BIOLOGICAL ACTIVITY OF BI-AND TRICYCLIC KETONES

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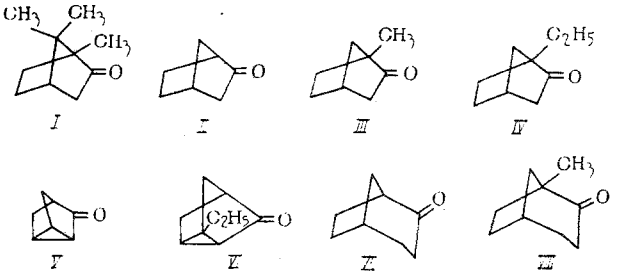
In the course of a search for soluble analogs of camphor (I), we synthesized several cyclic ketones (II-VIII) and compared their biological activity with that of camphor (I). Like camphor, the compounds contain a keto group in the bridged cyclic molecule, but differ from camphor by the number and length of the alkyl groups (II-IV), by the presence of a trimembered ring (V, VI), or by belonging to the homocamphor series (VII, VIII). The physical properties of the compounds, their solubility in water, and purity, as determined by gas–liquid chromatography (GLC), are shown in Table 1.



All the ketones II-VIII are more readily water soluble than camphor. Norcamphor II and nortricyclanone V, which contain no alkyl groups in the molecule, have the highest solubility (30 and 60 times, respectively, higher than camphor).

EXPERIMENTAL

Pharmacology

To reveal the cardiotonic action of the cyclanones, we studied their influence on intact frog hearts isolated according to Straub and on the background of depression by potassium chloride (0.05%) or acetylcholine (1:1,000,000). Like camphor, none of the compounds changed the cardiac activity in dilutions of 1:50,000-1:10,000, but on decreasing the dilution to 1:1000, they showed a depressing action (bradycardia, lowering of the contraction amplitude to complete stoppage of the heart).

Compounds I-IV and VI exhibited a tonic action on frog heart on the background of potassium chloride depression, with the activity changing in the following sequence: campor > norcamphor > 1-ethylnortricyclan-3-one > ethylnorcamphor > methylnorcamphor. The same compounds prevented the acetylcholin-induced heart stoppage and restored the rhythm of contractions to up to 76-88% of the initial one and the amplitude to 42-67% of the initial amplitude. No cardiotonic action was observed with cyclanones V, VII, and VIII, while compound V even intensified the toxic effect of potassium chloride.

Thus, with regard to cardiotonic activity, norcamphor, which has no methyl groups in the molecule, is most similar to camphor, while the action of III is less pronounced. Nortricyclanone, in contrast to camphor, showed no cardiotonic activity, but compounds IV and VI corresponding to it, with an ethyl group in the side chain, had activity comparable to camphor.

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TABLE 1. Physical Properties of Compounds Tested

Compound	Boiling point, °C/mm	Melting point, °C	n_D^{20}	d_4^{20}	Purity according to GLC,* %	Solubility, g/1000 g of water
Camphor (I)	209,1/759	174,8	—	—	99,1	1
Norcamphor (II)	125/136	96	—	—	99,5	30
1-Methylnorcamphor (III)	65/16	—	1,4663	—	99,8	9—12
1-Ethylnorcamphor (IV)	63/7	—	1,4684	0.9701	99,8	14—19
Nortricyclanone (V)	72/16	—	1,4862	—	99,8	60
1-Ethylnortricyclan-3-one (VI)	69/5	—	1,4769	1,0055	99,9	8—11
Bicyclo[3, 2, 1]octan-2-one(VII)	—	113	—	—	92,0 †	6—8
1-Methylbicyclo[3, 2, 1]-octan-2-one (VIII)	78/11	—	1,4824	0,9919	98,8	4

*Capillary column (50 m × 0.25 mm) with Apiezone-L.

† The product contained admixtures of isomeric ketones: 6% of bicyclo[2,2,2]octan-2-one and 2% of bicyclo[3,3,0]octan-2-one.

TABLE 2. Antishock and Antiarrhythmic Action of Norcamphor and Camphor (mean of 8-10 experiments)

	Parameter	Physiological solution	Norcamphor	Camphor
Histamine shock	Reduction of arterial pressure, % of background	40	75	97
	Survival, %	0	30	50
Calcium chloride arrhythmia	Duration of arrhythmia, min	0,5—1,0 (time of survival)	1,55±0,35	1,2±0,17
	Survival, %	0	67	92

The pronounced cardiotonic action of norcamphor led to our experimental study of its effectiveness on white rats during histamine and calcium chloride arrhythmia. Experimental shock was induced in the rats by intraperitoneal introduction of histamine in a dose of 0.5 g/kg. The systemic arterial pressure was measured in the common carotid artery. A steady lowering of the arterial pressure, up to 30-60 mm Hg, occurred 3-5 min after the introduction of histamine. Solutions of norcamphor and camphor in a dilution of 1:100,000 were introduced intravenously at a rate of 8-10 drops per min.

To produce arrhythmia in rats, 2 ml/kg of a 10% solution of calcium chloride was introduced intraperitoneally. The antiarrhythmic effect of the preparations in the form of 10% alcoholic solutions, introduced subcutaneously 15 min after the injection of calcium chloride, was evaluated from ECG with double-standard leads. Norcamphor, in a 1:100,000 dilution, introduced dropwise intravenously, showed, like camphor [1], antishock activity: A partial normalization of the systemic arterial pressure and increase in the rate of survival of the experimental animals was noted (Table 2). The preparation, in a dose of 100 mg/kg introduced subcutaneously for prophylactic purposes, weakened the severity of arrhythmia, and in two thirds of the experiments prevented the death of the animals.

Thus, norcamphor shows cardiotonic, antiarrhythmic, and antishock activity, but with regard to the effectiveness, it is inferior to camphor.

Chemistry

Norcamphor (II). Compound II was prepared according to the method described in [2] by reacting cyclopentadiene with vinyl acetate, with subsequent saponification and oxidation. The product was purified in the form of its semicarbazone.

1-Methylnorcamphor (III) and 1-Ethylnorcamphor (IV). Compounds III and IV were prepared by reacting acetic acid with 2-methylenenorbornane [3], and 2-ethylidenenorbornane [4], respectively, with subsequent saponification and oxidation. The products were purified by distillation on a column.

Nortricyclanone (V). The reaction of acetic acid with 2,5-norbornadiene [5] gave a mixture of nortricyclanol and norbornenol acetates (4:1), from which the main component was isolated by distillation on a column, and then saponified and oxidized.

1-Ethylnortricyclan-3-one (VI) [6]. The reaction of 96.5% formic acid with 5-ethylidene-2-norbornene at room temperature and with vigorous stirring gave a mixture of cis- and trans-1-ethylnortricyclan-3-ol and 2-ethylidenenorbornan-6-ol and 2-ethylidenenorbornan-6-ol formates (82:18). The individual trans-1-ethylnortricyclan-3-ol formate, bp 99° (19 mm), n_D^{20} 1.4674, was isolated by distillation on a column and then saponified and oxidized. The ketone obtained was purified by distillation on a column.

Bicyclo[3,2,1]octan-2-one (VII). Compound VII was prepared by the method described in [7,8] by acetolysis of 2-hydroxymethylnorbornane tosylate with subsequent saponification and hydrolysis. The product was purified in the form of its semicarbazone.

1-Methylbicyclo[3,2,1]octan-2-one (VIII). Compound VIII was prepared by adding acetic acid to 2-methylenebicyclo[2,2,2]octane [9], with subsequent saponification and oxidation.

Determination of Solubility of the Ketones in Water. A sample of the ketone studied weighed with an accuracy to the fourth decimal place was added to a measured volume (3-5 ml) of bidistilled water at room temperature and with stirring by magnetic stirrer. After the complete dissolution of the sample, another weighed sample of the same ketone was added, and this operation was repeated until the dissolution ceased. Each experiment was repeated twice. The results obtained are listed in Table 1.

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