SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF DERIVATIVES OF HARMAN AND HARMINE

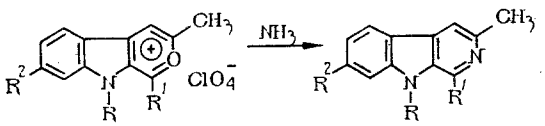
I. V. Komissarov, N. S. Semenov,
V. I. Luk'yanenko, V. F. Donets,
A. T. Dolzhenko, L. V. Dulenko,
and V. I. Dulenko

UDC 615.31:547.944.8].012.1

Some derivatives of carboline are known to have valuable therapeutic properties [1, 2]. Important among these compounds are the β-carbolines, one of which is reserpine [2].

Derivatives of β-carbolines are usually prepared by the Bischler–Napieralski or the Pictet–Spengler reaction. However, these most widely used methods give dihydro and tetrahydro derivatives of β-carboline, and an additional dehydrogenation step is required to obtain harman and harmine.

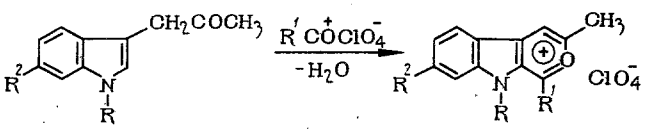
In our opinion, a more convenient method, which omits the dehydrogenation step, is the method in which indolyl [2,3-c] pyrylium salts are converted to the corresponding β-carboline by ammonia [3, 4].



I-VII

The purpose of the present work is to study this reaction further and to investigate the physiological activity of derivatives of the alkaloids harman and harmine.

The required indolyl [2,3-c] pyrylium salts were synthesized by the acylation of 3-acetonyl derivatives of indole and 6-methoxyindole



3-Acetonyl-6-methoxyindole was obtained from the reaction of 6-methoxyindole with acetylcarbene [5], and 3-acetonylindole from 3-indolylacetic acid by the Dakin–West reaction [6].

These salts were converted to derivatives of harman and harmine by heating with an alcoholic solution of ammonia. The hydrochlorides were used for pharmacological testing; they were prepared by treating a methanolic solution of the corresponding β-carboline with a saturated solution of hydrogen chloride in ether (Table 1).

The structures of the compounds prepared were confirmed by IR and NMR spectroscopy. Thus, the NMR spectrum of 2-ethyl-4-methylindolyl [2,3-c] pyrylium perchlorate contained a singlet corresponding to the methyl group (δ = 2.56 ppm), and also triplet and quadruplet peaks due to the ethyl substituent, and in the low-field region there are peaks corresponding to the protons of the aromatic rings.

The IR spectra of indolyl [2,3-c] pyrylium salts contain a series of bands (1650-1630, 1560-1540, 1470, and 1420 cm^{-1}), similar to the bands of 2-benzopyrylium salts [7]. An intense, broad band at 1100 cm^{-1} is associated with the absorption of the ClO_4^- anion.

Institute of Physicoorganic Chemistry and Carbon Chemistry, Academy of Sciences of the Ukrainian SSR, Donets Medical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 5, pp. 93-97, May, 1977. Original article submitted December 6, 1976.

TABLE 1. β-Carboline Hydrochlorides

Compound	R	R_1	R_2	Yield, %*	Melting point, deg	Found, %				Empirical formula	Calculated, %			
						C	H	Cl	N		C	H	Cl	N
I·HCl	H	CH_3	H	96	285—7	67,34	5,48	15,04	12,17	$C_{19}H_{12}N_2 \cdot HCl$	67,10	5,59	15,27	12,04
II·HCl	H	C_3H_7	H	78	221—2	69,24	6,69	13,34	10,78	$C_{15}H_{16}N_2 \cdot HCl$	69,09	6,52	13,63	10,75
III·HCl	CH_3	CH_3	H	86	324—5	68,39	6,26	14,01	11,41	$C_{14}H_{14}N_2 \cdot HCl$	68,17	6,08	14,39	11,39
IV·HCl	C_2H_5	CH_3	H	80	174—6	69,27	6,73	13,19	10,85	$C_{15}H_{16}N_2 \cdot HCl$	69,09	6,52	13,63	10,75
V·2HCl	$(CH_2)_2N(CH_3)_2$	CH_3	H	92	316—8	60,32	6,62	20,63	12,42	$C_{17}H_{21}N_3 \cdot 2HCl$	60,0	6,67	20,88	12,35
VI·HCl	H	CH_3	CH_3O	98	292—3	64,22	5,66	13,21	10,81	$C_{14}H_{14}N_2O \cdot HCl$	64,00	5,71	13,52	10,67
VII·HCl	H	C_2H_5	CH_3O	89	298—9	64,76	6,27	13,00	10,21	$C_{15}H_{16}N_2 \cdot HCl$	65,09	6,15	12,84	10,13

*All the compounds were recrystallized from a mixture of alcohol and acetone.

TABLE 2. Toxicity and Pharmacological Properties of β-Carboline Derivatives

Compound	LD_{50}, mg/kg	Dose, % of LD_{50}	Action on effects				
			phenamine (Δt min, stereotypy)	reserpine (Δt deg after 3 h)	hexenal (Δt min, lateral position)	arecoline† (Δt sec, tremor)	nicotine† (Δt sec, convulsions)
I·HCl	123±20,0	5	+71*	−1,1±0,85	+2,6	+84*	+186*
		30	+89*	+0,66*	—		
II·HCl	97±21,0	5	+97*	−0,7±0,54*	−1,1		
		30	+135*	+0,7±0,6*	+28,4*	+19	+79*
III·HCl	59±7,8	5	+21*	−0,9±0,6*	−11,3	+185*	−105*
		30	+30*	+1,6±1,0*	+7,6*		
IV·HCl	77±14,9	5	+11	+0,2±0,8*	−3,5	+68*	−105*
		30	+51*	+0,6±0,49*	+6,4		
V·HCl	51±19,4	5	+3	−1,0±1,0	−3,0	−67*	+7
		30	+49*	−0,8±0,54	+2,9		
VI·HCl	107±30,0	5	+31*	−0,9±0,98	−4,4		
		30	—	−0,1±0,8*	+21,6*	+59*	−105*

*Statistical reliability P = 0.05.
†Doses of compounds are 20% of the LD_{50}.

The structures proposed for the 1,2,4-trimethyl- and 2,4-dimethylinodolyl [2,3-c] pyrylium salts are also confirmed by their reaction with ammonia which converts them easily and in high yield to the corresponding 1,4-dimethyl and 4-methylharman (III, I) indicating complete identity with the compound described in [8].

EXPERIMENTAL

Pharmacology

The pharmacological study of the neurotropic activity of the compounds was carried out by the usual methods [9].

All the compounds in the study displayed central adrenosensitizing activity, appreciably prolonging phenamine stereotypy in rats, and counteracting the hypothermic effect of reserpine (Table 2). With compounds I and II, the adrenopositive action occurs at doses of 5% of the LD_{50} and is comparable to the activity of the tricyclic antidepressant imipramine. The central adrenosensitizing activity of the compound is apparently not associated with monoamino oxidase depression: The noradrenaline and dopamine content of the brain of a rat did not change appreciably after injection of II and V.

The depressing action of the compounds on the central nervous system is small: Only at doses of 25-30% of the LD_{50} were they observed to depress the motor activity and the righting reflex and to cause loss of motor coordination. In small doses, the compounds do not alter the narcotic effect of hexenal and in larger doses (30% of the LD_{50}), they increased it only slightly (II, III, and VI). Apart from compound V, which has characteristic M-cholinolytic properties, all the compounds lengthen arecoline tremor in mice, thus displaying M-cholinopositive activity. From the way in which the compounds affect the duration of nicotine-induced convulsions in mice (see Table 2), it can be seen that I and II display N-cholinopositive, and III, IV, and VI N-cholinolytic activity. Some of the compounds displayed antagonism to 5-hydroxytryptophan, which could be of importance. Unlike imipramine, compounds II and V quantitatively decrease the "head shaking" in mice caused by 5-hydroxytryptophan.

Compound I was studied in greatest detail (Table 3); it was found to be the least toxic and to possess a marked adrenopotentiating activity. It was noted that the activity of this compound is similar to that of imipramine except that it does not possess cholinolytic properties.

A comparison of the chemical structure of the compounds and their pharmacological activity shows that substitution of the indole nitrogen with alkyl groups leads to a decrease in both sedative and adrenosensitizing activity, together with an increase in their toxicity.

TABLE 3. Comparative Pharmacological Activity of Compound I and Imipramine

Preparation	LD_{50}, mg/kg							
	depression of motor activity	depression of righting reflex	myorelaxation	potentiation of hexenal sleep	elimination of corazole convulsions	antagonism to arecoline	antagonism to nicotine	potentiation of apomorphine stereotypy
I	22±8,4	25±8,4	31±10,4	56±16,0	0	0	0	20,6±6,4
Imipramine	25±9,8	37±3,3	37±3,3	56±7,7	0	29±18,2	39±6,4	9,8±4,7

Thus, the compounds exhibited central adrenopositive and central cholinopositive activity. They are like the tricyclic type of antidepressants in their spectrum of activity and in the mechanism of their pharmacological activity. As in other tricyclic systems which possess antidepressant activity, in the harman derivatives there is a transition from compounds with adrenosensitizing properties to compounds with a depressing action on the central nervous system (harmans substituted on the indole nitrogen).

Chemistry

The IR spectra were recorded on a UR-29 apparatus in the frequency range 3600-600 cm^{-1} in potassium bromide pellets or in carbon tetrachloride solution (NH band). The NMR spectra were taken on NMR-5535 and RYa-2305 spectrometers at frequencies 40 and 60 MHz, respectively, in solutions of trifluoroacetic acid and chloroform; concentrations of the studied compounds was 10-20%, room temperature.

Chemical shifts were measured relative to hexamethyldisiloxane and cyclohexane which were used as internal standards and converted to the tetramethylsilane scale.

3-Acetonyl-6-methoxyindole. To a solution of 6-methoxyindole [10] (5.88 g) in absolute benzene (25 ml) and powdered copper (0.5 g) at 75°C was added a solution of diazoacetone (2.52 g) in absolute benzene (15 ml) over a period of 30 min. After the addition of the diazoacetone, the reaction mixture was heated for 1 h at 70-75°, cooled, the copper filtered off, and the solvent removed. The residue was chromatographed on an aluminum oxide column and eluted successively with petroleum and diethyl ether. Yield, 1.8 g (30%) of 3-acetonyl-6-methoxyindole, mp 131-132° (colorless needles from ethanol). Found, %: C 70.83; H 6.62; N 7.15. $C_{12}H_{13}NO_2$. Calculated, %: C 70.90; H 6.42; N 6.94.

Semicarbazone, mp 176-178° (from ethanol). Found, %: N 21.20. $C_{13}H_{16}N_4O_2$. Calculated, %: N 21.34. IR spectrum: $\nu_{C=O}$ = 1715 cm^{-1}.

2,4-Dimethyl-8-methoxyindolyl[2,3-c]pyrylium Perchlorate. To a solution of 3-acetonyl-6-methoxyindole (1 g) in glacial acetic acid (5 ml) at 0° was added the acylating mixture prepared from acetic anhydride (7 ml) and perchloric acid (0.7 ml; 70%). The reaction mixture was mixed and left at room temperature. After 30 min it was filtered and washed with ether. Yield, 1.43 g (88%), mp 225-226° (from a mixture of alcohol and nitromethane, 4:1). Found, %: C 51.34; H 4.60; Cl 10.61. $C_{14}H_{14}ClNO_6$. Calculated, %: C 51.29; H 4.41; Cl 10.80.

2-Ethyl-4-methyl-8-methoxyindolyl[2,3-c]pyrylium Perchlorate. This was prepared in 90% yield by the method outlined above, mp 175-177° (from ethanol). Found, %: C 52.27; H 5.01; Cl 10.12. $C_{15}H_{16}ClNO_6$. Calculated, %: C 52.71; H 4.68; Cl 10.40.

The other indolylpyrylium salts were prepared by the same method as that described for 2,4-dimethyl-8-methoxyindolyl[2,3-c] perchlorate [3, 4].

4-Methylharmine. To 2,4-dimethyl-8-methoxyindolyl[2,3-c]pyrylium perchlorate (1 g) was added ethanol (10 ml), and this was saturated with gaseous ammonia over a period of 15-20 min. The reaction mixture was refluxed for 30 min, cooled, and poured into cold water (100 ml). After 1.5-2 h the precipitated material was filtered off, washed with water, and dried. Yield, 0.59 g (84%), mp 150-151° (from methanol). Found, %: N 12.13. $C_{14}H_{14}N_2O$. Calculated, %: N 12.34.

4-Methylharmine Hydrochloride. 4-Methylharmine (0.5 g) was dissolved in methanol and an ethereal solution of hydrogen chloride was added until the pH was 2.0. The precipitated material was filtered off and washed with absolute ether. The yield was quantitative, mp 292-294° (from a mixture of alcohol and acetone, 1:3).

The other derivatives of β-carbolines, apart from V, were prepared by a similar method and data are given in Table 1. Compound V was synthesized by alkylation of the Ind-Na salt of 4-methylharman with dimethylaminoethyl chloride [11].

LITERATURE CITED

1. R. C. Elderfield (editor), Heterocyclic Compounds, Vol. 7, Wiley, New York (1957) [Russian translation: Moscow (1965), p. 248].
2. M. D. Mashkovskii, Drugs [in Russian], Vols. 1 and 2, Moscow (1972).
3. G. N. Dorofeenko and L. V. Dulenko, Khim. Geterotsikl. Soedin., No. 3, 417 (1969).
4. G. N. Dorofeenko, L. V. Dulenko, and N. S. Semenov, Khim. Geterotsikl. Soedin., No. 2, 245 (1970).
5. J. Novak, J. Ratusky, V. Sneberk, et al., Coll. Cech. Chem. Commun., 1836 (1957).
6. J. Brown, H. Henbest, and E. Jons, J. Chem. Soc., 3172 (1952).
7. G. N. Dorofeenko, A. D. Semenov, V. I. Dulenko, et al., Zh. Org. Khim., 2, 1442 (1966).
8. A. N. Lomakii and I. V. Terent'eva, Khim. Geterosikl. Soedin., No. 1 1041 (1968).
9. N. K. Barkov and V. V. Zakusov, Farmakol. Toksikol., 36, 730 (1973).
10. N. N. Suvorov, M. V. Fedotova, O. B. Ogareva, et al., Zh. Obshch. Khim., 30, 3118 (1960).
11. M. F. Marshalkin, A. I. Polezhaeva, M. D. Mashkovskii, et al., Khim. Farm. Zh., No. 11, 11 (1973).

BIOLOGICAL ACTIVITY OF MODIFIED STEROIDS.

VIII. SYNTHESIS AND THE HORMONAL ACTIVITY OF CERTAIN 16α,17α-OXAZOLINES OF THE PREGNANE TYPE

A. I. Terekhina, I. V. Vesela, A. V. Kamernitskii, and L. I. Lisitsa

UDC 615.256.52.012.1

In our earlier publications we showed that some 16,17-cyclosulfates [1], cyclothiocarbonates [2], dioxolanes and oxathiolanes [3] of pregnane 20-ketosteroids exhibit a strong gestagenic activity that is similar to the activity of progesterone. However, these compounds did not exceed progesterone in the intensity and the duration of the effect, and at the same time they acted with a lower degree of specificity showing some other hormonal properties together with the gestagenic activity.

To continue our previous study, we decided to prepare and study 16α,17α-oxazoline analogs of the previously prepared modified steroids. It was of a particular interest to compare their properties with those of the corresponding dioxolanes and oxathiolanes, containing the oxygen or sulfur atoms instead of the nitrogen atom in the position 17.

A possibility that 16α,17α-oxazolines of pregnane 20-ketosteroids could serve as the starting material for preparing compounds containing a stable iminoxy radical condensed with the ring D was also of some interest. This radical group can be detected by the ESR method, and the compounds could therefore be used for studying the principles of its transport through the organism, and for studying its interactions with the hormonal receptors of the steroid type progestins. So far, it has only been possible to introduce the iminoxy radical into the A ring of steroids that did not contain the Δ^4-3-keto group, and having, in consequence, the corresponding biological activity [4].

Institute of Biological Studies of Chemical Compounds, Moscow Region. N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow.

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 5, pp. 97-100, May, 1977. Original article submitted December 6, 1976.

0091-150X/77/1105-0681$07.50