SYNTHESIS AND STUDY OF HETEROCYCLIC DERIVATIVES WITH BIOLOGICAL PROPERTIES

VII. Some Benzotriazole Derivatives*

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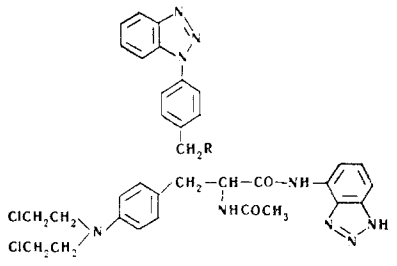
Certain derivatives of benzotriazole containing the cytotoxic bis(β-chloroethyl)amino group are synthesized. They are 1-p-[ω-bis(β-choroethyl)amino]tolylbenzotriazole and (benzotriazolyl-4)-amidoacetylsarcolysine.

It is known that a number of triazole derivatives [1] and compounds where the triazole is condensed with a benzene [2] or heterocyclic ring [3] can, owing to their structural peculiarities, interfere with the metabolism of nucleic acids, and apparently this is related to the antitumor and antivirus activities of some of them [2, 4].

From that point of view, the synthesis and investigation of the quality of so-called alkylating agents, derivatives of benzotriazole, containing the bis(β-chloroethyl)amino group (I and IV), were of interest.

1-p-[ω-Bis(β-chloroethyl)amino]tolylbenzotriazole I is obtained as its dihydrochloride, by treating 1-p-[ω-Bis(β-hydroxyethyl)amino]tolylbenzotriazole II, with thionyl chloride, and II is in its turn obtained by reacting 1-p-(ω-bromo)tolylbenzotriazole III with diethanolamine; it is isolated as its hydrochloride. III is obtained by brominating 1-p-tolybenzotriazole with bromosuccinimide in the presence of benzoyl peroxide.



I R = $N(CH_2CH_2Cl)_2$
II R = $N(CH_2CH_2OH)_2$
III R = Br

VI

The amide of acetylsarcolysine IV is obtained by reacting together acetylsarcolysine and 4-aminobenzotriazole in the presence of dicyclohexylcarbodiimide, by analogy with the preparation of heterocyclic amides of sarcolysine [5].

The starting 4-aminobenzotriazole was obtained by reducing 4-nitrobenzotriazole [6] with stannous chloride, by analogy with the preparation of 5-aminobenzotriazole [7].

EXPERIMENTAL

1-p-(ω-Bromo)tolylbenzotriazole (III). A flask, fitted with a stirrer and condenser, was charged with 0.5 g (0.0024 mole) 1-p-tolylbenzotriazole [8], 0.45 g (0.0024 mole) bromosuccinimide, benzoyl peroxide, and 10 ml CCl_4, and the whole refluxed for 4 hr 30 min. The products were filtered hot to remove succinimide, the filtrate cooled, the solid filtered off, and recrystallized from CCl_4. Yield 0.2 g (30%) pale yellow crystals, mp 125°–126° C. Found: Br 26.79; N 14.40%. Calculated for $C_{13}H_{10}BrN_3$: Br 27.70; N 14.60%.

1-p-[ω-Bis(β-hydroxyethyl)amino]tolylbenzotriazole. (II). A mixture of 0.5 g (0.0017 mole) III, 0.54 g (0.005 mole) diethanolamine, and 10 ml $CHCl_3$ was refluxed for 40 min. The solvent was distilled off, and the residue of oil washed with water. The residue, which was halogen-free, gave, on treatment with ether and conc HCl, 0.3 g (55%) colorless crystals, mp 146.5°–147° C (ex dry EtOH). Found: C 58.70; H 6.17; N 16.04%. Calculated for $C_{17}H_{20}N_4O_2 \cdot HCl$: C 58.54; H 6.03; N 16.07%.

1-p-[ω-Bis(β-chloroethyl)amino]tolybenzotriazole dihydrochloride. 0.5 g (0.0014 mole) Hydrochloride II was dissolved in water, the solution made alkaline with ammonia, which precipitated an oil, which was extracted with $CHCl_3$. Recrystallization from aqueous EtOH then gave 0.3 g (27%) colorless crystals, mp 182° C. Found: C 48.89; H 4.89; Cl 33.80%. Calculated for $C_{17}H_{18}Cl_2N_4 \cdot 2HCl$: C 48.50; H 4.75; Cl 34.12%.

4-Aminobenzotriazole. 25 g (0.15 mole) 4-Nitrobenzotriazole [6] was added in portions to a solution of 77.5 g (0.5 mole) $SnCl_2 \cdot 2H_2O$ in 250 ml conc. HCl, with stirring, and when addition was complete, the mixture stirred for 1 hr more. The precipitate was filtered off, dissolved in water, and H_2S passed in, the precipitate filtered off, and conc. HCl added to the filtrate, which was then evaporated to dryness. The resultant amine hydrochloride was dissolved in water, made alkaline with ammonia, and the whole again evaporated to dryness. The residue was extracted with benzene, cooling precipitated from the benzene solution 8.2 g (40%) amine mp 148°–150° C (according to [6] mp 249° C).

(Benzotriazolyl-4)amide of acetylsarcosine IV: A mixture of 2.8 g (0.008 mole) acetylsarcolysine [9] in 20 ml $CHCl_3$, 1.65 g (0.012 mole) 4-aminobenzotriazole in 5 ml EtOH, and 1.1 g dicyclohexylcarbodiimide were shaken together for 2 hr in a jar with a ground-glass stopper. The dicyclohexylurea which separated was filtered off, the filtrate evaporated, and the residual oil crystallized from dry ether. Yield 1.7 g (43.5%) colorless crystals, mp 175° C

*For Part VI see [10].

(ex dry EtOH). Found: C 52.24; H 5.14; Cl 14.02; N 17.24%. Calculated for $C_{21}H_{24}Cl_2N_4O_2 \cdot H_2O$: C 52.50; H 5.40; Cl 14.75; N 17.40%.

REFERENCES

1. Tanade Drug Mfg. Co., Japanese Patent no. 1819, 1960; C. A. 55, 571, 1961.

2. H. B. Gillespie, M. Engelman, and S. Graff, J. Am. Chem. Soc., 76, 3531, 1954.

3. Takeda Pharmaceutical Industries, Japanese Patent no. 3326, 1959; C.A., 54, 14278, 1960.

4. H. Kano and Y. Makisumi, Chem. Pharm. Bull., Tokyo, 6, 583, 1958; C.A., 54, 14259, 1960.

5. A. Ya. Berlin and V. P. Bronovitskaya, ZhOKh, 30, 324, 1960.

6. K. Fries, H. Güterbock, and H. Kuhn, Ann., 511, 213, 1934.

7. R. Nietzki and N. Prinz, Ber., 26, 2956, 1893.

8. W. Borsche and M. Feise, Ber., 40, 378, 1907.

9. E. N. Shkodinskaya, M. N. Vasil'eva, O. S. Basina, and A. Ya. Berlin, ZhOKh, 29, 3776, 1959.

10. V. N. Konyukhov, G. S. Sakovich, L. V. Krupnova, and Z. V. Pushkareva, ZhOrKh, 1, 1487, 1965.

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