = Me	R'' = Ph
XIII	R = Ph(Et)CH	R' = Me	R'' = PhCH <sub>2</sub>
XIV	R = Ph(Et)CH	R' = Me	R'' = Ph(Et)CH
XV	R = PhCH <sub>2</sub>	R' = Et	R'' = Ph(Et)CH

The corresponding alkyl *N*-acyl iminoesters were prepared by condensation of the iminoesters with acyl chlorides in the usual manner<sup>12,14</sup>. *N*-Acetyl-2-phenylbutyramide (Xb) was also obtained from 2-phenylbutyramide and ketene according to the procedure described by Dunbar and White<sup>15</sup>. As a by-product of this reaction 2-phenylbutyronitrile was obtained. This is in agreement with the mechanism proposed by Smirnova *et al.*<sup>16</sup>.

The prepared *N*-acyl-2-phenylbutyramides are well crystallized colourless substances, soluble in ethanol, benzene, ether and hot water. The alkyl *N*-acyl iminoesters 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 infrared spectra of synthesized *N*-acyl-2-phenylbutyramides have been recorded. The values are tabulated in Table I and its representative spectrum is shown in Fig. 1. We have also recorded the infrared spectrum of 3-ethyl-3-phenyl-2,6-dioxo-piperidine (Fig. 1) and compared it with the spectra of the *N*-acyl-2-phenylbutyramides. The values are in accordance with the absorption bands reported for the compounds of this type<sup>17,18</sup>.

A report on the pharmacology of these compounds will be published elsewhere.

TABLE I  
Infrared absorption bands ( $\mu$ )

Compound	N-H stretching frequencies		C=O stretching frequencies		Ph ring frequencies	
Xb	3.09	3.18	5.81		6.25	6.67
XIb	3.09	3.18	5.81	5.89	6.23	6.62
XIIb	3.09		5.85	5.99	6.25	6.67
XIIIb	3.28	3.21	5.81		6.27	6.65
XIVb	3.10	3.19	5.81		6.27	6.65

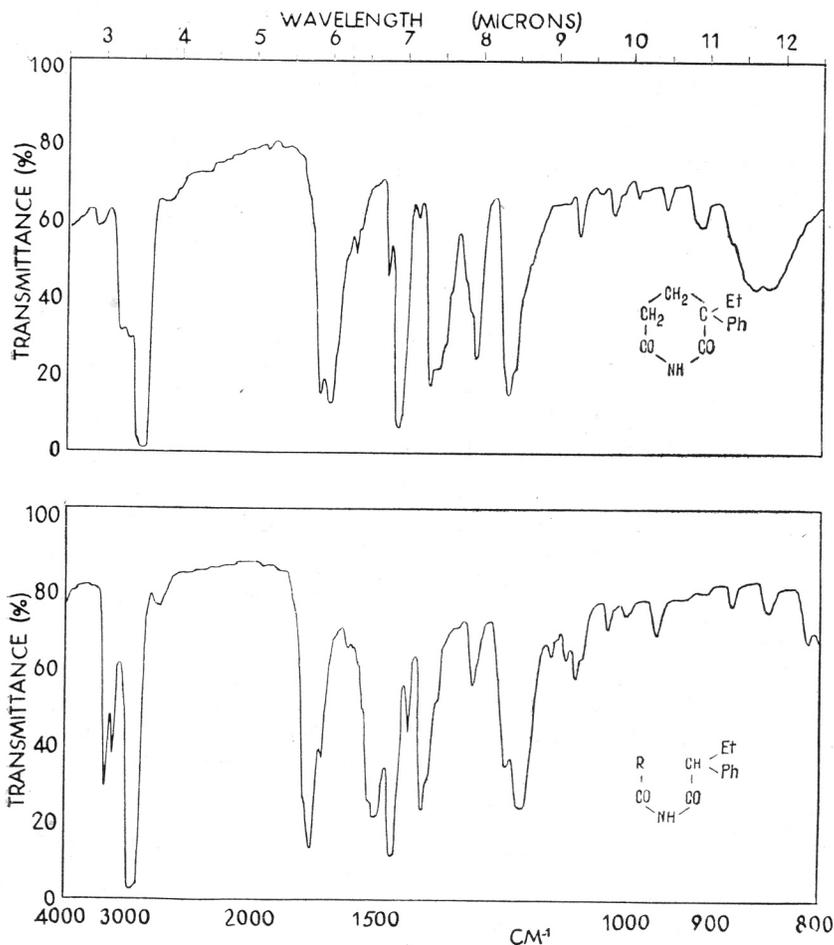


Fig. 1. Infrared absorption spectra in Nujol  
(Perkin-Elmer Mod. 134 spectrophotometer NaCl prisms)

#### EXPERIMENTAL

All melting points are uncorrected.

#### *Methyl 2-phenyliminobutyrate*

Following the procedure of McElvain and Stevens<sup>19</sup>, 213.5 g. of methyl 2-phenyliminobutyrate hydrochloride<sup>20</sup> was neutralized with a solution of 276 g. of potassium carbonate in 500 ml. of water and immediately taken up in 200 ml. of ether. The layers were separated and the aqueous layer was extracted with 100 ml. of ether. The combined ether solutions were dried and distilled. The yield of methyl 2-phenyliminobutyrate, b. p. 91–93° (2 mm.), was 129 g. (73%). The analytical sample was redistilled at 92–94°/2 mm,  $n_D^{25}$  1.5120,  $d_4^{25}$  1.0019.

Anal. 10.79 mg. subst.: 29.60 mg. CO<sub>2</sub>, 8.41 mg. H<sub>2</sub>O  
C<sub>11</sub>H<sub>15</sub>ON (177.24) calc'd.: C 74.54; H 8.53%  
found: C 74.86; H 8.72%

#### *General procedure for the preparation of alkyl N-acyl iminoesters*

To a solution of 0.1 mole of alkyl iminoester in 20 ml. of ether 0.05 mole of the appropriate acid chloride in 10 ml. of ether was gradually added and the mixture

stirred and cooled in an ice-bath. After standing for ten hours at room temperature the precipitated iminoester hydrochloride was filtered off and washed with ether. The solvent was evaporated and the remaining liquid was distilled *in vacuo* giving alkyl N-acyl iminoester. The yields ranged from 40—70%.

*Methyl N-acetyl-2-phenyliminobutyrate (Xa)*

Prepared from acetyl chloride and methyl 2-phenyliminobutyrate as described in the general procedure. Yield: 50%, b. p. 118—120°/2.5 mm,  $n_D^{25}$  1.5080.

*Anal.* 11.51 mg. subst.: 30.15 mg. CO<sub>2</sub>, 8.10 mg. H<sub>2</sub>O  
C<sub>13</sub>H<sub>17</sub>O<sub>2</sub>N (219.27) calc'd.: C 71.20; H 7.82%  
found: C 71.48; H 7.87%

*Methyl N-propionyl-2-phenyliminobutyrate (XIa)*

Prepared from propionyl chloride and methyl 2-phenyliminobutyrate. Yield: 47%, b. p. 118—122°/1.5 mm,  $n_D^{25}$  1.5074,  $d_4^{25}$  1.0235.

*Anal.* 13.83 mg. subst.: 36.45 mg. CO<sub>2</sub>, 10.00 mg. H<sub>2</sub>O  
C<sub>14</sub>H<sub>19</sub>O<sub>2</sub>N (233.30) calc'd.: C 72.07; H 8.21%  
found: C 71.92; H 8.09%

*Methyl N-benzoyl-2-phenyliminobutyrate (XIIa)*

Prepared from benzoyl chloride and methyl 2-phenyliminobutyrate. Yield: 69%, b. p. 145°/0.3 mm,  $n_D^{25}$  1.5620,  $d_4^{25}$  1.0944.

*Anal.* 9.71 mg. subst.: 27.40 mg. CO<sub>2</sub>, 5.70 mg. H<sub>2</sub>O  
5.50 mg. subst.: 0.112 ml. N<sub>2</sub> (22°, 760 mm.)  
C<sub>18</sub>H<sub>19</sub>O<sub>2</sub>N (281.34) calc'd.: C 76.84; H 6.81; N 4.98%  
found: C 77.00; H 6.56; N 5.18%

*Methyl N-phenacetyl-2-phenyliminobutyrate (XIIIa)*

Prepared from phenacetyl chloride and methyl 2-phenyliminobutyrate. Yield: 44%, b. p. 151—156°/0.5 mm,  $n_D^{25}$  1.5526,  $d_4^{25}$  1.0844.

*Anal.* 10.91 mg. subst.: 30.79 mg. CO<sub>2</sub>, 6.91 mg. H<sub>2</sub>O  
C<sub>19</sub>H<sub>21</sub>O<sub>2</sub>N (295.36) calc'd.: C 77.26; H 7.17%  
found: C 77.02; H 7.08%

*Methyl N-(2-phenylbutyryl)-2-phenyliminobutyrate (XIVa)*

Obtained as colourless viscous oil from 2-phenylbutyryl chloride and methyl 2-phenyliminobutyrate. Yield: 47%, b. p. 180—182°/2.0 mm,  $n_D^{25}$  1.5415,  $d_4^{25}$  1.0602.

*Anal.* 10.81 mg. subst.: 30.86 mg. CO<sub>2</sub>, 7.49 mg. H<sub>2</sub>O  
C<sub>21</sub>H<sub>25</sub>O<sub>2</sub>N (323.42) calc'd.: C 77.98; H 7.79%  
found: C 77.90; H 7.75%

*Ethyl N-(2-phenylbutyryl)-phenyliminoacetate (XVa)*

Prepared from 2-phenylbutyryl chloride and ethyl phenyliminoacetate<sup>21</sup> as described in the general procedure. Yield: 39.5%, b. p. 175—176°/2.0 mm.

*Anal.* 10.52 mg. subst.: 29.85 mg. CO<sub>2</sub>, 6.81 mg. H<sub>2</sub>O  
C<sub>20</sub>H<sub>23</sub>O<sub>2</sub>N (309.39) calc'd.: C 77.64; H 7.49%  
found: C 77.43; H 7.24%

*General procedure for the preparation of N-acyl-2-phenylbutyramide*

To an ice-cold solution of the alkyl N-acyl iminoester in ether a few drops of concentrated hydrochloric acid were added. The mixture was kept three hours at room temperature and after evaporation *in vacuo* the residue was recrystallized from dilute ethanol.

*N*-Acetyl-2-phenylbutyramide (Xb)

A. Prepared from methyl *N*-acetyl-2-phenyliminobutyrate and concentrated hydrochloric acid as described in the general procedure. Yield: 66%, colourless crystals from 70% ethanol, m.p. 116—118°. The sample for analysis was recrystallized twice from diluted ethanol, m. p. 118—119°.

*Anal.* 11.07 mg. subst.: 28.41 mg. CO<sub>2</sub>, 7.17 mg. H<sub>2</sub>O  
 3.11 mg. subst.: 0.193 ml. N<sub>2</sub> (26°, 760 mm.)  
 C<sub>12</sub>H<sub>15</sub>O<sub>2</sub>N (205.25) calc'd.: C 70.22; H 7.37; N 6.82%  
 found: C 70.04; H 7.24; N 7.08%

B. The corresponding *N*-acyl iminoester was also prepared from 2-phenylbutyryl chloride and ethyl iminoacetate<sup>22</sup>, as described in the general procedure. The product was distilled at 130—140°/2.0 mm. and the obtained oil crystallized after keeping overnight at room temperature. Crude product melted at 106—110°. After two recrystallizations from 70% ethanol the product melted at 118—119° and showed no depression when mixed with the above compound.

C. The same compound was obtained by acetylation of 2-phenylbutyramide with ketene. A solution of 8.18 g. (0.05 mole) 2-phenylbutyramide<sup>23</sup> in 140 ml. of benzene and three drops of concentrated sulphuric acid was stirred at room temperature whilst passing 0.05 mole of ketene through the solution. The mixture was washed with 24 ml. portions of water until the washings were neutral to litmus, and the solvent was evaporated. The resulting oily product was allowed to stand overnight in the refrigerator and the semicrystalline mass filtered off giving 2.7 g. of crystals, m. p. 102—108°. After recrystallization from ethanol the product melted at 118—119°. The identity of the two samples was established by mixed m. p.

The oily filtrate was distilled at 113—115°/13 mm. giving 2-phenylbutyronitrile.

*N*-Propionyl-2-phenylbutyramide (XIb)

Prepared from methyl *N*-propionyl-2-phenyliminobutyrate as described in the general procedure. Yield: 65%, colourless needles from diluted ethanol, m. p. 91—92.3°.

*Anal.* 10.19 mg. subst.: 26.54 mg. CO<sub>2</sub>, 6.85 mg. H<sub>2</sub>O  
 2.50 mg. subst.: 0.142 ml. N<sub>2</sub> (24°, 762 mm.)  
 C<sub>13</sub>H<sub>17</sub>O<sub>2</sub>N (219.27) calc'd.: C 71.20; H 7.82; N 6.39%  
 found: C 71.08; H 7.52; N 6.54%

*N*-Benzoyl-2-phenylbutyramide (XIIb)

Obtained as colourless crystals from methyl *N*-benzoyl-2-phenyliminobutyrate. Yield: 71.8%, m. p. 114—117° (from ethanol).

*Anal.* 10.60 mg. subst.: 29.75 mg. CO<sub>2</sub>, 5.95 mg. H<sub>2</sub>O  
 4.27 mg. subst.: 0.200 ml. N<sub>2</sub> (23°, 762 mm.)  
 C<sub>17</sub>H<sub>17</sub>O<sub>2</sub>N (267.31) calc'd.: C 76.38; H 6.41; N 5.24%  
 found: C 76.59; H 6.28; N 5.41%

*N*-Phenacetyl-2-phenylbutyramide (XIIIb)

Prepared from methyl *N*-phenacetyl-2-phenyliminobutyrate. Yield: 58.5%, m. p. 126—127° (from ethanol).

*Anal.* 10.22 mg. subst.: 28.85 mg. CO<sub>2</sub>, 6.02 mg. H<sub>2</sub>O  
 2.30 mg. subst.: 0.102 ml. N<sub>2</sub> (27°, 760 mm.)  
 C<sub>18</sub>H<sub>19</sub>O<sub>2</sub>N (281.34) calc'd.: C 76.84; H 6.81; N 4.98%  
 found: C 77.03; H 6.59; N 5.04%

The same compound was obtained from ethyl *N*-(2-phenylbutyryl)-phenyliminoacetate and concentrated hydrochloric acid as described in the general procedure in 25.8% yield. The identity was established by m. p. and mixed m. p.

*N*-Bis-2-phenylbutyramide (XIVb)

Prepared from methyl *N*-(2-phenylbutyryl)-2-phenyliminobutyrate and concentrated hydrochloric acid in 41% yield. Colourless crystals from ethanol, m. p. 127—128°.

*Anal.* 10.00 mg. subst.: 28.50 mg. CO<sub>2</sub>, 6.52 mg. H<sub>2</sub>O  
 3.33 mg. subst.: 0.142 ml. N<sub>2</sub> (25° 738 mm.)  
 C<sub>20</sub>H<sub>23</sub>O<sub>2</sub>N (309.39) calc'd.: C 77.64; H 7.49; N 4.53%  
 found: C 77.77; H 7.31; N 4.74%

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## IZVOD

**Supstance koje djeluju na centralni nervni sistem. I.  
Derivati *N*-acil-2-fenilbutiramida***S. Kukolja i Lj. Polak*

Djelovanjem kiselinskih klorida na metil 2-feniliminobutirat u eteru priređeni su pripadni metil *N*-acil-2-feniliminobutirati (X—XIVa). Također su priređeni odgovarajući *N*-acil imino esteri polazeći od 2-fenilbutiril klorida i etil iminoacetata, te etil feniliminoacetata. Svi pripremljeni alkil *N*-acil imino esteri prevedeni su djelovanjem koncentrirane solne kiseline u eteru u *N*-acil-2-fenilbutiramide (X—XIVb). Ovi amidi izolirani su u obliku stabilnih kristaliziranih spojeva.

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ZAGREB

Primljeno 16. siječnja 1960.