SYNTHESIS OF CARBAMAZEPINE AND ITS ANTIALCOHOL ACTIVITY

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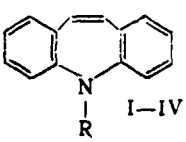
Carbamazepine (Tegretol, Finlepsin), or 5-carbamoyl-5H-di-benz[b,f]azepine (IV), is a psychotropic preparation with anticonvulsant activity. With respect to its pharmacological activity, carbamazepine is related to a number of preparations that are used in the treatment of epilepsy, chiefly in the case of severe convulsive seizures (geksamezin, benzonal, Diphenine, Chloracon, metindion); however, in contrast to them, it has a broader spectrum of activity. It is also used in mixed (primarily in the case of a combination of severe seizures with psychotropic manifestations) and local (of post-traumatic and postencephalitic origin) forms. Carbamazepine is effective in neuralgia of the trigeminal nerve and intercostal neuralgia [3]. Compound IV has found extensive application in medical practice. Information regarding the use of IV for the treatment of patients afflicted with alcoholism has recently appeared in the literature [18, 20]. The preparation is used to alleviate the abstinent syndrome.

In order to develop a method for obtaining carbamazepine we conducted studies on the selection and realization of an optimal scheme for its synthesis. In addition, to extend the spectrum of activity of the preparation we conducted biological investigations of its antialcohol activity.

The known methods for obtaining IV differ primarily with respect to the sequence and methods of introducing a double bond in the 10 and 11 positions of the iminodibenzyl ring, the reagents that are used for this, and the methods of introducing an N-carbamoyl group. For example, a method has been described for obtaining IV by phosgenation of 5H-dibenz[b,f]azepine (I) with subsequent amidation of the resulting 5-chlorocarbonyldibenz[b,f]azepine (II) with ammonia in alcohol [5] or with ammonium hydroxide in toluene [15] to give desired product IV.



I—IV

R = H (I), COCl (II), COBr (III), $CONH_2$ (IV)

Since the known methods for the transition from 10,11-dihydro-5H-dibenz[b,f]azepine (V) to dibenzazepine I — both catalytic with the use of palladium catalysts or sulfur [9, 19] and through a number of chemical transformations of V, viz., acetylation with acetyl chloride, bromination in the 10 position, and dehydrobromination with subsequent hydrolysis of the acyl group [7,8,10,16] — are characterized by low yields (50-70% based on V), such schemes are evidently unsuitable for the synthesis of IV.

The methods for obtaining IV by acylation of I with various acylating agents such as acyl isocyanates [4, 12], acyl isothiocyanates [2], and trichloroacetyl chloride [17] with subsequent alkaline or acidic hydrolysis to the desired product are limited not only by the fact that starting I is difficult to obtain but also by the low degree of accessibility and often the high toxicities of the acylating reagents used.

In our opinion, the most expedient method for obtaining IV is a sequence of steps that includes phosgenation of V, introduction of a bromine atom into the 10 position by various brominating reagents, subsequent dehydrobromination, and amidation of the 5-chlorocarbonyl group.

The introduction of a chlorocarbonyl group into the 5 position is accomplished by the reaction of V with phosgene in toluene [11, 13]; 5-chlorocarbonyl-10,11-dihydro-5H-di-benz[b,f]azepine (VI) is obtained in 95% yield [11].

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TABLE 1. Effect of Carbamazepine on the Consumption of Alcohol and Water in Rats

Investigation period	Control			Expt.		
	5% alcohol, ml	water, ml	Percentage of 5% alcohol in the total vol. of the drinking liquid	5% alcohol, ml	Water, ml	Percentage of 5% alcohol in the total vol. of the drinking liquid
Starting level	28,3±0,3	1,2±0,1	95,9±1,2	30,2±0,5	0,9±0,1	97,1±1,2
During the expt.	29,1±0,3	0,9±0,1	97±1,4	22,3±1,5**	3,4±0,5**	86,6±2,4*
10 days later	29,3±0,9	1,1±0,2	96,4±1,7	28,0±1,9	3,1±0,4**	90,0±5,3

*p 0.05.
**p 0.01.

For the formation of the double bond of the azepine ring, bromine is introduced into the 10 position by refluxing VI in CCl4 with 1,3-dibromo-5,5-dimethylhydantoin in the presence of benzoyl peroxide; and the bromo derivative (VII) is obtained in ~ 90% yield [11]. Compound IV is obtained by heating VII in an autoclave in xylene or benzene saturated with ammonia [11] for 3 h at 100°C. It is not possible to evaluate the method of simultaneous dehydrobromination and amidation because of the lack of data on the yields and quality of final product IV. Another method for obtaining IV is known and includes the reaction of VI with bromine in CCl4 in the presence of diisopropyl peroxide dicarbonate and oxalic acid, thermal dehydrobromination at 140°C, and subsequent amidation with ammonia in an inert solvent or by passing ammonia through an aqueous methanol solution with refluxing of the reaction mixture for 2.5 h [13]. The yield of the final product also was not indicated.

Dehydrobromination of derivative VII in the presence of Ac_2O (heating at 150°C with removal of the AcBr and AcOH by distillation) or heating of fused bromo derivative VII at 140-150°C for 2-3 h with simultaneous removal of HBr by distillation was proposed in an East German patent [12]. The yield of 5-chlorocarbonyldibenz[b,f]azepine (II) was 80% based on starting VII [12].

The introduction of bromine is also accomplished by direct bromination with bromine at 130-200°C of fused chlorocarbonyl derivative VI or a solution of VI in a suitable solvent (1,3-dichloropropane, dibromoethane, chlorobenzene, dichlorobenzene) at 135 = 155°C. Subsequent treatment of the reaction mass with gaseous ammonia in refluxing methanol for 2.5 h, removal of the methanol by distillation, and refluxing of the residue with water lead to crude carbamazepine in 91% yield [14].

It should be noted that the authors of the patent [14] detected the presence of pairs of intermediates such as VII and VIII and II and III, and their structures were confirmed by PMR spectroscopy. The formation of these products is explained as follows: partial replacement of the chlorine atom in the 5-chlorocarbonyl group by a bromine atom upon reaction with gaseous HBr occurs in bromination at the 10 position. The authors of the patent [14] established that the isolated mixture of bromination products contained up to 20% III; however, this does not interfere with obtaining IV from this mixture during subsequent amidation.

The last method [14] for the formation of the dibenzazepine ring and its amidation to IV seems most convenient to us because of the use of an accessible brominating reagent and the absence of dangerously explosive peroxides in the synthetic scheme.

We have developed a method for obtaining VI similar to the method in [11] by bubbling a gentle stream of phosgene into a toluene solution of V at 90-95°C for 3 h; the yield was 90%. The end of the phosgenation reaction was determined by thin-layer chromatography (TLC) on Silufol UV-254 plates (Czechoslovakia) in benzene–hexane (1:1) (V had R_f 0.8, and 5-chlorocarbonyl derivative VI had R_f 0.57). Detection was accomplished by scanning in UV light and by development with iodine. The end of the phosgenation reaction was determined from disappearance of the spot of starting V on the chromatogram.

The experiments carried out to obtain IV in analogy with the method in [14] involving the bromination of VI in chlorobenzene at 145-150°C for 1.5 h, dehydrobromination at 150-155°C

TABLE 2. Effect of Carbamazepine on the Consumption of Alcohol and Water in Mice

Investigation period	Control			Expt. (50 mg/kg)			Expt. (100 mg/kg)		
	5% alcohol, ml	water ml	Percentage of 5% alcohol in the total vol. of the drinking liquid	5% alcohol, ml	water ml	Percentage of 5% alcohol in the total vol. of the drinking liquid	5% alcohol, ml	water ml	Percentage of 5% alcohol in the total vol. of the drinking liquid
Starting level	3,6±0,2	1,3±0,2	73,5±2,4	3,7±0,2	1,4±0,1	72,5±1,2	3,6±0,3	1,3±0,3	73,5±3,7
During the expt.	3,7±0,2	1,1±0,1	77,1±2,3	3,3±0,4	1,2±0,2	73,3±2,7	1,9±0,4**	2,1±0,5	47,5±7,6*
10 days later	3,7±0,3	1,2±0,2	75,5±1,9	3,4±0,5	1,2±0,2	73,9±3,3	3,7±0,4	1,4±0,3	72,5±4,1

for 2 h, and subsequent amidation of intermediate II in methanol without its prior isolation led to significantly contaminated IV, with mp 176-182°C, in 91% yield based on VI; this product was purified with difficulty by repeated crystallization from butyl acetate and alcohol.

Compound IV was obtained in 30-35% yield based on V. It should be noted that information on both the quality of crude product IV and on methods for the purification of IV to give the pharmacopeial product is virtually absent in the literature.

As a result of these investigations it was shown that the crude product and the purified product contain admixed 5-carbamoyl-10,11-dihydro-5H-dibenz[b,f]azepine (IX), which has obtained by alternative synthesis in the reaction of VI with ammonia in methanol.

Compound IX is evidently formed as a consequence of incomplete bromination of VI and its subsequent amidation along with IV.

The difficulty involved in the purification of carbamazepine IV to remove admixed IX can evidently be explained by the similarity in their physicochemical properties. Thus their solubilities at 20°C are as follows: IV in alcohol 1:40, IX in alcohol 1:90, IV in chloroform 1:10, IX in chloroform 1:38, IV in butyl acetate 1:100, and IX in butyl acetate 1:150. In investigations by TLC on Silufol UV-254 plates their R_f values were close in most systems. The best results with respect to their separation were obtained in chloroform — acetone (3:2) (IV had R_f 0.36, and IX had R_f 0.4; development in UV light).

In order to stabilize the quality of the crude and pharmacopeial IV we developed a method for obtaining it with isolation of intermediate II after carrying out bromination and dehydrobromination with subsequent amidation of it in methanol at an excess pressure of 2-3 gage atmospheres. When halocarbonyl derivative derivative II is precipitated with methanol it is purified to remove unchanged VI, and the formation of admixed IX during subsequent amidation is thereby excluded.

A comparative chemical and spectral study of the carbamazepine obtained and the preparation Finlepsin confirmed the complete identity of these preparations. With respect to their quality, the carbamazepine samples obtained met the requirements of foreign pharmacopeias (East German, 1975 edition; British, 1973 edition).

EXPERIMENTAL CHEMICAL PART

10,11-Dihydro-5-chlorocarbonyl-5H-dibenz[b,f]azepine (VI). A 185-g (0.9 mole) sample of 95% iminodibenzyl (V) [6] was dissolved by heating in 1500 ml of toluene, and a gentle stream of phosgene was then bubbled through the solution at 90-95°C for 3-3.5 h. The excess phosgene and hydrogen chloride were then removed by purging with nitrogen for 2 h. Activated charcoal (14 g) was added to the solution, and the mixture was refluxed for 20 min. The charcoal was removed by filtration and washed with 50 ml of hot toluene, and the filtrate was evaporated to one third of its original volume. The concentrate was cooled to 0°C, and the precipitate that accumulated in 4 h was removed by filtration, washed with two 40-ml portions of cold toluene, and dried at 50-60°C to give 194.4 g of crystals with mp 121-123°C. The filtrate was evaporated and treated similarly with activated charcoal to give an additional 14.2 g of crystals with mp 119-121°C for a total of 208.6 g (90%) of VI (mp 121-123°C [11]).

10,11-Dihydro-5-carbamoyl-5H-dibenz[b,f]azepine (IX). A stream of ammonia was passed with stirring at 57-59°C in the course of 1.5 h through a mixture of 38.5 g (0.15 mole) of VI, 430 ml of methanol, and 50 ml of water, after which 2 g of activated charcoal was added, and the mixture was refluxed for 15 min. It was then filtered, and the filtrate was evaporated to dryness. Water (400 ml) was added to the residue, and the aqueous mixture was refluxed with stirring for 1 h. It was then cooled to 20°C, and the precipitate was removed by filtration, washed with 10 ml of alcohol, and dried at 75°C for 4 h to give 32.7 g of a substance with mp 198-205°C. The precipitate was recrystallized from 320 ml of methanol with 2 g of activated charcoal to give 30.3 g (85.35%) of IX in the form of colorless crystals with mp 205-206.5°C (mp 206-208°C [12]).

5-Carbamoyl-5H-dibenz[b,f]azepine (IV). A mixture of 19.3 g (0.075 mole) of VI and 8 ml of chlorobenzene was heated to 145°C, and 14.4 g (0.09 mole) of bromine was added dropwise with stirring at 145-150°C under the layer of the reaction mass in the course of 1.5 h at such a rate that the condenser did not become colored by bromine vapors. The reaction mass was then stirred for 2 h at 150-155°C to complete dehydrobromination, after which it

was cooled to 90°C and treated with 45 ml of methanol. The reaction mass with the resulting precipitate was cooled to 5°C, and the precipitate was removed by filtration and washed with two 10-ml portions of methanol. The 23.9 g of 75% II paste was loaded into a 0.165-liter autoclave, 102 ml of methanol and 28.3 ml (0.376 mole) of 25% NH_4OH were added, and the mixture was heated with stirring at 75-85°C for 5 h. It was then cooled to ~20°C and emptied, into a single-neck round-bottom flask; the autoclave was washed with 50 ml of hot methanol, and the wash solution was added to the principal reaction mass. The mixture was refluxed with 4 g of activated charcoal for 30 min, after which the charcoal was removed by filtration and washed with 10 ml of boiling methanol. A total of 150 ml of methanol was removed from the filtrate by distillation at 64-66°C, and 20 ml of distilled water was added to the residue. The mixture was heated to the boiling point and refluxed for 1 h, after which the reaction mass was cooled to 15°C, and the precipitate was removed by filtration, washed with two 25-ml portions of distilled water, and dried at 75-80°C for 8-10 h to give 14.5 g of IV with mp 184-186°C; this amount was 81.87% of the theoretical yield based on VI.

The 14.5 g of crude carbamazepine IV was loaded into a single-neck round-bottom flask equipped with a reflux condenser, 60 ml of alcohol was added, and the mixture was heated until the solid material dissolved. Activated charcoal (2 g) was added, and the mixture was refluxed for 30 min. The charcoal was removed by filtration and washed with two 5-ml portions of hot alcohol, and the filtrate was cooled and maintained at 0°C for 4 h.

The resulting precipitate was removed by filtration, washed with two 5-ml portions of cold alcohol, and dried in a vacuum desiccator at 65-70°C to give 10.7 g of pharmacopeial carbamazepine (IV) with mp 190-191.5°C. Evaporation of the mother liquor and crystallization of the residue gave an additional 1.1 g of IV with mp 189.5-191.5°C. The overall yield of IV was 11.8 g; this amount was 66.7% of the theoretical yield based on VI or 60% based on starting V.

EXPERIMENTAL PHARMACOLOGICAL PART

The experiments were carried out on mongrel mice and rats (males)in confirmity with the method that we used in [1]. Prior to administration of the preparation, the animals consistently preferred 5% alcohol, the percentages of which in the overall volume of the drinking liquid were 65-75% for mice and 90-98% for rats. Carbamazepine was administered intraperitoneally in the course of 10 days in a dose of 50 mg/kg for the rats and in a doses of 50 and 100 mg/kg for the mice. An equal volume of the solvent was administered to the control animals in the corresponding period. There were 10 rats and 15 mice in each experimental group.

RESULTS AND DISCUSSION

As a result of the investigations it was established that carbamazepine suppresses addiction to alcohol in the experimental animals. It is apparent from the data presented in Table 1 that administration of the preparation to rats decreased the average daily consumption of 5% ethanol solution by 7.9 ml, which corresponds to 26.2% of the starting level. The maximum decrease in the consumption of alcohol in the administration period was noted after the first injection of carbamazepine (by 35.1% as compared with the starting level). In addition to a decrease in the consumption of the alcohol-containing solution, a significant increase in the consumption of the alcohol-free liquid was observed under the influence of the preparation. In the period during which the preparation was administered the consumption of water by the rats increased by a factor greater than 3.5. The differently directed changes in the consumption of alcohol and water substantially decreased the percentage of alcohol in the total volume of the drinking liquid.

The preparation does not have a residual effect. After its administration was discontinued, the alcohol consumption was restored to the starting level, although the water consumption remained increased. Substantial changes in the consumption of the alcohol-containing solution and water were not noted among the control animals during the experimental period (see Table 1).

The antialcohol activity of carbamazepine was expressed more weakly in mice. The preparation in a dose of 50 mg/kg did not have a substantial effect on the consumption of alchol and water. However, in contrast to the control group, a tendency for a decrease in the average daily consumption of the alcohol-containing solution was noted for the experimental

animals during the period of administration of the preparation and after it was discontinued (Table 2).

Doubling the dose of carbamazepine leads to substantial suppression of addiction to alcohol in mice. Administration of the preparation in a dose of 100 mg/kg decreased alcohol consumption in the experimental animals by ~50% (see Table 2). The maximum effect was noted in the first 2 days of administration of the preparation. Water consumption increased somewhat during the administration period. It is apparent from Table 2 that the average daily water consumption during the administration period was higher than the consumption of 5% alcohol, while prior to administration of the preparation the consumption of the alcohol-containing solution was greater by a factor of approximately three as compared with the water consumption.

The significant decrease in the consumption of the alcohol-containing solution was reflected substantially in the percentage of alcohol in the total volume of the drinking liquid. Whereas this index was greater than 70% prior to administration of the preparation, it was less than 50% during the administration period. Discontinuance of the preparation leads to restoral of all of the investigated parameters to the starting level.

As in the preceding experiments, substantial changes in the consumption of the alcohol-containing solution and water were not noted among the group of animals (see Table 2).

Thus in the experiments it was established that carbamazepine suppresses addiction to alcohol. The observed effect provides evidence for the expediency of using this preparation in clinics and to suppress the craving for alcohol (carbamazepine is presently used primarily for alleviation of the abstinence syndrome).

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