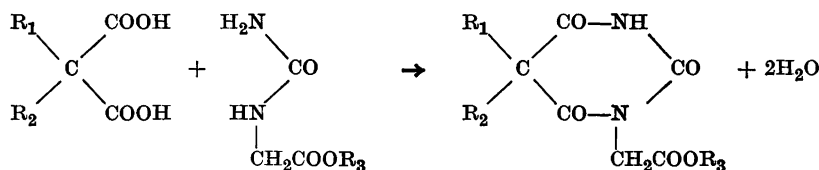


Some New Hydantoic Acid Derivatives

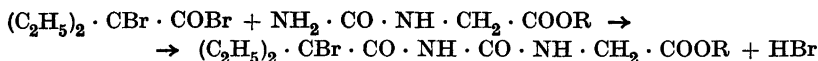
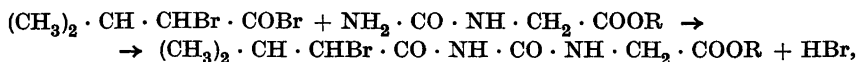
OLOV ROSÉN

Department of Organic Chemistry, Kungl. Farmaceutiska Institutet, Stockholm, Sweden

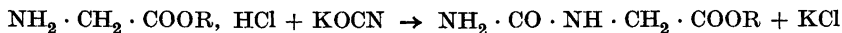
Ureides of certain brominated monocarboxylic acids have been used in medicine owing to their sedative effect. Most important among these compounds are α -bromo-*isovaleryl*-urea (bromyl, bromural) and bromodiethyl-acetyl-urea (carbromal, adalin), both of which are included in several modern pharmacopoeias. Barbituric acid, parent substance of the hitherto dominating group of synthetic hypnotics, is the ureide of the dicarboxylic malonic acid. Rosén and Sandberg^{1,2} (1944, 1950) have shown that malonic acid, or a C-substituted malonic acid, and an ester of hydantoic acid can be converted under suitable conditions into barbituric acid derivatives:



If R_1 and R_2 both are alkyl radicals, such as ethyl, allyl or phenyl, the reaction product is a hypnotic one, though weaker and of shorter duration of action than the corresponding substance without any substituent on the N-atom. In this connection it would be of interest to synthesize analogous variants of the bromural-adalin-type and to test their sedative effect. For this reason α -bromo-*isovaleryl* bromide and bromodiethyl-acetyl bromide respectively were brought into reaction with an ester of hydantoic acid:



In the first case four different esters of hydantoic acid were used, namely methyl-, ethyl-, *n*-propyl- and *isopropyl*-. Only the ethyl ester has been described before, as far as the author is aware, and some data on the other three hydantoic acid esters will now be reported. They have been prepared throughout by condensing glycocoll ester hydrochloride with potassium cyanate, as is described for the ethyl ester by Harries and Weiss³:



The ester hydrochlorides were obtained by passing dry hydrochloric acid into a boiling mixture of glycocoll and the alcohol in question (Harries and Weiss³; Abderhalden and Suzuki⁴).

EXPERIMENTAL

Hydantoic acid methyl ester

A cold solution of 126 g of glycocoll methylester hydrochloride (1 mol) in 120 g of water was poured under stirring into a cold solution of 90 g of potassium cyanate (1 mol + 10 per cent) in 145 g of water. The mixture soon got warm and after a while it was cooled. No precipitate appeared. The solution was first evaporated *in vacuo* and afterwards on a water-bath at atmospheric pressure until a solid residue was obtained, which proved to be the intended ester and potassium chloride. The ester was separated by extraction with boiling alcohol and crystallized as beautiful needles on cooling the filtrate. Yield: 76 g = 58 per cent. Easily soluble in alcohol and water, sparingly soluble in benzene, insoluble in ether. Melting point 97–98° C. The percentage content of carbon and hydrogen was determined in a Reihlen-Weinbrenner-apparatus, and that of nitrogen according to Kjeldahl.

Found	C	36.45	H	5.99	N	21.16
Calc.	»	36.36	»	6.10	»	21.21

Hydantoic acid *n*-propyl ester

A cold solution of 154 g of glycocoll *n*-propylester hydrochloride (1 mol) in 50 g of water was poured under stirring into a cold solution of 90 g of potassium cyanate in 145 g of water. The mixture got warm and turbid. On cooling a coarse precipitate appeared. This was filtered off, washed with water and dried. Weight 120 g. The product was then dissolved in the equal quantity of boiling water, the solution being treated with charcoal. From the filtrate pure ester was obtained as irregular, coarse prismatic crystals. Yield: 85 g = 53 per cent. The ester could also be recrystallized from alcohol, as it was slightly soluble in cold alcohol. Melting point 115–116° C. Found: N 17.37 per cent, calculated 17.49 per cent.

Hydantoic acid *isopropyl ester*

The synthesis was carried out in an analogous way to described above and it took place mainly in a similar manner. The *isopropyl ester*, however, crystallized much slower than the normal propyl ester and it sometimes formed supersaturated solutions. From 1 mol ester hydrochloride 77 g of pure hydantoic acid ester (= 48 per cent) was obtained. Feeble needles melting at 94–95° C. It is remarkable that the *isopropyl ester* has a lower melting point than the normal one. The *iso-ester* was easily soluble in cold alcohol, but it could be precipitated from the alcoholic solution by the addition of ether. Found: N 17.39 per cent, calculated 17.49 per cent.

 α -Bromo*isovaleryl*-hydantoic acid ester

A mixture of 1 mol of bromo*isovaleryl*-bromide and 2 mols of hydantoic acid ester was kept at 75° C for 3 à 4 hours. The ester soon dissolved and the clear solution gradually darkened. Any evolution of hydrogen bromide was hardly discernible. The reaction product, after cooling, formed a viscid mass, which was mixed under stirring with an equal weight of water and neutralised with sodium bicarbonate. On the addition of water the desired substance, light yellow in colour, separated out. It was sucked off and washed. Yield almost quantitative. Easily soluble in alcohol, benzene and ether, sparingly soluble in water. Recrystallizations from aqueous alcohol (50 per cent) gave the pure esters. They occurred as colourless needle-like crystals, or as a white, crystalline powder. Table 1 gives the melting points and the percentage of bromine and nitrogen. In this series the melting point of the *isopropyl ester* is higher than that of the normal one.

Table 1. Analytical data of esters of α -bromo-*isovaleryl*-hydantoic acid

Esters of α -bromo- <i>isovaleryl</i> -hydantoic acid	Melting point uncorr.	Br per cent		N per cent	
		found	calc.	found	calc.
Methyl ester	113–114°	27.08	27.08	9.45	9.49
Ethyl ester	87–88°	25.72	25.85	9.02	9.06
<i>n</i> -Propyl ester	90–91°	24.61	24.73	8.63	8.67
<i>iso</i> -Propyl ester	101–111°	24.74	24.73	8.63	8.67

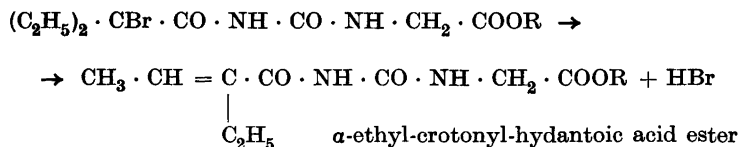
The hypnotic efficiency of the methyl-, ethyl- and *isopropylesters* of α -bromo-*isovaleryl*-hydantoic acid was tested on male albino rats weighing 150–190 g by observing the body righting reflexes.

The compounds were suspended in 5 per cent acacia solution, the suspension containing 100 mg/ml, and administered by stomach tube to the rats deprived of food 18—21 hours prior to administration.

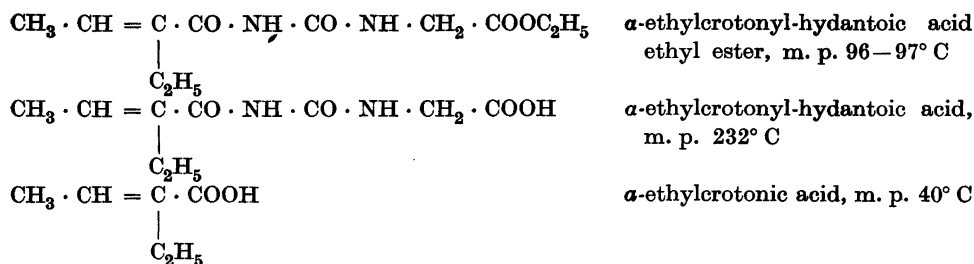
All derivatives were ineffective in doses up to and including 1500 mg/kg bodyweight. — This biological test was carried out by F. Sandberg.

Bromodiethyl-acetyl-hydantoic acid ethyl ester

A mixture of 0.1 mols of bromodiethyl-acetyl bromide (25.8 g) and 0.2 mols of hydantoic acid ethyl ester (29.2 g) was heated on a water-bath for 4 hours. Firstly a clear, almost colourless solution was formed, which gradually darkened and got turbid by the formation of a precipitate. After cooling 50 ml water was added together with sufficient sodium bicarbonate to give a neutral reaction. The precipitate formed during the heating remained insoluble, and in addition to this a light brown, viscid oil separated. The solid substance mainly consisted of hydantoin. The oil was taken up in ether, and the ethereal solution was repeatedly extracted with water and dried with sodium sulphate. On distilling off the solvent 17 g of a light yellow, viscid oil remained, from which a crystalline precipitate separated very slowly and sparingly. However, the main part of the oil failed to crystallize. After 14 days only about 1 g of the solid substance was isolated. In contrast to the oil, these crystals (bromodiethyl-acetyl-hydantoic acid) were insoluble in benzene and could therefore be washed with this liquid. The remaining oil was probably bromodiethyl-acetyl-hydantoic acid ethyl ester, though not quite pure. If a solution of the oil in pyridine was boiled for some minutes, the following reaction took place:



The α -ethyl-crotonyl-hydantoic acid ester formed could be converted into the corresponding carboxylic acid and further into α -ethylcrotonic acid. These three decomposition products were isolated in pure form and analyzed. Only α -ethylcrotonic acid has been previously described. More data about these reactions will be reported in a later paper.



Bromodiethyl-acetyl-hydantoic acid ethyl ester was not tested biologically owing to its oily consistence.

Bromodiethyl-acetyl-hydantoic acid

The crystalline product isolated from the above mentioned oil was bromodiethyl-acetyl-hydantoic acid. After recrystallizations from alcohol or water the substance occurred as thin flat needles melting at 173–175° C. By titrating the alcoholic solution with 0.1 *N* sodium hydroxide solution, using phenolphthalein as an indicator, a satisfactory endpoint of the titration was obtained. Equivalent weight: found 293.4, calculated 295.1; Br: found 27.0 per cent, calculated 27.1 per cent.

SUMMARY

The methyl-, *n*-propyl- and *isopropyl* esters of hydantoic acid, bromodiethyl-acetyl-hydantoic acid and its ethyl ester have been prepared and their chemical properties are reported.

The methyl-, ethyl-, *n*-propyl- and *isopropyl* esters of α -bromo-*isovaleryl*-hydantoic acid have been prepared, their chemical properties determined and their hypnotic efficiency tested.

REFERENCES

1. Rosén, O. *Svensk Farm. Tid.* **48** (1944) 497.
2. Rosén, O., and Sandberg, F. *Acta Chem. Scand.* **4** (1950) 666.
3. Harries, C., and Weiss, M. *Ann.* **327** (1903) 365, 366.
4. Abderhalden, E., and Suzuki, S. *Z. physiol. Chem.* **176** (1928) 101.

Received March 7, 1950.