

Synthesis of Bis(β -chloroethyl)-amides and Bis-ethylenimides of Some Dicarboxylic Acids

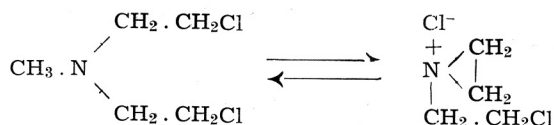
D. Fleš and A. Markovac-Prpic

Research Department »Pliva« Pharmaceutical and Chemical Works,
Zagreb, Croatia, Yugoslavia

Received October 28, 1954

Bis(β -chloroethyl)-amides and bis-ethylenimides of muconic acid, dihydromuconic acid, 4,4'-dicarboxy-diphenylether and 4,4'-bis(carboxymethyl)-diphenylether were prepared as possible cytotoxic agents.

After it has been discovered that *N*-methyl-bis(β -chloroethyl)-amine, a potent cytotoxic agent shows in neutral solution the ethylenimine structure¹



a large number of ethylenimine derivatives has been synthesized and tested biologically. As a result of these investigations, 2,4,6-tris(1-ethylenimino)-*s*-triazine was found to be an active cytotoxic agent.² Some other derivatives of ethylenimine have shown a marked inhibitory effect on the growth of cancer tissue.³

We are dealing in this paper with the synthesis of some hitherto undescribed bis(β -chloroethyl)-amides and bis-ethylenimides of muconic acid, dihydromuconic acid, 4,4'-dicarboxy-diphenylether and 4,4'-bis(carboxymethyl)-diphenylether.

Ethylenimine can be smoothly acylated with acid chlorides in the presence of alkali. Gabriel and Stelzner⁴ using the Schotten-Baumann reaction, prepared benzoyl-ethylenimine by condensing benzoyl chloride with ethylenimine. Better results were obtained when the reaction was carried out in an indifferent solvent such as benzene or ether in the presence of triethylamine which forms a hydrochloride insoluble in many organic solvents, especially in ether.

A large number of acylations of ethylenimine with acid chlorides in the presence of triethylamine has been reported by Bestian *et al.*⁵ If the acylation of ethylenimine is performed without alkali, an opening of ethylenimine ring occurs and β -chloroethylamides are obtained as the main reaction products.

The β -chloroethylamides for which the physical constants and analyses are listed in Table I, were prepared according the standard method by dissolving the ethylenimine into a chloroform solution of the corresponding acid chloride. β -Chloroethylamides were obtained in good yields as nice crystalline products, stable at room temperature. The experimental conditions were essentially the same as given for the preparation of muconyl-bis(β -chloroethylamide). (See experimental part).

The ethylenimides listed in Table II, were prepared by dropping a solution of acid chloride into a chilled mixture of ethylenimine and triethylamine dissolved in ether or benzene. After the reaction was accomplished the triethylamine hydrochloride was filtered off, and the ethylenimides were obtained after the evaporation of the solvent.

The ethylenimide of muconic acid was prepared in benzene solution and purified from isopropanol. If pure, the product was very stable at room temperature. The other ethylenimides were prepared in ether at a temperature of -5 to -10° . Ethylenimide of 4,4'-dicarboxy-diphenylether was obtained as a very stable crystalline product. Dihydromuconic acid gave an ethylenimide in the form of long needles, which after few days at room temperature polymerized to a yellow mass insoluble in ether. The ethylenimide of 4,4'-bis(carboxymethyl)-diphenylether was isolated as yellow oil which polymerized very readily at room temperature. An analytical sample was obtained from the crude oil by repeated dissolving in ether at a temperature of -5° . After evaporation of the solvent the oily product was dried for several hours at a temperature of 0° in a vacuum of 0.1 mm.

The experimental conditions used for the preparation of ethylenimides were essentially the same as described for the preparation of ethylenimide of dihydromuconic acid.

EXPERIMENTAL*

Acid Chlorides

The acid chlorides were prepared by boiling the acids with an excess of thionyl chloride. After the excess of thionyl chloride was removed under reduced pressure, the acid chlorides were purified in an appropriate manner.

Muconyl dichloride⁶ was twice recrystallized from a mixture of benzene and petroleum ether (b. p. $40-60^{\circ}$) and formed colorless needles which melted at $98-99^{\circ}$.

Dihydromuconyl dichloride⁷ was purified by distillation under reduced pressure. B. p. $66-70^{\circ}$ at 3 mm.

4,4'-Dicarboxy-diphenylether dichloride⁸ was crystallized from petroleum ether. M. p. $83-84^{\circ}$ (reported m. p. $82-83^{\circ}$).

4,4'-Bis(carboxymethyl)-diphenylether dichloride was purified in the following manner: the crude acid chloride obtained from 1.2 g. of 4,4'-bis(carboxymethyl)-diphenylether was dissolved in 6 ml. of dry benzene and the impurities were precipitated with 15 ml. of petroleum ether. The mother liquor was decanted, evaporated under reduced pressure, and the resulting oil was dried for 6 hours at 80° and a pressure of 0.3 mm.

Anal. 3.555 mg. subst.: 77.58 mg. CO_2 , 12.49 mg. H_2O
 $\text{C}_{16}\text{H}_{12}\text{O}_8\text{Cl}_2(323.17)$ calc'd.: C 59.46; H 3.74%
 found: C 59.55; H 3.93%.





Muconyl-bis(β -chloroethyl)-amide

Nine hundred milligrams (0.021 mole) of ethylenimine dissolved in 10 ml. of dry chloroform was placed in a round three-necked flask equipped with a mercury-sealed stirrer, dropping funnel and a condenser with a calcium chloride tube. The flask was immersed in an ice bath and 1.8 g. (0.01 mole) of muconyl dichloride dissolved in 15 ml. of chloroform was added dropwise during half an hour. The reaction mixture was stirred for additional half an hour. The crystalline precipitate was filtered and washed with 40 ml. of cold chloroform. A crystalline product (2.7 g.) which decomposed at 222° (under previous softening at 205°) was obtained. After two

* Melting points are uncorrected

recrystallizations from a water-ethanol mixture (1:2), a pure product was obtained. It crystallized in needles and decomposed at 228—229°. The analysis concerning this compound is recorded in Table I.

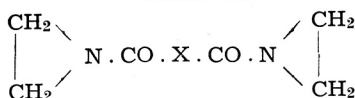
TABLE I.
ClCH₂ . CH₂ . NH . CO . X . CO . NH . CH₂ . CH₂Cl





X	M. P.	Yield %	Calc'd			Found		
			C	H	N	C	H	N
—CH=CH—CH=CH— a	228—229°D	99	45.27	5.33	10.57	45.25	5.20	10.63
—CH ₂ —CH=CH—CH ₂ — b	146—147°	97	44.95	6.04	10.49	44.84	6.24	10.63
—  —O—  — b	181—182°	30*	56.71	4.76	7.35	56.71	4.91	7.21
—CH ₂ —  —O—  —CH ₂ — b	192—192.5°	65	58.67	5.42	6.84	58.72	5.29	6.91

Dihydromuconyl-bis-ethylenimide

A mixture of 0.86 g. (0.02 mole) of ethylenimine and 2.2 g. (0.022 mole) of triethylamine dissolved in 20 ml. of dry ether, was placed in a round three-necked flask equipped with a mechanical stirrer, dropping funnel and a condenser with a calcium chloride tube. The flask was immersed in an ice-salt bath and under vigorous stirring 1.8 g. (0.01 mole) of dihydromuconyl dichloride dissolved in 15 ml. of dry ether was added dropwise. The separation of triethylamine hydrochloride started immediately. The ice-bath temperature was kept during the addition of acid chloride at 0° to —5°. The reaction mixture was stirred for additional 45 minutes at a temperature of 0°. The crystalline precipitate was filtered off and washed with 10 ml. of dry ether. The ethereal solution was evaporated under reduced pressure without heating. 1.7 g. of a nice crystalline product was obtained. A sample for analysis was dissolved in ether at room temperature, the ether was partly evaporated in vacuo and the remaining solution was cooled to —10° for half an hour. The product crystallized in shining needles, m. p. 59°. The analysis for the compound is recorded in Table II.

TABLE II.



X	M. P.	Yield %	Calc'd			Found		
			C	H	N	C	H	N
—CH=CH—CH=CH— b	110° D	71	62.49	6.29	14.57	62.68	6.11	14.24
—CH ₂ —CH=CH—CH ₂ — c	59°	89	61.85	7.27	14.42	61.43	7.00	14.25
—  —O—  — c	114°	41	70.12	5.23	9.09	70.02	5.06	9.04
—CH ₂ —  —O—  —CH ₂ —	oil	67	71.42	5.99		70.84	5.94	

a. crystallized from ethanol-water (2:1)

b. crystallized from iso-propanol

c. crystallized from ether

D. decomposition

* crude acid chloride was used

Acknowledgment. Microanalyses for carbon and hydrogen were performed by Mr. N. Manger and Miss E. Jaeger. Those for nitrogen were done by Mr. N. Simić. Thanks are due to Mr. R. Marušić for assistance.

REFERENCES

1. C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11** (1946) 518.
2. F. L. Rose, J. A. Hendry and A. L. Walpole, *Nature* **165** (1950) 993.
3. J. A. Hendry, R. F. Homer, F. L. Rose and A. L. Walpole, *Brit. J. Pharmacol.*, **6** (1951) 357.
4. S. Gabriel and R. Stelzner, *Ber.* **28** (1895) 2929.
5. H. Bestian, J. Heyna, A. Bauer, G. Ehlers, B. Hirsekorn, T. Jacobs, W. Noll, W. Weibezahl and F. Romer, *Ann.* **566** (1950) 210.
6. P. S. Bailey and J. S. Ross, *J. Am. Chem. Soc.* **71** (1949) 2370.
7. C. Grundmann, *Ann.* **524** (1936) 31.
8. M. W. Partridge, *J. Pharm. Pharmacol.* **4** (1952) 533.

IZVOD

Sinteza bis (β -kloretil)-amida i bis-etilenimida nekih dikarbonskih kiselina.

D. Fleš i A. Markovac-Prpić

Djelovanjem mukonil diklorida, dihidromukonil diklorida i diklorida 4,4'-dikarboksi-difeniletera i 4,4'-bis(karboksimetil)-difeniletera na etilenimin u kloroformu, priređeni su pripadni bis(β -kloretil)-amidi. Opisani su bis(β -kloretil)-amidi stabilne kristalizirane tvari. Analize tih spojeva iznesene su tabeli I.

Ako je aciliranje etilenimina s navedenim kiselinskim kloridima provedeno u prisutnosti trietilamina, dobiveni su odgovarajući bis-etilenimidi. Bis-etilenimidi mukonske kiseline i 4,4'-dikarboksi-difeniletera izolirani su u obliku stabilnih kristaliziranih spojeva. Bis-etilenimid dihidromukonske kiseline kristalizirao je u dugim iglicama iz etera, ali je nakon nekoliko dana stajanja kod sobne temperature polimerizirao u žutu masu netopivu u eteru. Bis-etilenimid 4,4'-bis(karboksimetil)-difeniletera dobiven je u obliku žutog ulja, koje već poslije nekoliko sati polimerizira kod sobne temperature u čvrstu staklastu masu. Analize priređenih bis-etilenimida iznesene su u tabeli II.

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICI FARMACEUTSKIH I KEMIJSKIH
PROIZVODA
ZAGREB

Primljeno 28. oktobra 1954.